FERRING
PHARMACEUTICALS

Cover page for Protocol

Sponsor name	Ferring Pharmaceuticals Inc.
NCT Number:	NCT02545127
Sponsor trial ID:	000050
Official title of trial:	A randomized, double-blind, placebo-controlled, multicenter trial exploring the efficacy and safety of intra-nasal administration of merotocin in increasing milk production in maternal subjects with preterm delivery and inadequate milk production
Document Date:	06 Apr 2022

CLINICAL TRIAL PROTOCOL

A randomized, double-blind, placebo-controlled, multicenter trial exploring the efficacy and safety of intra-nasal administration of merotocin in increasing milk production in maternal subjects with preterm delivery and inadequate milk production

MERMAID
Merotocin in Mothers with Inadequate Milk Production and Infants Delivered Prematurely

Trial 000050

IND Number:	105928
Investigational Medicinal Product:	Merotocin, FE 202767 (Selective oxytocin-receptor agonist, nasal spray)
Indication:	Induction and support of lactation in women with preterm delivery and inadequate milk production
Phase:	2
Name and Address of Sponsor:	Ferring Pharmaceuticals Inc. 100 Interpace Parkway Parsippany, NJ 07054 United States Tel: [redacted]
GCP Statement:	This trial will be performed in compliance with GCP.

SYNOPSIS

TITLE OF TRIAL

A randomized, double-blind, placebo-controlled, multicenter trial exploring the efficacy and safety of intra-nasal administration of merotocin in increasing milk production in maternal subjects with preterm delivery and inadequate milk production

SIGNATORY INVESTIGATOR

[redacted] MD, [redacted]

TRIAL CENTERS

Approximately 15 trial centers in the United States

PLANNED TRIAL PERIOD		CLINICAL PHASE
Estimated First Patient First Visit:	Q4 2019	2
Estimated Last Patient Last Visit:	Q2 2023	

OBJECTIVES

Primary Objective

- To evaluate the effect of merotocin on increasing milk production in women with preterm delivery and with inadequate milk production

Secondary Objectives

- To evaluate the effect of merotocin on milk production after treatment discontinuation
- To evaluate the amount of mother's own milk (MoM) in the infant enteral nutritional intake and changes in infant body weight
- To evaluate any amount of merotocin from maternal plasma into the milk expressed by women with preterm delivery exposed to merotocin
- To characterize the safety profile of merotocin in women with preterm delivery and their infants

Exploratory Objective

- To explore the relationship between merotocin exposure in maternal plasma and milk volume
- To evaluate composition of milk produced during treatment with merotocin in women with preterm delivery

Post-trial Objectives

- To explore post-trial feeding patterns and key parameters of neonatal intensive care unit (NICU) hospitalization of infants from women with preterm delivery and inadequate milk production
- To assess the post-trial long-term development of infants from women with preterm delivery and inadequate milk production

ENDPOINTS

Primary Endpoint

- Volume of mother's own milk produced over Days 1 to 14

Secondary Endpoints

- Time to the first occurrence of a daily volume of MoM ≥500 mL and ≥750 mL
- Proportion of maternal subjects with a daily volume of MoM ≥500 mL and ≥750 mL over Days 1 to 14
- Volume of MoM produced over Days 15 to 17 (after treatment discontinuation)
- Volume of MoM fed to the infant over Days 1 to 14
- Volume of formula/donor milk fed to the infant over Days 1 to 14
- Merotocin concentration in milk produced at Day 3 and Day 10 visits
- Changes in infant body weight over Days 1 to 14
- Frequency and intensity of adverse events (AEs) in maternal subjects
- Frequency and intensity of AEs in infants
- Changes in routine safety laboratory parameters in maternal subjects and proportion of subjects with markedly abnormal changes at Day 15/End-of-Treatment visit

Exploratory Endpoints

- Merotocin concentration in maternal plasma at Day 3 and Day 10 visits
- Composition of milk (including lipids, protein, caloric content, lactose, and Human Milk Oligosaccharides) produced by maternal subjects at Day 3 and Day 10 visits

Post-trial Endpoints

- Time to tolerance of full (150 mL/kg/day) enteral feed of the infant
- Time to NICU discharge of the infant
- Number of days the infant requires total parenteral nutrition (TPN) until time of discharge from NICU
- Proportion of maternal subjects who are lactating at time of infant's discharge from NICU

- Proportion of infants who are fed with MoM/formula/donor milk at time of discharge from NICU
- Body weight, length, and head circumference of the infant at time of discharge from NICU
- Incidence of infant's morbidity events of special interest (including necrotizing enterocolitis (NEC), intra-ventricular hemorrhage, bronchopulmonary dysplasia (BPD), respiratory distress syndrome (RDS), late-onset sepsis, retinopathy of prematurity (ROP), and hemodynamically significant patent *ductus arteriosus*) until time of discharge from NICU
- Proportion of infants with an Ages and Stages Questionnaire-3 (ASQ-3) score in the black zone in any domain at 9 months, 18 months and 24 months of corrected gestational age

METHODOLOGY

This is a randomized, double-blind, placebo-controlled, multicenter trial exploring the efficacy and safety of intra-nasal administration of 400 µg merotocin in increasing milk production in women with preterm delivery and inadequate initial milk production.

The trial population consists of maternal subjects who have delivered a preterm singleton (gestational age from 24 weeks + 0 days to 34 weeks + 2 days), who wish to provide MoM to their infants but have inadequate initial milk production and who are willing to express milk at least 5 times every 24 hours during the observation period and 6 to 8 times every 24 hours during the treatment and post-treatment follow-up periods throughout the trial. No specific trial procedures are required for infants.

The trial consists of a screening period, a treatment period and a post-treatment follow-up period. In addition, there is a post-trial follow-up of infants.

- Screening Period: The screening period starts from the signing of informed consent and ends at randomization, which occurs between 96 to 192 (+4) hours of delivery. The screening period must include an observation period of a minimum of 48 hours for the collection of milk expression data.
- Treatment Period: Once the observation period is completed, eligible women will be randomized in a 1:1 ratio to receive either merotocin or placebo. The treatment period is 14 days and includes visits on Days 3 and 10, as well as an End-of-Treatment visit on Day 15 or the day after the last dose of investigational medicinal product (IMP) in case of premature discontinuation.
- Post-treatment Follow-up Period: The post-treatment follow-up period includes a Day 18/ Follow-up visit, scheduled 3 days after the Day 15/End-of-Treatment visit.

Note that Day 3, Day 10, Day 15/End-of-Treatment and Day 18/Follow-up visits can all be postponed for a maximum of 2 days.

Trial Activities

Maternal subjects who provide informed consent for participation will enter the screening period as soon as possible following delivery. The screening period runs from the signing of informed consent to randomization and includes an observation period of a minimum of 48 hours for the collection of milk expression data. Maternal subjects should enter the observation period within 144 hours of delivery as soon as the initial eligibility check has been completed and blood sampling for analysis of safety laboratory parameters has been performed. The observation period starts with the first milk expression session using the breast pump (i.e., pumping session) under supervision at the site. The observation period ends with the last pumping session at the trial center prior to randomization. Milk volume produced for the last 24 hours of the observation period (i.e., the 24-hour baseline interval) will be calculated to assess the inadequacy of milk production.

Throughout the trial, maternal subjects will be instructed to express milk; at least 5 times every 24 hours during the observation period and 6 to 8 times every 24 hours during the treatment and post-treatment follow-up periods, including at least once during the night and with no more than 5 hours between milk expression sessions (see milk expression procedures detailed later). Each session of milk expression will be recorded by subjects themselves every day.

Before treatment on the day of randomization, a physical examination of eligible subjects will be performed and vital signs will be recorded. For the analysis of milk composition, if the volume of production is, at the discretion of the investigator, adequate to meet the nutritional needs of the infant, a sample from the milk expressed prior to randomization will be obtained.

Randomization will occur between 96 and 192 (+4) hours of delivery. Every effort should be made to randomize maternal subjects as early as possible, but not earlier than 96 hours of delivery. To be eligible for randomization, maternal subjects must have 1) attempted initial milk expression within 12 hours of delivery; 2) attempted milk expression at least 3 times every 24 hours from 24 hours of delivery to the start of the observation period; 3) attempted milk expression using the breast pump at least 5 times every 24 hours for the last 48 hours of the observation period; 4) produced <200 mL milk in total from any expression method (i.e., pumping, hand expression and breastfeeding) for the last 24 hours of the observation period (i.e., the baseline interval).

Eligible maternal subjects will be randomly assigned in a 1:1 ratio to intra-nasal treatment with either merotocin (400 µg per dose, divided into 2 sprays with 1 spray in each nostril) or placebo. Randomization is stratified by gestational age group (<27 weeks and ≥27 weeks) and by site.

After instruction and guidance, treatment will be administered intra-nasally as 1 spray in each nostril approximately 5 to 10 minutes before each milk expression session. In this trial, treatment days start from the time of randomization, with Day 1 being the first 24 hours after randomization, Day 2 being 24 to 48 hours after randomization, and so on. The treatment period

will include 14 such consecutive intervals of 24 hours from the time of randomization, corresponding to 14 treatment days (Days 1 to 14). Trial visits can be scheduled according to calendar days without considering 24-hour periods. Each administration of IMP and milk expression will be self-recorded by maternal subjects on milk container labels. Maternal subjects should stop the administration of IMP as soon as having completed 14 days' treatment, rather than continue dosing until the Day 15/End-of-Treatment visit. Trial visits after randomization include Day 3, Day 10, Day 15/End-of-Treatment and Day 18/ Follow-up visits. At all of these visits, AEs and concomitant medications of maternal subjects will be collected and a review of the dosing (as applicable) and milk expression documentation will be performed.

Specifically, at Day 3 and Day 10 visits at the trial center, milk samples will be taken for the analysis of merotocin concentration in the milk and for the analysis of milk composition. Milk samples are taken only if the volume of production is, at the discretion of the investigator, adequate to meet the needs of the infant. In addition, for the analysis of merotocin concentration in the blood, 7 blood samples will be drawn for a subset of minimum 20 maternal subjects at Day 3 and Day 10 visits using an indwelling catheter at predefined time points from pre-dose until 1 hour after dosing. For the pre-dose sample of merotocin concentration, blood sampling should always be performed a minimum of 3 hours after the previous dose. Vital signs will also be measured at Day 3 and Day 10 visits.

Additional Day 15/End-of-Treatment visit procedures consist of a physical examination, vital signs and blood sampling (safety laboratory).

All maternal subjects who complete the assigned treatment of Days 1 to 14 will be asked to continue daily recording of MoM expression through the end of Day 17. The expressed milk will be collected at Day18/Follow-up visit to document the volume of milk produced during the post-treatment follow-up period.

No specific trial procedures are required for infants. All infant data are based on hospital records. Infant body weight and infant enteral feeds (volume of MoM and formula/donor milk fed to the infant) will be collected from hospital records for all days as available from Day 1 to Day 14. Concomitant medications and AEs including morbidity events of special interest (NEC, intra-ventricular hemorrhage, BPD, RDS, late-onset sepsis, ROP, and hemodynamically significant patent *ductus arteriosus*) will be collected from hospital records from signing of informed consent.

Milk Expression Procedures

Maternal subjects will attempt to express milk with a multi-user, electric, double-pumping breast pump (Medela Symphony, Medela Inc., McHenry, Illinois) at least 5 times every 24 hours during the observation period and 6 to 8 times every 24 hours during the treatment and post-treatment follow-up periods, including at least once during the night and with no more than 5 hours between milk expression sessions. Both breasts should be pumped and emptied in accordance

with the instructions provided in the lactation manual for subjects. Maternal subjects will also receive instructions on hand expression and hands-on pumping; use of the two methods is at subject's own choice. All maternal subjects will receive detailed and standardized lactation instructions and expert lactation support. Steps will be taken to standardize best supportive care across trial centers.

Milk expression will be conducted mostly with the breast pump, occasionally by hand expression (as subject wishes) or by breastfeeding the infant (only when the infant is considered by NICU staff to be capable of being breastfed). Breastfeeding will always be followed by further expression with the breast pump. Hand expression is permitted both immediately after a pumping session and in between pumping sessions during the observation period; however, once the subject has been randomized, hand expression is permitted only immediately after a pumping session. Hand expression in between pumping sessions during the observation period is to be recorded as a separate session but will not be included in the stated goal of milk expression frequency, i.e., at least 5 times every 24 hours.

The expressed milk will be collected into supplied containers in accordance with the instructions provided in the lactation manual for subjects. Maternal subjects may bring bottles of expressed milk to the trial center any day during the trial, and the weights of the milk expressed will be recorded. The recorded weight of milk expressed in grams will be converted to a volume of milk using a conversion of 1 g to 1 mL. Expressed milk will be stored for feeding to the infant after recording the milk weights.

Should breastfeeding occur, the amount of breastfed milk is established by weighing the infant before and after the breastfeeding has been completed by following standardized weighing instructions and by using a standardized scale. Breastfeeding will only occur when the trial center staff consider the infant has the ability to achieve a nutritional feed through breastfeeding. The weights before and after breastfeeding will be recorded. After breastfeeding her infant, the maternal subject should continue to express milk using the breast pump in accordance with instructions provided in the lactation manual for subjects and record the milk expression.

The fed volumes of MoM and of other enteral feedings (formula/donor milk) will be recorded by trial center staff based on the hospital records. It is expected that the majority of the infants will be hospitalized for the predominant or entire duration of the trial due to their prematurity. If the infant is discharged prior to the Day 18/Follow-up visit, the maternal subject will be instructed to continue to use the trial medication as planned and continue to record milk expression as instructed in the lactation manual for subjects and milk weighing procedures manual. Two standardized scales will be offered to the maternal subject for the recording of milk expression at home, one for measuring the weight of the expressed milk and one for measuring the weight of the infant before and after feeds (if the subject is breastfeeding).

Post-trial Activities

As part of post-trial activities after the Day18/Follow-up visit, infant AEs and concomitant medications will continue to be collected from hospital records through infant's discharge from NICU or until the last milk sample expressed during maternal subject's treatment with IMP is either consumed by the infant or discarded, whichever occurs last. Information on infant's morbidity events of special interest is collected through infant's discharge from NICU based on hospital records.

In addition, the following data will be collected from the hospital records as available when the infant is discharged from NICU: infant body weight, length and head circumference at time of discharge from NICU, time to full enteral feeds, time to discharge from NICU, number of days the infant requires TPN until discharge from NICU, type of feeding (MoM and formula/donor milk) at time of discharge from NICU, and whether the maternal subject is lactating at time of infant's discharge from NICU.

A further post-trial activity is to establish a contact with the maternal subject (by phone or other means) about one month after the infant's NICU discharge to inquire about any hospital re-admission of the infant and the reason for such.

For long-term follow-up, the Ages and Stages Questionnaire-3 (ASQ-3) will be provided to all infants at 9 months, 18 months and 24 months of corrected gestational age. A primary caregiver of the infant will answer the questionnaire that consists of approximately 30 questions covering five domains of development, including communication, gross motor, fine motor, problem-solving, and personal-social skills.

Data from post-trial activities will be provided in an addendum to the clinical trial report.

NUMBER OF SUBJECTS

The sample size calculation is based on the comparison of MoM produced over Days 1 to 14 between the merotocin group and the placebo group using a repeated measures analysis of covariance (ANCOVA). The primary analysis will be based on the full analysis set (FAS), defined as all randomized and exposed maternal subjects providing data on volume of MoM produced for at least 1 day after dosing initiation. The FAS will be based on the actual treatment received. A sample size of 100 maternal subjects, allocated equally to each treatment group, is estimated to provide approximately 80% power to detect a 50% increase in the daily volume of MoM produced over Days 1 to 14, compared to placebo. It is estimated that approximately 250 maternal subjects will need to be screened.

CRITERIA FOR INCLUSION

Inclusion criteria for entry into observation period:

Maternal subject:

1. Signed and dated informed consent for the maternal subject and parental consent for the infant, prior to any trial activity.
2. Aged 18 to 44 years at the time of informed consent.
3. Delivered at the hospital system associated with the trial center.
4. Delivered a preterm singleton at a gestational age of 24 weeks + 0 days to 34 weeks + 2 days.
5. Attempted initial milk expression within 12 hours of delivery.
6. Attempted milk expression at least 3 times every 24 hours from 24 hours of delivery to the start of observation period (at least 3 times between 24 and 48 hours of delivery for subjects who enter the observation period within 48 hours of delivery).
7. Is willing to express milk at least 5 times every 24 hours during the observation period and 6 to 8 times every 24 hours during the treatment and post-treatment follow-up periods, including at least once during the night and with no more than 5 hours between milk expression sessions, during the trial (up to 23 days).
8. Is willing to refrain from sexual intercourse during the trial.

Inclusion criteria for randomization (in addition to the criteria above):

Maternal subject:

9. Attempted milk expression using the breast pump at least 5 times every 24 hours for the last 48 hours of the observation period, i.e., the 48 hours prior to the last pumping session before randomization.
10. Accurately recorded timing of milk expression after providing informed consent.
11. Produced <200 mL milk for the last 24 hours of the observation period (the 24-hour baseline interval), i.e., the 24 hours prior to the last pumping session before randomization.
12. Delivered 96 to 192 (+4) hours prior to randomization.

CRITERIA FOR EXCLUSION

At screening, maternal subjects meeting any of the criteria listed below are **not** eligible for participation in the trial.

Maternal subject:

1. Has a pre-pregnancy body mass index (BMI) >50.
2. Has chronic or temporary medical conditions that would cause her to be unable to comply with the protocol or be unable to attend all trial visits.
3. Has mastitis.
4. Had known breast trauma, previous breast surgery (including breast augmentation or

breast reduction) or nipple piercing.

5. Has known prolactin-releasing pituitary tumor, a history of Sheehan's syndrome, or had previous pituitary surgery or radiation therapy.
6. Has any known maternally driven contraindication to breastfeeding.
7. Has known pre-pregnancy severe cardiovascular disease (e.g., uncontrolled chronic hypertension, severe arrhythmias, or Grade 3-4 New York Heart Association cardiac failure). Note: preeclampsia is allowed.
8. Has known pre-pregnancy insulin-dependent diabetes mellitus, polycystic ovarian syndrome, or any other condition that would impact lactation in the opinion of the investigator. Note: gestational diabetes is allowed (also when requiring the use of insulin for treatment).
9. Has unstable thyroid disease, i.e., has required dose adjustment of thyroid replacement or anti-thyroid medication in the 12 months prior to delivery.
10. Has known moderate or severe renal or hepatic impairment.
11. Has significant history of mental illness, including diagnosed postpartum depression, which could impede trial participation.
12. Has significant nasal congestion or mucous production that would impede use of a nasally administered product in the opinion of the investigator.
13. Has used or is currently using any of the following concomitant medications:
    - Any anti-psychotic drugs during the previous 12 months. Note: anxiolytic and antidepressant medications are allowed
    - Any other non-registered investigational drugs from 90 days prior to delivery or within 5 half-lives of the drugs, whichever is longer
    - Any hormonal contraception at any point following delivery
    - Any pharmacologic or complementary (e.g., herbal) galactagogue therapy at any point following delivery. However, use of oxytocin for prevention or treatment of postpartum hemorrhage prior to randomization is not exclusionary
    - Any concomitant medication that could suppress lactation at any point following delivery
    - Orally or parenterally administered steroids at any dose or inhaled steroids at doses >600 µg/day at any point following delivery
    - Prostaglandins at any point following delivery
14. Had postpartum hemorrhage of >1500 mL requiring transfusion or with current severe anemia (hemoglobin <8 g/dL).
15. Currently abuses or has previously abused (within 12 months prior to delivery) drugs or currently abuses or has previously abused (within 12 months prior to delivery) alcohol (i.e., >7 units/week).
16. Has suspected allergy to oxytocin or merotocin or to any of the excipients in the investigational medicinal products (IMPs) used in the trial.
17. Is unable to understand language(s) spoken or provided in writing to her at the trial center.

18. Has previously participated in the current trial.

At randomization the following exclusion criteria apply in addition to the screening criteria:

Maternal subject:

19. Has used or is currently using methergine within 12 hours prior to randomization.
20. Has any conditions that would require the concomitant use of any intranasal medications or any diuretic drugs throughout the trial.
21. Any clinically significant abnormal findings of safety laboratory parameters considered by the investigator to be unsuitable to participate in the trial.

Infant:

1. Has low probability of viability, as judged by the investigator.
2. Was transferred to another hospital system during screening, or is likely to be transferred to another hospital system during treatment period as judged by the investigator.
3. Has used any non-registered investigational drugs since delivery.

MEDICINAL PRODUCTS

Merotocin nasal spray (400 µg intra-nasally per dose, divided into 2 sprays with 1 spray in each nostril) administered 6 to 8 times every treatment day. Placebo nasal spray administered 6 to 8 times every treatment day.

The active IMP is a stock solution consisting of merotocin dissolved in an isotonic citrate/phosphate buffer of pH 5.5 at a concentration of 2 mg/mL. The placebo IMP is an isotonic citrate/phosphate buffer solution of pH 5.5. The IMPs are identical in appearance.

DURATION OF TREATMENT

Maternal subjects will be exposed to either merotocin or placebo for 14 days.

STATISTICAL METHODS

All statistical tests will be two-sided, using a 5% significance level. All statistical analyses will be performed using SAS software (SAS Institute, Inc, Cary, North Carolina) (Version 9.2 or later). The analysis of efficacy will be performed for the FAS and per protocol (PP) analysis set.

The primary analysis will be performed using the FAS, defined as all randomized and exposed maternal subjects providing data on volume of MoM produced for at least 1 day after dosing initiation. The FAS will be analyzed according to the actual treatment received. Analysis performed using the PP analysis set, defined as all randomized maternal subjects without major protocol deviations, will be considered supportive.

Primary Endpoint: Primary Analysis

The primary objective of this proof of concept (PoC) trial is to evaluate the effect of merotocin on increasing milk production in women with preterm delivery. The primary endpoint of the trial

is the volume of MoM produced over Days 1 to 14.

Repeated Measures ANCOVA Model:
The primary endpoint will be analyzed using a repeated measures ANCOVA with a general (unstructured) covariance matrix. The daily volume of MoM produced will be the dependent variable. The model will include the baseline volume of MoM produced as a covariate, with treatment group, treatment day, treatment-by-day interaction, and gestational age group (<27 weeks and ≥27 weeks) as factors. The baseline volume of MoM produced is defined as the volume obtained at the 24-hour interval for eligibility during the observation period. The average treatment effect across treatment days and the within-day treatment effect will be reported along with the corresponding two-sided 95% confidence intervals and p-values.

PoC will be considered to be established if the repeated measures ANCOVA model results in a significant positive average treatment effect of merotocin compared to placebo across the treatment period in the FAS.

Primary Endpoint: Sensitivity/Supportive Analyses
Sensitivity analyses exploring the robustness of the primary analysis results to the underlying assumption that missing data is missing completely at random will be carried out for the FAS and PP analysis set. For these analyses, missing data will be imputed under a missing-not-at-random (MNAR) assumption based on the pattern-mixture model with control-based pattern imputation. Additional sensitivity analyses will investigate the robustness of the primary analysis results based on the choice of the covariance structure and potential treatment interactions with gestational age group (<27 weeks and ≥27 weeks).

Although the randomization will be stratified by site, it will not be included in the model for the primary analysis because issues may arise when adjusting for a large number of small centers (with respect to the number of randomized subjects). Additionally, common methods, such as pooling small centers together to form one large center, lack scientific justification. To ensure that the trial conclusions are not substantially affected by this exclusion, sensitivity analyses will examine the relationship between the effect of treatment and center. This will be carried out by including center and the center*treatment interaction as factors in the repeated measures ANCOVA model specified for the primary endpoint.

Sensitivity analyses will be performed to assess the relationship between the time of randomization from delivery and the effect of treatment on the volume of MoM produced over Days 1 to 14. This will be carried out by including the time of randomization from delivery and the time of randomization from delivery by treatment interaction in the repeated measures ANCOVA model specified for the primary endpoint.

Further, the above primary analysis will be repeated to examine the consistency of the relationship between treatment and the volume of MoM produced over Days 1 to 14 after having

adjusted for additional covariates (age of maternal subject, ethnicity, presence of fetal growth restriction, birth weight, caesarean section, primipara versus multipara, use of antenatal steroids and pre-pregnancy BMI). Each covariate will be added to the model one by one and tested at a two-sided significance level of 20%. In case 2 or more covariates are significant at the 20% level, a forward selection process will be applied with a threshold for adding effects at a two-sided significance level of 20% to identify the final model.

Interim Analysis

An unblinded interim analysis for futility assessment is planned once approximately 50% of the planned 100 subjects have completed assigned treatment period of Days 1 to 14 of the trial. The primary endpoint, volume of MoM produced over Days 1 to 14, will be evaluated for futility. Stopping the trial due to lack of merotocin benefit (i.e., futility) could be considered if the conditional power is lower than 10%.

The interim analysis will be performed by an independent Data Monitoring Committee (DMC) based on cleaned data, and the recruitment will continue at the time of interim analysis unless otherwise notified. The DMC will review unblinded interim data and make a recommendation on whether the trial should be terminated early due to the futility (non-binding).

There is no planned interim analysis with the intention to stop the trial early due to overwhelming efficacy.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

List of Abbreviations

AE	adverse event
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical Classification System
ASQ-3	Ages and Stages Questionnaire -3
BMI	body mass index
CRO	Contract Research Organization
DMC	Data Monitoring Committee
e-CRF	electronic case report form
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GPV	Global Pharmacovigilance Department
h	hour(s)
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IMP	Investigational Medicinal Product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
ITT	intention-to-treat
LC-MS/MS	liquid chromatography tandem mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
min.	minimum
MNAR	missing-not-at-random
MoM	mother’s own milk
NEC	necrotizing enterocolitis
NICU	neonatal intensive care unit
PK	pharmacokinetic(s)
PoC	proof of concept
PP	per protocol
PT	preferred term

ROP	retinopathy of prematurity
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time to maximum observed concentration
TPN	total parenteral nutrition
WHO	World Health Organization

Definition of Terms

Hand expression	A method in which breasts are emptied through the use of hands
Hands-on pumping	A method of massaging the breasts to supplement pumping. Either the breasts are massaged during the actual pumping or the massage is performed intermittently to pumping
Milk expression session	One session of milk expression is defined as one round of pumping, one round of pumping followed immediately by hand expression or one round of breastfeeding followed immediately by pumping. In case of pumping combined with either breastfeeding or hand expression, the volume/weight of MoM expressed through pumping and through the other method will be recorded separately. However, if hand expression occurs in between pumping sessions during observation period, this should be considered a separate session but is not included the stated goal of milk expression frequency, i.e., at least 5 times every 24 hours
Pumping	A method in which milk is expressed from the breasts using a breast pump
Time to Tolerance	The infant has been on a feeding volume of 150mL/kg/day for at least 24 to 48 hours

1 INTRODUCTION

1.1 Background

Women with preterm delivery encounter special challenges in providing their infants with mother's own milk (MoM). Not only has the breast of the preterm woman not yet fully undergone the physiological and morphological changes in preparation for lactation, a woman with a preterm infant also faces worry and stress that is counterproductive for lactation. Further, she may also have to depend on a breast pump rather than the suckling of the baby, which deprives her of important lactation stimuli. Only about 48% of women with preterm delivery wanting to lactate had adequate milk production 6 weeks after delivery, as compared to about 83% among women with term delivery in the same prospective study.[1]

MoM is of particular value to the preterm infant's health and development as numerous studies have shown that bovine-based formula milk causes pro-inflammatory changes in the preterm infant's intestines. These effects are correlated with various morbidities of inflammatory origin that are often severe and sometimes fatal. Lower incidences of necrotizing enterocolitis (NEC),[2,3,4,5] retinopathy of prematurity (ROP),[6] sepsis[7,8] and bronchopulmonary dysplasia (BPD)[9,10,11] have been demonstrated in preterm infants receiving human milk than for infants receiving formula exclusively. Another documented benefit of providing human milk to preterm infants is a shorter time to tolerance of full enteral feedings.[3,12,13] Human donor milk is sometimes regarded as a better option than formula milk[14] but availability is limited. It also has to be pasteurized, which compromises nutritional, immunologic, and other milk components.[15] MoM is therefore the preferred option.

The rationale for the use of an oxytocin receptor agonist for the purpose of supporting lactation is based on several physiological observations and experimental data. First, a complete emptying of the breasts is of importance both in establishment of lactation and its continuation. Residual milk in the mammary glands will otherwise exert a negative feed-back on milk production and lead to an associated involution of mammary tissue. Oxytocin is well established as the major hormone responsible for milk ejection in humans. It is therefore postulated that enhanced milk ejection by administration of an exogenous oxytocin receptor agonist will increase the likelihood of full emptying of the mammary glands, and thereby diminish the negative feed-back of residual milk on milk production and the associated involution of mammary tissue. Secondly, oxytocin has been shown to increase the secretion and release of prolactin,[16] the major hormone responsible for milk synthesis in animals and humans. An increase in protein transfer in rabbit mammary tissue when exposed to oxytocin has also been demonstrated.[17] These data suggest that oxytocin plays a role in milk synthesis, secretion and ejection. In clinical studies, intramuscular injections of oxytocin were able to reverse stress-induced reduction in milk volume in maternal subjects.[18] Taken together, these data suggest that activation of oxytocin receptors can affect multiple critical pathways in lactation physiology with the ensuing possibility of increasing milk production.

Merotocin is a selective oxytocin receptor agonist that is being developed for the indication of induction and support of lactation in women with preterm delivery and inadequate milk production, with the expectation that it will increase the mother's milk production so that the infant's need of MoM will be met both in the short-term and long-term perspective, i.e., it will improve milk volume output and improve the lactation continuation rate over time. A notable feature of merotocin is its very low vasopressin receptor activity. It is therefore expected that merotocin can be administered at doses that are higher than what is advisable with natural oxytocin without encountering vasopressin receptor-mediated side effects. As the clinically effective dose may be higher than what is tolerable with natural oxytocin due to its dose-limiting side effects, merotocin would be more likely to meet the medical need. Merotocin is also degradable by chymotrypsin, which minimizes the risk of systemic exposure in the infant receiving MoM, in case milk transfer of merotocin should occur.

1.2 Scientific Justification for Conducting the Trial

The initial clinical development of merotocin was a combined single ascending and multiple ascending dose phase 1 trial to assess safety, tolerability and pharmacokinetics (PK) of merotocin in healthy non-lactating women. No safety or tolerability concerns were raised in that trial with doses up to 400 µg intra-nasally every 3 hours for 45 hours.[19]

Subsequently, the transfer of merotocin from blood to breast milk was investigated in a single-dose milk transfer trial in healthy women with full-term delivery. In that trial, merotocin was administered as an intravenous dose of 20 µg equivalent to 400 µg intra-nasally. For all subjects, the concentration of merotocin in the milk was below the lower limit of quantification.[19] The infants of maternal subjects exposed to merotocin in this trial can therefore be fed with MoM with no expectation that the infants will be exposed to the drug.

A proportion of mothers with preterm birth that are dependent on a breast pump have difficulty establishing adequate milk supply to meet their infants' nutritional needs. A product to enhance lactation so that prematurely born infants to a higher degree can be nourished with MoM would address a medical need. The current trial is the first investigation in the target population of women with preterm delivery and inadequate initial milk production who are generally breast pump dependent. The primary objective of the trial is to explore the efficacy of intra-nasally administered merotocin in increasing milk production in the target population and thereby to provide efficacy information for the planning of future trials. In the current trial, merotocin will be administered as a nasal spray. This is a common mode of administration for peptidic products in order to avoid the enzymatic degradation that would occur with oral administration and the subsequent low bioavailability.

Further objectives of the trial are to obtain information on safety in the maternal subjects and their infants when infants are fed with MoM from maternal subjects exposed to merotocin.

1.3 Benefit/Risk Aspects

The present trial will be the first to provide efficacy data in the target population. As a proof of concept (PoC) trial, the primary purpose is to test the hypothesis that exposure to merotocin results in increased milk production in women with preterm delivery and inadequate milk production.

A double electric breast pump will be provided to all maternal subjects entering the observation period. Maternal subjects will receive lactation counselling comprised of best supportive care for this population at trial entry and ongoing support throughout the trial. This is an important benefit of participation because postnatal lactation support is associated with increased rates of breastfeeding and improved infant outcomes.[20,21]

A potential benefit of the trial in general is identification of a pharmacologic intervention that will increase the maternal subjects' ability to produce an adequate amount of MoM to meet their infants' nutritional needs. There are known clinical benefits to premature infants receiving human milk, including shorter time to tolerance of full enteral feedings[3,12,13] and reduced risk of NEC,[2,3,4,5] ROP,[6] sepsis,[7,8] BPD[9,10,11] and respiratory distress syndrome (RDS)[22].

The risk profile to date is described in the Investigator's Brochure.[19] Merotocin has previously been given to healthy women without any significant undesirable effects. During the single ascending dose and multiple ascending dose trial in healthy women, the most frequently reported adverse events (AEs) were headache, dry mouth, and flushing (hot flush). In that trial, an increased heart rate was observed following a constant rate intravenous infusion which gave rise to high plasma concentrations. During the other phase 1 trial that investigated the transfer of merotocin from blood to breast milk in healthy women, the most frequently reported AEs were uterine spasm, breast engorgement, and headache.

Other effects associated with the pharmacological activity that is possibly mediated by the oxytocin receptor may occur. As such, undesirable effects reported for oxytocin following rapid intravenous bolus and intravenous infusions include cardiac arrhythmia, hypotension, bradycardia, and hypersensitivity.

The present trial is the first investigation in the target population of women with preterm labor and the first investigation with merotocin exposure beyond 45 hours. The proposed dosing regimen is 400 µg intra-nasal dose (divided into two sprays of 200 µg each) administered 6 to 8 times every 24 hours. The nasal spray can be used at consecutive sessions at least two hours apart for a maximum of 8 times every 24 hours. In the multiple ascending dose part of the phase 1 trial, the harmonic mean terminal half-life ($t_{½}$) with the 400 µg intra-nasal dose was 0.56 hours. With this $t_{½}$,, merotocin concentrations are negligible at two hours after dosing (3.6 half-lives) and merotocin is considered to be eliminated at three hours after dosing (5 half-lives).

Regarding exposure of merotocin to the infants, transfer of merotocin from blood to breast milk was not observed in the phase 1 trial in healthy postpartum women specifically investigating this

risk, as the concentration of merotocin in the milk of all subjects was below the lower limit of quantification. Milk samples obtained in the present trial will also be evaluated for merotocin.

The blood sampling performed as part of the trial might be associated with mild discomfort, bruising, and a very rare risk of infection.

In conclusion, the evaluation of the benefits and risks indicates that participation in this trial is associated with a favorable benefit-risk ratio.

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary Objective

- To evaluate the effect of merotocin on increasing milk production in women with preterm delivery and with inadequate milk production

Secondary Objectives

- To evaluate the effect of merotocin on milk production after treatment discontinuation
- To evaluate the amount of mother's own milk (MoM) in the infant enteral nutritional intake and changes in infant body weight
- To evaluate any amount of merotocin from maternal plasma into the milk expressed by women with preterm delivery exposed to merotocin
- To characterize the safety profile of merotocin in women with preterm delivery and their infants

Exploratory Objectives

- To explore the relationship between merotocin exposure in maternal plasma and milk volume
- To evaluate composition of milk produced during treatment with merotocin in women with preterm delivery

Post-trial Objectives

- To explore post-trial feeding patterns and key parameters of neonatal intensive care unit (NICU) hospitalization of infants from women with preterm delivery and inadequate milk production
- To assess the post-trial long-term development of infants from women with preterm delivery and inadequate milk production

2.2 Endpoints

Primary Endpoint

- Volume of MoM produced over Days 1 to 14

Secondary Endpoints

- Time to the first occurrence of a daily volume of MoM ≥500 mL and ≥750 mL

- Proportion of maternal subjects with a daily volume of MoM ≥500 mL and ≥750 mL over Days 1 to 14
- Volume of MoM produced over Days 15 to 17 (after treatment discontinuation)
- Volume of MoM fed to the infant over Days 1 to 14
- Volume of formula/donor milk fed to the infant over Days 1 to 14
- Merotocin concentration in milk produced at Day 3 and Day 10 visits
- Changes in infant body weight over Days 1 to 14
- Frequency and intensity of AEs in maternal subjects
- Frequency and intensity of AEs in infants
- Changes in routine safety laboratory parameters in maternal subjects and proportion of subjects with markedly abnormal changes at Day 15/End-of-Treatment visit

Exploratory Endpoints

- Merotocin concentration in maternal plasma at Day 3 and Day 10 visits
- Composition of milk (including lipids, protein, caloric content, lactose, and Human Milk Oligosaccharides) produced by maternal subjects at Day 3 and Day 10 visits

Post-trial Endpoints

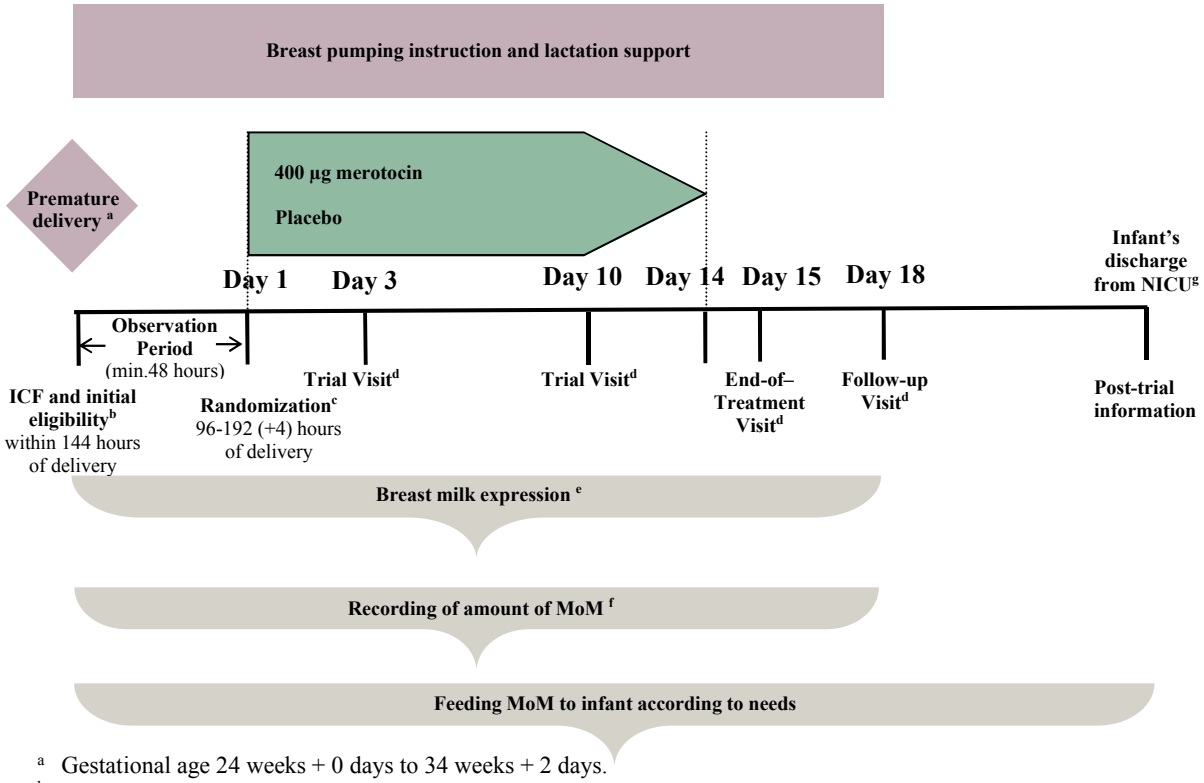
- Time to tolerance of full (150 mL/kg/day) enteral feed of the infant
- Time to NICU discharge of the infant
- Number of days the infant requires total parenteral nutrition (TPN) until time of discharge from NICU
- Proportion of maternal subjects who are lactating at time of infant's discharge from NICU
- Proportion of infants who are fed with MoM/formula/donor milk at time of discharge from NICU
- Body weight, length, and head circumference of the infant at time of discharge from NICU
- Incidence of infant's morbidity events of special interest (including necrotizing enterocolitis (NEC), intra-ventricular hemorrhage, bronchopulmonary dysplasia (BPD), respiratory distress syndrome (RDS), late-onset sepsis, ROP, and hemodynamically significant patent *ductus arteriosus*) until time of discharge from NICU
- Proportion of infants with an Ages and Stages Questionnaire-3 (ASQ-3) score in the black zone in any domain at 9 months, 18 months and 24 months of corrected gestational age

3 INVESTIGATIONAL PLAN

3.1 Overall Trial Design

3.1.1 Trial Design Diagram

A trial design diagram is provided in Figure 1.



[a] Gestational age 24 weeks + 0 days to 34 weeks + 2 days.
[b] Informed consent form (ICF) should be signed as soon as possible after delivery. Initial eligibility check must be completed within 144 hours of delivery.
[c] Randomization occurs between 96 and 192 (+4) hours of delivery. Treatment is administered intra-nasally as 1 spray in each nostril approximately 5 to 10 minutes before each milk expression session.
[d] In this trial, treatment days start from the time of randomization, with Day 1 being the first 24 hours after randomization, Day 2 being 24 to 48 hours after randomization, and so on. The treatment period includes 14 such consecutive intervals of 24 hours from the time of randomization, corresponding to 14 treatment days (Days 1 to 14). Maternal subjects should stop the administration of IMP as soon as having completed 14 days' treatment, rather than continue dosing until the Day 15/End-of-Treatment visit. Day 3, Day 10, Day 15/End-of-Treatment and Day 18/Follow-up visits can be postponed a maximum of 2 days.
[e] Maternal subjects will attempt to express milk at least 5 times every 24 hours during the observation period and 6 to 8 times every 24 hours during treatment and follow-up periods, including at least once during the night and with no more than 5 hours between milk expression sessions.
[f] MoM volume from the first milk expression session up to Day 18/Follow-up visit will be recorded.
[g] Infant's discharge from NICU or until the last milk expressed during maternal subject's treatment with IMP is either consumed or discarded, whichever occurs last. Long-term follow-up of infants through 24 months of corrected gestational age (section 3.6.8).

Abbreviations: ICF=informed consent form, min.=minimum, IMP=investigational medicinal product, MoM=mother's own milk, NICU=neonatal intensive care unit.

Figure 1 Overall Trial Design

3.1.2 Overall Design and Control Methods

This is a randomized, double-blind, placebo-controlled, multicenter trial exploring the efficacy and safety of intra-nasal administration of 400 µg merotocin in increasing milk production in women with preterm delivery and inadequate initial milk production.

The trial population consists of maternal subjects who have delivered a preterm singleton (gestational age from 24 weeks + 0 days to 34 weeks + 2 days), who wish to provide MoM to their infants but have inadequate initial milk production and who are willing to express milk 6 to 8 times every 24 hours throughout the trial. No specific trial procedures are required for infants.

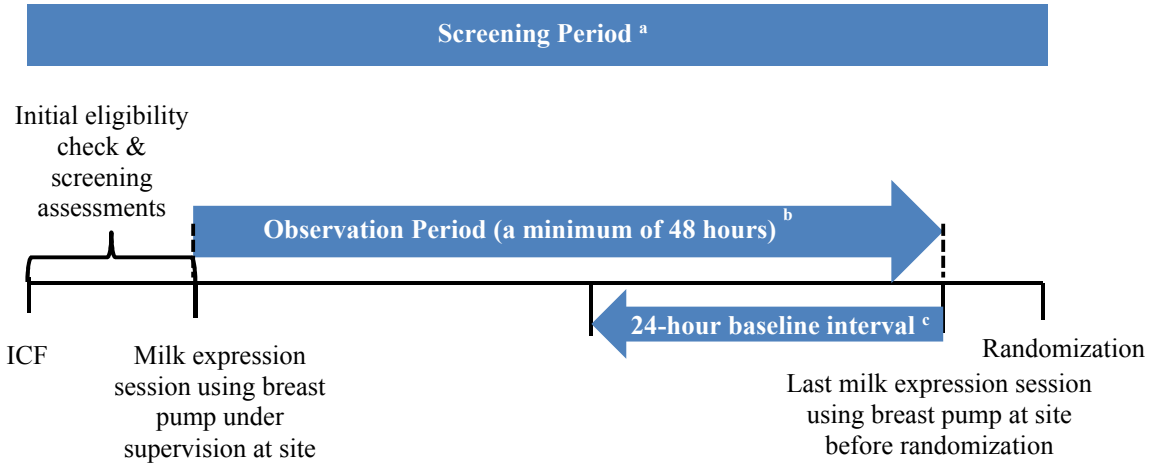
The trial consists of a screening period, a treatment period and a post-treatment follow-up period. In addition, there is a post-trial follow-up of infants.

- Screening Period: The screening period starts from the signing of informed consent and ends at randomization, which occurs between 96 to 192 (+4) hours of delivery. The screening period must include an observation period of a minimum of 48 hours for the collection of milk expression data.
- Treatment Period: Once the observation period is completed, eligible women will be randomized in a 1:1 ratio to receive either merotocin or placebo. The treatment period is 14 days and includes visits on Days 3 and 10, as well as an End-of-Treatment visit on Day 15 or the day after the last dose of investigational medicinal product (IMP) in case of premature discontinuation.
- Post-treatment Follow-up Period: The post-treatment follow-up period includes a Day 18 / Follow-up visit, scheduled 3 days after the Day 15/End-of-Treatment visit.

Note that Day 3, Day 10, Day 15/End-of-Treatment and Day 18/Follow-up visits can all be postponed for a maximum of 2 days.

Trial Activities

Maternal subjects who provide informed consent for participation will enter the screening period as soon as possible following delivery. The screening period runs from the signing of informed consent to randomization and includes an observation period of a minimum of 48 hours for the collection of milk expression data. Maternal subjects should enter the observation period within 144 hours of delivery as soon as the initial eligibility check have been completed and a blood sampling for analysis of safety laboratory parameters has been performed. The observation period starts with the first milk expression session using the breast pump (i.e., pumping session) under supervision at the site. The observation period ends with the last pumping session at the trial center prior to randomization. Milk volume produced for the last 24 hours of the observation period (i.e., the 24-hour baseline interval) will be calculated to assess the inadequacy of milk production. See Figure 2.



[a] Screening period runs from the signing of informed consent to randomization.
[b] The observation period starts with the first pumping session under supervision at the site and ends with the last pumping session at the site before randomization.
[c] The 24-hour baseline interval goes 24 hours backwards from the last pumping session before randomization. The milk expressed at the last pumping session before randomization is included in the 24-hour baseline interval.

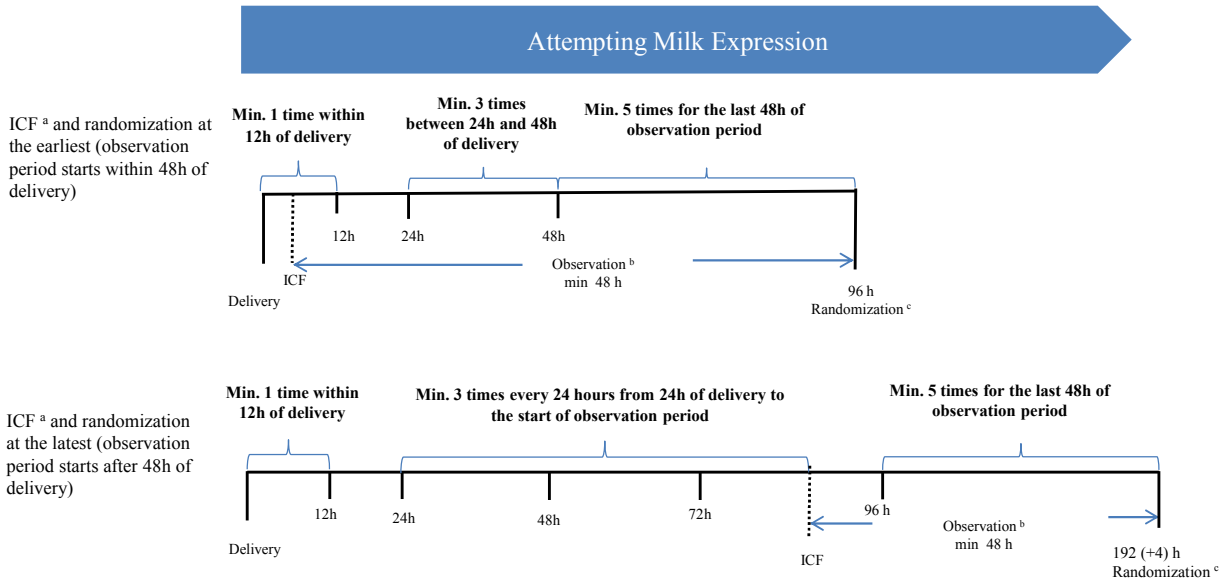
Figure 2 Screening Period, Observation Period and the 24-Hour Baseline Interval

Throughout the trial, maternal subjects will be instructed to express milk; at least 5 times every 24 hours during the observation period and 6 to 8 times every 24 hours during the treatment and post-treatment follow-up periods, including at least once during the night and with no more than 5 hours between milk expression sessions (see milk expression procedures detailed later). Each session of milk expression will be recorded by subjects themselves.

Before treatment on the day of randomization, a physical examination of eligible subjects will be performed and vital signs will be recorded. For the analysis of milk composition, if the volume of production is, at the discretion of the investigator, adequate to meet the nutritional needs of the infant, a sample from the milk expressed prior to randomization will be obtained.

Randomization will occur between 96 and 192 (+4) hours of delivery. Every effort should be made to randomize maternal subjects as early as possible, but not earlier than 96 hours of delivery. To be eligible for randomization, maternal subjects must have 1) attempted initial milk expression within 12 hours of delivery; 2) attempted milk expression at least 3 times every 24 hours from 24 hours of delivery to the start of the observation period [a]; 3) attempted milk expression using the breast pump at least 5 times every 24 hours for the last 48 hours of the observation period; 4) produced <200 mL milk in total from any expression method (i.e., pumping, hand expression and breastfeeding) for the last 24 hours of the observation period (i.e., the baseline interval). See Figure 3.

[a] At least 3 times between 24 and 48 hours of delivery if subjects enter observation period within 48 hours of delivery.



[a] ICF should be signed as soon after delivery as possible. Initial eligibility check must be completed within 144 hours of delivery.
[b] Observation period should start within 144 hours of delivery and should last a minimum of 48 hours; however, observation may be longer as randomization cannot occur before 96 hours of delivery. Subjects are instructed to attempt milk expression at least 5 times every 24 hours including at least once during the night and with no more than 5 hours between milk expression sessions during the observation period. Those who have attempted at least 5 milk expressions with the breast pump every 24 hours for the last 48 hours of the observation period and have produced <200 mL milk in total from any expression method (i.e., pumping, hand expression and breastfeeding) for the last 24 hours of the observation period (the 24-hour baseline interval) are eligible for randomization. Subjects are required to have attempted milk expression at least 3 times every 24 hours from 24 hours of delivery to the start of observation period (or at least 3 times between 24 and 48 hours of delivery if they start the observation period early), in addition to an initial milk expression attempt within 12 hours of delivery.
[c] Randomization occurs between 96 and 192 (+4) hours of delivery. Every effort should be made to randomize maternal subjects as early as possible, but not earlier than 96 hours of delivery.
Abbreviations: h=hours, ICF=informed consent form, min.=minimum.

Figure 3 Frequencies of Milk Expression from Delivery to Randomization

Eligible maternal subjects will be randomly assigned in a 1:1 ratio to intra-nasal treatment with either merotocin (400 µg per dose, divided into 2 sprays with 1 spray in each nostril) or placebo. Randomization is stratified by gestational age group (<27 weeks and ≥27 weeks) and by site.

After instruction and guidance, treatment will be administered intra-nasally as 1 spray in each nostril approximately 5 to 10 minutes before each milk expression session. In this trial, treatment days start from the time of randomization, with Day 1 being the first 24 hours after randomization, Day 2 being 24 to 48 hours after randomization, and so on. The treatment period will include 14 such consecutive intervals of 24 hours from the time of randomization, corresponding to 14 treatment days (Days 1 to 14). Trial visits can be scheduled according to calendar days without considering 24-hour periods. Each administration of IMP and milk expression will be self-recorded

by maternal subjects. Maternal subjects should stop the administration of IMP as soon as having completed 14 days' treatment, rather than continue dosing until the Day 15/End-of-Treatment visit.

Trial visits after randomization include Day 3, Day 10, Day 15/End-of-Treatment and Day 18/ Follow-up visits. At all of these visits, AEs and concomitant medications of maternal subjects will be collected and a review of the dosing (as applicable) and milk expression documentation will be performed.

Specifically, at Day 3 and Day 10 visits at the trial center, milk samples will be taken for the analysis of merotocin concentration in the milk and for the analysis of milk composition. Milk samples are taken only if the volume of production is, at the discretion of the investigator, adequate to meet the needs of the infant. In addition, for the analysis of merotocin concentration in the blood, 7 blood samples will be drawn for a minimum of 20 maternal subjects at Day 3 and Day 10 visits using an indwelling catheter at predefined time points from pre-dose until 1 hour after dosing. For the pre-dose sample of merotocin concentration, blood sampling should always be performed a minimum of 3 hours after the previous dose. Vital signs will also be measured at Day 3 and Day 10 visits.

Additional Day 15/End-of-Treatment visit procedures consist of a physical examination, vital signs and blood sampling (safety laboratory).

All maternal subjects who complete the assigned treatment of Days 1 to 14 will be asked to continue daily recordings of milk expression through the end of Day 17. The recordings and the expressed milk will be collected at the Day 18/Follow-up visit to document the volume of milk produced during the post-treatment follow-up period.

No specific trial procedures are required for infants. All infant data are based on hospital records. Infant body weight and infant enteral feeds (volume of MoM and formula/donor milk fed to the infant) will be collected from hospital records for all days as available from Day 1 to Day 14. Concomitant medications and AEs including morbidity events of special interest (NEC, intra-ventricular hemorrhage, BPD, RDS, late-onset sepsis, ROP, and hemodynamically significant patent *ductus arteriosus*) will be collected from hospital records from signing of informed consent. See Section 6 for further details.

Milk Expression Procedures

Maternal subjects will attempt to express milk with a multi-user, electric, double-pumping breast pump (Medela Symphony, Medela Inc., McHenry, Illinois) at least 5 times every 24 hours during the observation period and 6 to 8 times every 24 hours during the treatment and post-treatment follow-up periods, including at least once during the night and with no more than 5 hours between milk expression sessions. Both breasts should be pumped and emptied in accordance with the instructions provided in the lactation manual for subjects. Maternal subjects will also receive instructions on hand expression and hands-on pumping; use of the two methods is at subject's own

choice. All maternal subjects will receive detailed and standardized lactation instructions and expert lactation support. Steps will be taken to standardize best supportive care across trial centers.

Milk expression will be conducted mostly with the breast pump, occasionally by hand expression (as subject wishes) or by breastfeeding the infant (only when the infant is considered by NICU staff to be capable of being breastfed). Breastfeeding will always be followed by further expression with the breast pump. Hand expression is permitted both immediately after a pumping session and in between pumping sessions during the observation period; however, once the subject has been randomized, hand expression is permitted only immediately after a pumping session. Hand expression in between pumping sessions during the observation period is to be recorded as a separate session but will not be included in the stated goal of milk expression frequency, i.e., at least 5 times every 24 hours.

The expressed milk will be collected into supplied containers in accordance with the instructions provided in the lactation manual for subjects (see Section 7.1.1). Maternal subjects may bring bottles of expressed milk to the trial center any day during the trial, and the weights of the milk expressed will be recorded in accordance with instructions provided in the milk weighing procedures manual by the trial center staff. The recorded weight of milk expressed in grams will be converted to a volume of milk using a conversion of 1 g to 1 mL.[23] Expressed milk will be stored for feeding to the infant after recording the milk weights. If expressed milk is fed to the infant before it is weighed, the fed volume should be noted separately.

Should breastfeeding occur, the amount of breastfed milk is established by weighing the infant before and after the breastfeeding has been completed by following standardized weighing instructions and by using a standardized scale.[24] Breastfeeding will only occur when the trial center staff consider the infant has the ability to achieve a nutritional feed through breastfeeding. The weights before and after breastfeeding will be recorded. After breastfeeding her infant, the maternal subject should continue to express milk using the breast pump in accordance with instructions provided in the lactation manual for subjects and record the milk expression.

The fed volumes of MoM and of other enteral feedings (formula/donor milk) will be recorded by trial center staff based on the hospital records. It is expected that the majority of the infants will be hospitalized for the predominant or entire duration of the trial due to their prematurity. If the infant is discharged prior to the Day 18/Follow-up visit, the maternal subject will be instructed to continue to use the trial medication as planned and continue to record milk expression as instructed in the lactation manual for subjects and milk weighing procedures manual. Two standardized scales will be offered to the maternal subject for the recording of milk expression at home, one for measuring the weight of the expressed milk and one for measuring the weight of the infant before and after feeds (if the subject is breastfeeding).

Post-trial Activities

As part of post-trial activities after the Day18/Follow-up visit, infant AEs and concomitant

medications will continue to be collected from hospital records through infant's discharge from NICU or until the last milk sample expressed during maternal subject's treatment with IMP is either consumed by the infant or discarded, whichever occurs last. Information on infant's morbidity events of special interest is collected through infant's discharge from NICU based on hospital records.

In addition, the following data will be collected from the hospital records as available when the infant is discharged from NICU: infant body weight, length and head circumference at time of discharge from NICU, time to full enteral feeds, time to discharge from NICU, number of days the infant requires TPN until discharge from NICU, type of feeding (MoM and formula/donor milk) at time of discharge from NICU, and whether the maternal subject is lactating at time of infant's discharge from NICU.

A further post-trial activity is to establish a contact with the maternal subject (by phone or other means) about one month after the infant's NICU discharge to inquire about any hospital re-admission of the infant and the reason for such.

For long-term follow-up, the Ages and Stages Questionnaire-3 (ASQ-3) will be administered in all infants at 9 months, 18 months and 24 months of corrected gestational age. A primary caregiver of the infant will answer the questionnaire that consists of approximately 30 questions covering five domains of development, including communication, gross motor, fine motor, problem-solving, and personal-social skills.

Data from post-trial activities will be provided in an addendum to the clinical trial report.

3.1.3 Trial Schedule

Estimated First Patient First Visit:	Q4 2019
Estimated Last Patient First Visit:	Q2 2023
Estimated Last Patient Last Visit/End-of-Trial:	Q2 2023
Post-trial activities completed:	Q2 2025

3.2 Planned Number of Trial Centers and Subjects

Approximately 100 maternal subjects will be randomized at approximately 15 trial centers in the United States. It is anticipated that approximately 250 maternal subjects will be screened. See Section 9.1.

3.3 Interim Analysis

An unblinded interim analysis for futility assessment is planned when approximately 50% of the planned 100 subjects have completed the assigned treatment period of the trial. The interim analysis

will assess the futility of merotocin compared to placebo (see Section 9.9).

3.4 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) consisting of medical and biostatistics experts will be established to review the interim clinical data for the futility assessment (see Section 9.9). The DMC have access to the unblinded interim data and will make a recommendation regarding the continuation of the trial. The responsibilities, membership, and procedure for the futility assessment, the measures used to protect the blind, the integrity of the trial, and the communication pathway to the Sponsor are specified in the DMC charter.

3.5 Safety Committee

A Safety Committee will be established by the Ferring Global Pharmacovigilance Department (GPV) and will consist of at least Ferring's pharmacovigilance physician, Ferring's global regulatory affairs representative, the trial statistician, the medical monitor and an external neonatology specialist as specified in the Safety Committee charter.

The Safety Committee will meet regularly, at least every third month, to evaluate the safety of the subjects in terms of AEs, safety laboratory parameters, results from milk composition analyses, and any concentration of merotocin in milk on an ongoing basis. In case of any safety concerns, the Safety Committee can recommend whether the trial should be stopped or should continue with or without modifications to ensure the safety of the subjects and to maintain an appropriate benefit/risk ratio for the subjects participating in the trial.

The Safety Committee will not routinely unblind data on the individual level but may decide to unblind data on the group level to allow further analysis. If unblinding on the individual treatment level is required, an ad hoc safety group consisting of an independent GPV representative, an independent statistician and an external neonatology expert other than the expert in the Safety Committee will be formed to analyze the unblinded data. None of the ad hoc safety group members will be involved in the conduct of the trial.

The analyses of merotocin concentrations in milk will be performed by the Bioanalysis Department on an ongoing basis throughout the trial. Any quantifiable amount of merotocin observed in any of the samples will be communicated to the Safety Committee in a blinded manner. If one or more milk samples with quantifiable amount of merotocin is reported, the treatment allocation will be unblinded on the individual level by an ad hoc safety group, consisting of an independent GPV representative, an independent statistician and an external neonatology expert other than the expert in the Safety Committee. The ad hoc safety group will also review unblinded safety data. The United States Food and Drug Administration (FDA) will be notified of the finding and will be provided with observed neonatal AEs.

A Safety Committee charter will specify the relevant details and responsibilities of the Committee.

3.6 Discussion of Overall Trial Design and Choice of Control Groups

3.6.1 Trial Design

This trial will investigate the efficacy and safety of repeated intra-nasal administrations of merotocin compared to placebo in increasing milk production in women with preterm delivery and inadequate initial milk production.

The trial design employs best practices for establishing an adequate milk supply. All maternal subjects will institute a high frequency milk expression regimen and will receive standardized lactation counselling and ongoing support consistent with guidelines for promoting lactation in this population.

There is no approved product for women with lactation deficiency in the country where the trial will be conducted. Some pharmacologic agents are used in clinical practice to increase milk supply, but there is only limited medical evidence to support the safety and efficacy of the use of these agents to correct lactation deficiency in women with preterm delivery.[25,26,27] For these reasons, a placebo comparator is necessary to evaluate the potential of merotocin to increase milk production in this population.

The window for randomization, originally set to 96 to 144 hours of delivery, was chosen to enhance the probability of selecting maternal subjects who truly have an inadequate milk supply but also to ensure that intervention is instituted early enough in the postpartum period to have an impact. By the amendment (dated 06-04-2022), the window was expanded to 96 to 192 (+4) hours of delivery to allow adequate time for the maternal subjects to appreciate and understand the value of participating in the trial, with a negligible risk for any negative impact on induction of lactation. Allowing randomization earlier in the postpartum period might select maternal subjects, whose milk supply appears inadequate due to delayed onset of lactogenesis II but who may ultimately establish an adequate milk supply without intervention.

The treatment period of 14 days was primarily chosen because, if merotocin is effective, it would act early in the process of establishing lactation by promoting full emptying of the breast via milk ejection and possibly by increasing prolactin levels to increase milk synthesis. Both of these are important to establish an adequate milk supply. The duration of treatment needed for merotocin to achieve its potential effect in increasing milk production is not known. A treatment duration of 14 days will allow for exploration of when the treatment effect of merotocin begins and how the effect may develop over time.

To obtain the required number of maternal subjects within the scheduled recruitment period and to produce generalizable results, a multicenter design has been chosen. Maternal subjects will be randomly assigned to their treatments, and both the maternal subjects and investigators will be

blinded to the assignment to reduce bias.

3.6.2 Selection of Endpoints

The primary endpoint for this trial is volume of MoM produced over Days 1 to 14. The volume of MoM produced for each treatment day will be recorded and derived for each subject. These daily volumes of MoM produced will be analyzed using a repeated measures analysis of covariance (ANCOVA) to allow for investigation of the overall treatment effect in the primary analysis and the onset of treatment effect of merotocin compared to placebo in supportive analyses.

The secondary endpoints (Section 2.2) will provide further evaluation of the milk volume produced over Days 1 to 14. The recommendation for a lactating mother of a non-nursing preterm infant is to establish an adequate milk supply, defined as a daily milk volume of ≥500 mL, during the first two weeks after delivery. Evidence suggested that adequate milk production at 1-2 weeks postpartum, particularly 1 week postpartum, is highly predictive of milk adequacy at 6 weeks postpartum.[1] Therefore it is clinically relevant to assess the time it takes for maternal subjects to reach the target daily milk volume of ≥500 mL or a more ambitious goal of ≥750 mL. Striving for reaching these targets sooner than later may also motivate mothers to continue milk expression on a regular basis. For the same purpose, an additional secondary endpoint, an assessment of the proportion of women with an 'adequate milk supply' over Days 1 to 14 is also included.

The secondary endpoints will also examine whether any observed treatment effect of merotocin is maintained over the three days after discontinuation of treatment. The infant body weight is a standard growth parameter to indicate that the infant is growing and developing as expected. The safety assessments selected are standard for the maternal subjects.

The effect of merotocin on milk composition as well as the relationship between merotocin exposure and milk volume will be explored.

For the post-trial endpoint related to time to tolerance of full enteral feed, 150 mL/kg/day is used to define full enteral feed in order to standardize the assessment.[28,29] For the long-term follow-up of infants, the administration of ASQ-3 has been recommended by both FDA and American Academy of Pediatrics to screen child developmental disorders.

3.6.3 Blinding

The present trial is double-blind. Investigators, trial center staff and maternal subjects will remain blinded to treatment allocation until the database has been locked and the trial has been unblinded. Blinding is achieved by randomizing subjects in a 1:1 ratio to merotocin nasal spray or placebo nasal spray, which are identical in appearance.

At Ferring, personnel at the Bioanalysis Department analyzing blood and milk samples for merotocin will be blinded to treatment allocation when performing the analyses. The rest of the

Ferring clinical trial team will be blinded to individual and group treatment allocation until breaking of the blind after database lock, except for the Safety Committee members who may be unblinded to group treatment allocation under special circumstances (see Section 3.5). DMC members will have access to unblinded interim data to assess the futility at the interim analysis (see Section 3.4).

3.6.4 Selection of Doses in the Trial

In a combined single ascending and multiple ascending dose trial in healthy non-lactating women, there were no safety concerns with intra-nasal doses up to 400 µg every 3 hours for 45 hours.[19]

A single-dose milk transfer trial in maternal subjects who had recently delivered a full term infant has been completed. In that trial, merotocin was administered as an intravenous dose of 20 µg equivalent to 400 µg intra-nasally without safety concerns. The concentration of merotocin in the milk of these subjects was below the lower limit of quantification in all samples.[19]

These previous trials provide the basis for a dose of 400 µg to be administered intra-nasally before the milk expression session 6 to 8 times every 24 hours in the current trial.

3.6.5 Selection and Timing of Dose for Each Subject

Following intra-nasal administration of merotocin, the time to maximum observed concentration (t_{max}) and $t_{½}$ are approximately 12 to 15 minutes and 25 to 35 minutes, respectively.[19] In the phase 1 milk transfer trial, pharmacodynamic effect of merotocin in the form of uterine contractions were observed within 5 to 10 minutes after an intravenous dose equivalent to 400 µg intra-nasally. Therefore, the treatment for the maternal subject is administered intra-nasally as 1 spray in each nostril approximately 5 to 10 minutes before each milk expression session.

3.6.6 Selection of the Trial Population

A high proportion of the mothers of premature infants experience challenges in establishing an adequate milk supply. Due to the prematurity of the infant and the infant's diminished ability to suckle, these mothers are often deprived of the natural stimulus for lactation and may be dependent upon a breast pump. Breast pump dependency means that the pump is the primary driver of milk removal and mammary gland stimulation even though the infant may be able to feed at the breast.[30] The stress of having a premature infant may further impede milk production. On the other hand, the potential benefits of MoM in preterm infants are well documented,[2,31] which is likely to highly motivate mothers of preterm infants to express milk. For benefits to both mothers and infants, there are minimal ethical concerns about requiring a stringent milk expression schedule.

The trial population is women with infants at a high degree of prematurity. A gestational age range of 24 weeks + 0 days to 31 weeks + 6 days was originally chosen. However, by the amendment

(dated 06-04-2022), the window was expanded to 34 weeks + 2 days because many women who deliver infants at this gestational age are breast pump dependent and struggle to achieve an adequate milk supply. The upper limit of the gestational age is chosen to ensure the infants who are primarily breastfeeding at the time of enrollment would not be eligible. More breastfeeding may occur towards the end of the trial period among women who have delivered infants at the upper end of the gestational age range per eligibility criteria; however, that is not necessarily indicative of breast pump independence. Prematurity is one of several reasons for breast pump dependency; however, it is a focus of this early phase trial because of the high proportion of milk supply inadequacy experienced by women with premature birth.

3.6.7 Post-treatment Follow-up Procedures

All maternal subjects who complete the assigned treatment of Days 1 to 14 should continue expressing milk and recording milk expression sessions through the end of Day 17. The Day 18/Follow-up visit, which can be postponed for a maximum of 2 days. At the Day 18/ Follow-up visit, trial center staff will document the milk expression session data during the post-treatment follow-up period, which will provide information on the maintenance of any observed treatment effect. Collection of AEs and concomitant medications will also be performed. Follow-up visit may occur early in case of premature discontinuation (i.e., 3 days after the End-of-Treatment visit), which can also be postponed for a maximum of 2 days.

3.6.8 Post-trial Activities

Collection of infant AEs and concomitant medications will continue after the Day 18/Follow-up visit. These AEs will be collected and reported separately from those collected and reported through the Day 18/Follow-up visit. The AE collection will stop on the date the infant is discharged from the NICU or the last milk sample expressed during maternal subject's treatment with IMP is either consumed by the infant or discarded, whichever occurs last.

Additional data will be collected from the hospital records of the infant when the infant is discharged from NICU. The additional data (if available) are body weight, length and head circumference at time of infant's discharge from NICU, time to full enteral feeds, time to infant's discharge from NICU, number of days the infant requires TPN until discharge from NICU, type of feeding (MoM and formula/donor milk) at time of infant's discharge from NICU, and whether the maternal subject is lactating at time of infant's discharge from NICU.

Information on infant's morbidity events of special interest occurring prior to the infant's discharge from NICU, including NEC, intra-ventricular hemorrhage, BPD, RDS, late-onset sepsis, ROP, and hemodynamically significant patent *ductus arteriosus*, are recorded at the time of discharge from NICU based on hospital records. The trial is not powered to draw conclusions on the incidences of these events, but they are collected in order to capture any trends on the impact of feeding patterns on their incidences.

A further post-trial activity is to establish a contact with the maternal subject (by phone or other means) about one month after the infant's NICU discharge to inquire about any hospital re-admission of the infant and the reason for such.

For long-term follow-up, the ASQ-3 will be provided for all infants at 9 months, 18 months and 24-months of corrected gestational age. A primary caregiver of the infant will answer the questionnaire that consists of approximately 30 questions covering five domains of development, including communication, gross motor, fine motor, problem-solving, and personal-social skills.

Data from post-trial activities will be provided in an addendum to the clinical trial report.

3.6.9 Access to Therapy after Day 15/End-of-Treatment

Concerning access to therapy after completion of the trial, merotocin is currently under clinical development and cannot be offered to subjects after participation in this clinical trial.

4 SELECTION OF TRIAL POPULATION

4.1 Trial Population

4.1.1 Inclusion Criteria

Inclusion criteria for entry into observation period:

Maternal subject:

1. Signed and dated informed consent for the maternal subject and parental consent for the infant prior to any trial activity.
2. Aged 18 to 44 years at the time of informed consent.
3. Delivered at the hospital system associated with the trial center.
4. Delivered a preterm singleton at a gestational age of 24 weeks + 0 days to 34 weeks + 2 days.
5. Attempted initial milk expression within 12 hours of delivery.
6. Attempted milk expression at least 3 times every 24 hours from 24 hours of delivery to the start of observation period (at least 3 times between 24 and 48 hours of delivery for subjects who enter the observation period within 48 hours of delivery).
7. Is willing to express milk at least 5 times every 24 hours during the observation period and 6 to 8 times every 24 hours during the treatment and post-treatment follow-up periods, including at least once during the night and with no more than 5 hours between milk expression sessions, during the trial (up to 23 days).
8. Is willing to refrain from sexual intercourse during the trial.

Inclusion criteria for randomization (in addition to the criteria above):

Maternal subject:

9. Attempted milk expression using the breast pump at least 5 times every 24 hours for the last 48 hours of the observation period, i.e., the 48 hours prior to the last pumping session before randomization.
10. Accurately recorded timing of milk expression after providing informed consent.
11. Produced <200 mL milk for the last 24 hours of the observation period (the 24-hour baseline interval), i.e., the 24 hours prior to the last pumping session before randomization.
12. Delivered 96 to 192 (+4) hours prior to randomization.

4.1.2 Exclusion Criteria

At screening, maternal subjects meeting any of the criteria listed below are **not** eligible for participation in the trial.

Maternal subject:

1. Has a pre-pregnancy body mass index (BMI) >50.
2. Has chronic or temporary medical conditions that would cause her to be unable to comply with the protocol or be unable to attend all trial visits.
3. Has mastitis.
4. Had known breast trauma, previous breast surgery (including breast augmentation or breast reduction) or nipple piercing.
5. Has known prolactin-releasing pituitary tumor, a history of Sheehan's syndrome, or had previous pituitary surgery or radiation therapy.
6. Has any known maternally driven contraindication to breastfeeding.
7. Has known pre-pregnancy severe cardiovascular disease (e.g., uncontrolled chronic hypertension, severe arrhythmias, or Grade 3-4 New York Heart Association cardiac failure). Note: preeclampsia is allowed.
8. Has known pre-pregnancy insulin-dependent diabetes mellitus, polycystic ovarian syndrome, or any other condition that would impact lactation in the opinion of the investigator. Note: gestational diabetes is allowed (also when requiring the use of insulin for treatment).
9. Has unstable thyroid disease, i.e., has required dose adjustment of thyroid replacement or anti-thyroid medication in the 12 months prior to delivery.
10. Has known moderate or severe renal or hepatic impairment.
11. Has significant history of mental illness, including diagnosed postpartum depression, which could impede trial participation.
12. Has significant nasal congestion or mucous production that would impede use of a nasally administered product in the opinion of the investigator.
13. Has used or is currently using any of the following concomitant medications:
    - Any anti-psychotic drugs during the previous 12 months. Note: anxiolytic and antidepressant medications are allowed
    - Any other non-registered investigational drugs from 90 days prior to delivery or within 5 half-lives of the drugs, whichever is longer
    - Any hormonal contraception at any point following delivery
    - Any pharmacologic or complementary (e.g., herbal) galactagogue therapy at any point following delivery. However, use of oxytocin for prevention or treatment of postpartum hemorrhage prior to randomization is not exclusionary
    - Any concomitant medication that could suppress lactation at any point following delivery

- Orally or parenterally administered steroids at any dose or inhaled steroids at doses >600 μg/day at any point following delivery
- Prostaglandins at any point following delivery

14. Had postpartum hemorrhage of >1500 mL requiring transfusion or with current severe anemia (hemoglobin <8 g/dL).
15. Currently abuses or has previously abused (within 12 months prior to delivery) drugs or currently abuses or has previously abused (within 12 months prior to delivery) alcohol (i.e., >7 units/week).
16. Has suspected allergy to oxytocin or merotocin or to any of the excipients in the investigational medicinal products (IMPs) used in the trial.
17. Is unable to understand language(s) spoken or provided in writing to her at the trial center.
18. Has previously participated in the current trial.

At randomization the following exclusion criteria apply in addition to the screening criteria:

Maternal subject:

19. Has used or is currently using methergine within 12 hours prior to randomization
20. Has any conditions that would require the concomitant use of any intranasal medications or any diuretic drugs throughout the trial.
21. Any clinically significant abnormal findings of safety laboratory parameters considered by the investigator to be unsuitable to participate in the trial.

Infant:

1. Has low probability of viability, as judged by the investigator.
2. Was transferred to another hospital system during screening, or is likely to be transferred to another hospital system during treatment period as judged by the investigator.
3. Has used any non-registered investigational drugs since delivery.

4.2 Method of Assigning Subjects to Treatment Groups

4.2.1 Recruitment

Maternal subjects who have delivered a preterm infant within the previous 144 hours and who meet all of the inclusion and none of the exclusion criteria will be recruited from the postpartum area of the hospital. Trial center staff will approach potential maternal subjects and discuss the trial, including potential risks and benefits, as well as trial procedures and timelines involved with participation. Subjects may also be approached prior to delivery where feasible to receive information about the trial, but no informed consent should be obtained, nor should any trial-related activities be performed, until after delivery.

Advertisements may be used if approved by the local Institutional Review Boards (IRBs) and regulatory authorities, as applicable according to local regulations.

A screening number will be allocated to each subject who has given written informed consent to participate in the trial. A subject must always be assigned the lowest available screening number at each trial center. A screening log must be maintained by the investigator.

4.2.2 Randomization

Randomization of eligible maternal subjects will occur between 96 and 192 (+4) hours of delivery and immediately after completion of the observation period. Every effort should be made to randomize maternal subjects as early as possible, but not earlier than 96 hours of delivery. Prior to randomization, maternal subjects must be followed during an observation period of at least 48 hours for the collection of milk expression data.

For the purpose of determining eligibility for randomization, the volume of milk produced for the 24-hour baseline interval of the observation period will be calculated automatically in the electronic case report form (e-CRF).

Randomization is stratified by gestational age group (<27 weeks and ≥27 weeks) and by site. An independent statistician at the Ferring Global Biometrics Department will prepare a computer-generated randomization list. The randomization will be performed in blocks. The block size will only be revealed when the trial database is declared clean and locked.

The randomization is performed centrally and electronically. The randomization number will be allocated to the subject together with the treatment allocation.

4.3 Restrictions

4.3.1 Prior and Concomitant Therapies

Any concomitant medication (from 90 days before delivery) will be recorded in the e-CRF, together with the main reason for its prescription. This information will be abstracted from the hospital records and provided by the maternal subject, as appropriate. The dose and dosage regimen will be documented in the e-CRF. Medication that is considered necessary for the maternal subject's safety and well-being may be given at the discretion of the investigator and recorded in the appropriate sections of the e-CRF.

4.3.2 Prohibited Therapy

The following concomitant medications are prohibited:

- Any anti-psychotic drugs during the previous 12 months (e.g., aripiprazole, asenapine maleate, clozapine, iloperidone, lurasidone, olanzapine, olanzapine/fluoxetine, paliperidone, quetiapine, risperidone, chlorpromazine, chlorprothixene, haloperidol, mesoridazine and trifluoperazine) (Note: anxiolytic and antidepressant medications are allowed)
- Any other non-registered investigational drugs from 90 days prior to delivery or within 5 half-lives of the drugs, whichever is longer
- Any hormonal contraception at any point following delivery
- Any pharmacologic or complementary (e.g., herbal) galactagogue therapy at any point following delivery (e.g., oxytocin, prolactin, metoclopramide, domperidone, sulpiride, fenugreek, shatavari, torbangun and milk thistle). However, use of oxytocin for prevention or treatment of postpartum hemorrhage prior to randomization is allowed
- Any concomitant medication that could suppress lactation (e.g., bromocriptine, cabergoline, ergotamine, ergometrine, lisuride, levodopa, pseudoephedrine, bupropion) at any point following delivery
- Orally or parenterally administered steroids at any dose or inhaled steroids at doses >600 μg/day at any point following delivery
- Prostaglandins at any point following delivery
- Methergine from 12 hours prior to randomization
- Any intra-nasally administered concomitant medication from the time of randomization
- Any diuretic drugs from the time of randomization

4.3.3 Other Restrictions

Other restrictions for maternal subjects continuing in the trial are the following:

- Subjects must not abuse drugs or abuse alcohol (i.e., >7 units/week)
- Subjects must not have significant nasal congestion or mucous production
- Subjects must not use hand expression in between pumping sessions after randomization

4.4 Discontinuation and Stopping Criteria

4.4.1 Discontinuation Criteria

Maternal subjects will be discontinued from the trial in the following circumstances:

- A subject's substantial non-compliance. Before discontinuing a subject from the trial due to substantial non-compliance, the investigator should contact the sponsor to discuss the discontinuation
- The investigator's opinion that a subject should be discontinued due to safety concerns, including any adverse event indicating that continued participation endangers the safety of the subject and the infant.
- Request for termination of the trial by regulatory authorities or sponsor

If, at the time of subject withdrawal, a dose of the IMP has already been administered, the subject must be advised on the importance of the follow-up safety investigations as outlined in the protocol.

For all discontinuations, the investigator will obtain all required details and document the date of the premature termination and the main reason in the e-CRF.

Withdrawal of consent

The maternal subjects have the right to withdraw from the trial at any time for any reason, without the need to justify the decision. However, the investigator should record the reason for the subject's withdrawal, if possible.

If the subject withdraws her consent, no further data will be obtained. However, already obtained samples or data may be analyzed. This will be described in the informed consent. The subject can request destruction of samples, which would otherwise have been kept in storage.

4.4.2 Trial Stopping Criteria

The Safety Committee will evaluate the safety of the maternal subjects in terms of AEs, safety laboratory parameters, results from milk composition analyses, and results of merotocin concentrations in milk on an ongoing basis.

If one or more milk samples with any quantifiable amount of merotocin in milk is reported, data will be unblinded on an individual level by the unblinded ad-hoc safety group consisting of an independent GPV representative, an independent statistician and an external neonatology expert other than the experts in the Safety Committee (see Section 3.5). In such cases, the ad-hoc safety group will analyze all infant data available in the database as well as other information in the hospital records. If a suspicion arises from these investigations that there is an AE, that is possibly related to the administration of merotocin, the Safety Committee will be informed and will consider appropriate action including that of a recommendation to stop the trial.

In case of the following safety concerns, the Safety Committee can recommend to stop or modify the trial (e.g. continue with reduced dose):

- Concentration of merotocin in the milk above the pre-defined safety margin (63.8 ng/mL)

In addition, the DMC may recommend to stop the trial depending on the finding of futility during the planned interim analysis.

4.5 Subject Replacement

Subjects who discontinue prematurely from the trial after randomization are not to be replaced. Randomization numbers are uniquely linked to each subject and cannot be re-used.

5 TREATMENTS

5.1 Treatments Administered

5.1.1 Investigational Medicinal Products

The IMPs of the trial include merotocin nasal spray and placebo nasal spray.

Eligible maternal subjects will be randomly assigned in a 1:1 ratio to receive either merotocin nasal spray (400 µg per dose, divided into 2 sprays with 1 spray in each nostril) or placebo nasal spray. Maternal subjects will use their assigned nasal spray a maximum of 8 times every 24 hours (a maximum daily dose of 3200 µg) from the time of randomization for 14 treatment days (i.e., Days 1 to 14). Treatment is administered intra-nasally as 1 spray in each nostril approximately 5 to 10 minutes before a milk expression session. Each single spray constitutes half a dose (200 µg) and maternal subject must administer the spray in both nostrils to receive the 400 µg dose.

Subjects should aim to express milk 6 to 8 times every 24 hours including at least once during the night and with no more than 5 hours between milk expression sessions. As the IMPs will be administered only prior to milk expression, the exact daily dose of merotocin may vary for each maternal subject on each treatment day. Table 1 presents the total daily dose of merotocin administered to maternal subjects based on milk expression frequency. The IMP should be administered prior to consecutive milk expression sessions at least 2 hours apart for a maximum of 8 times per treatment day. Subjects should follow instructions on how to use the nasal spray correctly and take precautions (e.g., washing hands after IMP administration but before milk expression) to avoid potential indirect transfer of IMP into milk.

Table 1 Total Daily Dose of Merotocin by Milk Expression Frequency

Milk Expression Frequency	Total Daily Dose of Merotocin (µg)
5 times per treatment day	2000
6 times per treatment day	2400
7 times per treatment day	2800
8 times per treatment day	3200
9 or more times per treatment day	3200

In this trial, treatment days start from the time of randomization, with Day 1 being the first 24 hours after randomization, Day 2 being 24 to 48 hours after randomization and so on. The treatment period will include 14 such consecutive intervals of 24 hours from the time of randomization, corresponding to 14 treatment days (Days 1 to 14).

Maternal subjects will be exposed to merotocin or placebo for 14 days, depending on randomization.

5.1.2 Non-Investigational Medicinal Product

No non-investigational medicinal product will be provided.

5.2 Characteristics and Source of Supply

All IMPs are provided by Ferring and will be handled according to the principles of Good Manufacturing Practice (GMP). Table 2 provides an overview of the presentation and manufacturer of each medicinal product.

Table 2 Characteristics of Investigational Medicinal Products

Medicinal Product	Compound Code	INN	Presentation/Packaging	Manufacturer
Merotocin	FE 202767	Merotocin	Merotocin is provided as a 9-mL nasal spray bottle containing 9 mL of 25 mM citrate/phosphate buffer solution (pH 5.5) with merotocin at a concentration of 2.0 mg/mL. The solution is clear and colorless.	Ferring Pharmaceuticals
Placebo	—	—	The placebo product is provided as a 9-mL nasal spray bottle containing 9 mL of 25 mM citrate/phosphate buffer solution (pH 5.5). The solution is clear and colorless.	Ferring Pharmaceuticals

Ferring will provide the trial center or the pharmacy at the trial center with merotocin and matching placebo nasal spray in amounts sufficient for the trial.

5.3 Packaging and Labelling

Packaging and labelling of the IMP will be done under the responsibility of the Ferring Clinical Trial Supply Department in accordance with GMP and national regulatory requirements.

The IMP will be labelled with trial-specific labels in accordance with applicable requirements in the country where the trial is conducted.

Each kit will be labelled with an unique IMP number.

5.4 Conditions for Storage and Use

The investigator will ensure that the IMP will be stored under appropriate conditions in a secure location with controlled access. The IMP should be stored refrigerated (2°C to 8°C) (36°F to 46°F, Do not freeze) until dispensed to the maternal subject. The storage compartment shall be monitored regularly and the temperature shall be documented. Deviations in storage temperature must be reported to the sponsor as instructed in the IMP guideline.

After dispensing the IMP to the maternal subject, the IMP can be stored under refrigeration or at room temperature over the course of the treatment period. Prior to initial use, the nasal spray should

be primed according to instructions provided with the product. The trial center staff will prime all nasal spray bottles of IMP prior to weighing and dispensing to the subject.

5.5 Blinding/Unblinding

5.5.1 Blinding

This trial is a double-blind design in which the investigators and the maternal subjects will be blinded to treatment allocation throughout the trial.

The IMP will be packaged according to a computer-generated randomization list prepared for all trial centers. Merotocin and placebo nasal spray will be indistinguishable with identical appearance. The Ferring Global Biometrics Department will store the randomization list according to Ferring's standard operating procedures. Maternal subject randomization numbers will be linked to IMP numbers via treatment codes. The randomization list will not be available to any person involved in the conduct and evaluation of the trial until the trial database is released to the statistician. All staff at each trial center including the trial medication delegates will be blinded to treatment allocation throughout the trial.

Ferring personnel at the Bioanalysis Department analyzing blood and milk samples for merotocin will be blinded to treatment allocation when performing the analyses. The rest of the Ferring clinical trial team will be blinded to individual and group treatment allocation until after database lock, except for Safety Committee members who may be unblinded to the group treatment allocation under special circumstances. DMC members will have access to unblinded interim data to assess the futility at the interim analysis and will keep the data and analyses confidential.

5.5.2 Unblinding of Individual Subject Treatment

An emergency procedure will be available to the investigator and designated persons at Ferring through the e-CRF. Breaking of the blind for individual subjects in emergency situations can be required in case of a suspected unexpected serious adverse reaction (SUSAR), in case of an important AE where the knowledge of the IMP in question is required for therapeutic decisions for the management of the maternal subject, or in case a quantifiable amount of merotocin in the milk (see Section 3.5).

As far as the emergency permits, the need to break the blind will be agreed by the investigator and Ferring. If the event requires immediate unblinding by the investigator, the sponsor must be informed of the unblinding as soon as possible and be provided with the rationale for unblinding.

The investigator who unblinds a maternal subject's treatment will use the e-CRF and is required to enter a password and record the reason for unblinding before the treatment code can be broken. The e-CRF records when and by whom the code is broken. The investigator must record the event of

unblinding in the maternal subject's medical record, including the reason for unblinding, but not the treatment allocation if this can be avoided.

Under special circumstances (Section 3.5), the treatment allocation will be unblinded on an individual level by an ad hoc safety group, consisting of an independent GPV representative, an independent statistician and an external neonatology expert other than the expert in the Safety Committee.

If Ferring needs to unblind a maternal subject's treatment, the e-CRF will be used for unblinding. It is required to enter a password and record the reason for unblinding before the treatment code can be broken. The e-CRF records also when and by whom the code is broken. The code break will occur according to corporate operational procedures for unplanned unblinding of trial subjects. It may be necessary to unblind an individual maternal subject's treatment for the purposes of expedited reporting to the authorities or IRBs. In that situation, every effort will be made to maintain blinding of Ferring personnel involved in data analysis and interpretation. Other personnel may be unblinded for SUSARs, including trial center staff as well as staff acting on behalf of Ferring.

Information on whether the blind has been broken for any maternal subjects is available in the e-CRF and must be collected before the database is declared clean, locked, and released to the statistician.

In case the e-CRF cannot be accessed by the investigator, and hence the emergency unblinding cannot be performed within the e-CRF system, the investigator should contact Ferring Pharmacovigilance using the contact details below:

Ferring Pharmacovigilance
US Toll-free number: [redacted]

If Ferring Pharmacovigilance cannot access the e-CRF, a back-up procedure involving the e-CRF vendor is in place.

5.6 Dispensing and Accountability, Return and Destruction

The IMP must only be dispensed to subjects who meet the eligibility criteria and are randomized in this trial. The delegated trial staff will use an interactive response technology (IRT) system to assign and dispense IMP kits per the randomization performed within the e-CRF. The delegated trial staff will also record the dates and quantities dispensed to and returned by each subject, as well as manage the overall drug accountability for each subject within the IRT system. The trial staff will be blinded to treatment allocation throughout the trial.

The monitor will verify drug accountability of IMP throughout the trial and will document any discrepancies. All dispensed IMP will be returned by maternal subjects for drug accountability.

Concerning destruction, the delegated trial staff must ensure destruction of dispensed IMP in accordance with local legislation after drug accountability has been verified by the monitor within the IRT system, while non-dispensed IMP will be returned for destruction as instructed by the Ferring Clinical Trial Supply Department.

5.7 Auxiliary Supplies

Ferring will be responsible for providing every maternal subject with a multi-user, electric, double-pumping breast pump, a breast pumping kit (with connectors and other necessities), a cooler set, weighing scale(s) with a carrying case (if applicable), breast shields, containers, labels, weighing worksheet (if applicable), scales for weighing milk and infant (if applicable) and a supplementary kit. Ferring will also ensure the trial centers receive sufficient amount of all auxiliary supplies for the maternal subjects.

6 TRIAL PROCEDURES

Before performing any trial procedures, consent for potential maternal subjects and infants will be obtained. The investigator must address all questions raised by the parent participants and a copy of the signed and dated informed consent form(s) will be provided to the maternal subjects and their partners (as applicable).

This trial will consist of the following:

- A screening period starting when informed consent has been obtained and ending at randomization between 96 to 192 (+4) hours of delivery; the screening period must have an observation period of a minimum of 48 hours for the collection of milk expression data.
- A treatment period of 14 days, including a Day 3 visit, a Day 10 visit and a Day 15/ End-of-Treatment visit. These visits can be postponed for a maximum of 2 days. In this trial, treatment days start from the time of randomization, with Day 1 being the first 24 hours after randomization, Day 2 being 24 to 48 hours after randomization, and so on. The treatment period will include 14 such consecutive intervals of 24 hours from the time of randomization, corresponding to 14 treatment days (Days 1 to 14). Trial visits can be scheduled according to calendar days without considering 24-hour periods. Maternal subjects should stop the administration of IMP as soon as having completed 14 days' treatment, rather than continue dosing until the Day 15/End-of-Treatment visit.
- A post-treatment follow-up period with a Follow-up visit on Day 18 for all maternal subjects who complete the assigned treatment of Days 1 to 14 or a Follow-up visit 3 days after the End-of-Treatment visit in case of premature discontinuation. The visit can be postponed for a maximum of 2 days.

No specific trial procedures are required for the infant.

6.1 Trial Flow Chart

Maternal subjects will undergo the procedures at the time points specified in the schedule of events as shown in Table 3. Infants will undergo the procedures at the time points specified in the schedule of events as shown in Table 4.

Table 3 Trial Flow Chart – Mother-related Activities

Procedure	Screening Visit[a] 0-144 hours of delivery	Randomization Visit 96-192 (+4) hours of delivery	Treatment			Follow-up
			Day 3 Visit[b]	Day 10 Visit[b]	Day 15[b]/ End-of-Treatment Visit	Day 18[b]/ Follow-up Visit
Written informed consent	X					
Inclusion/exclusion criteria	X	X[c]				
Demographics	X					
Medical history	X					
Obstetric history[d]	X					
Lactation history[e]	X					
Antenatal and peripartum history[f]	X					
Pre-pregnancy BMI	X					
Instructions and support for providing MoM	X...…….....X					
Breast pump and data collection instructions	X					
Record weights of milk[g]	X…..……X[c]…….....X					
Dosing (as applicable) and milk expression documentation review	X…..……X[c]…….....X					
Physical examination		X[c]			X	
Vital signs		X[c]	X	X	X	
Blood sampling (safety parameters)	X				X	
Randomization		X				
IMP dispensing and weighing		X	X	X		
IMP administration at trial center		X[h]	X[h]	X[h]		
Milk expression at trial center	X	X[c] , X[i]	X	X		
Milk sampling for merotocin concentration[j]			X	X		
Milk sampling for milk composition[k]		X[c]	X	X		
Blood sampling (PK)[l]			X	X		
Drug accountability			X	X	X	
Concomitant medications	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
End-of-Trial form[m]						X

a Screening period runs from the signing of informed consent to randomization and includes an observation period of a minimum of 48 hours. Maternal subject-related activities may be performed at more than 1 screening visit.
b Day 3, Day 10, Day 15/End-of-Treatment and Day 18/Follow-up visits can be postponed a maximum of 2 days. The maternal subjects should stop the administration of IMP as soon as having completed 14 days' treatment, rather than continue dosing until the Day 15/End-of-Treatment visit.
c Performed before randomization.
d Including parity and pregnancy outcomes.
e Including number and duration of lactation following previous deliveries (if any) and lactation data from the current postpartum period (number of milk expression sessions, timing of the first milk expression attempt, occurrence of skin-to-skin contact, and use of hand expression).
f Including gestational age, time and method of delivery, reason for preterm delivery, other pregnancy complications, presence of fetal growth restriction, birth weight, spontaneous or induced labor, use of antenatal steroids, and any use of oxytocin postpartum.
g Milk weights are to be recorded for all containers brought to sites during unscheduled and scheduled visits in accordance with instructions provided in the milk weighing procedures manual. Should breastfeeding occur, the amount of breastfed milk is established by weighing the infant before and after the breastfeeding has been completed by following standardized weighing instructions and by using a standardized scale.

h IMP should be administered approximately 5 to 10 minutes before a milk expression session. IMP administration at sites at Day 3 and Day 10 visits for PK sampling should occur a minimum of 3 hours after the previous dose.
i Two milk expression sessions are to be performed at the site at randomization: one prior to randomization, the other after IMP administration.
j At Day 3 and Day 10 visit, a milk sample will be taken from milk expressed at the trial center for analysis of merotocin concentration in the milk. Samples are taken only if milk production is, at the discretion of the investigator, adequate to meet the needs of the infant.
k At randomization, a milk sample will be taken from milk expressed at the trial center prior to randomization for milk composition analysis. At Day 3 and Day 10 visits, milk samples will be taken from milk expressed at the trial center. Samples are taken only if milk production is, at the discretion of the investigator, adequate to meet the needs of the infant.
l Seven PK samples for measurement of merotocin concentration will be collected at Day 3 and Day 10 visits using an indwelling catheter at the following time points: pre-dose, 5, 10, 20, 30, 45, and 60 minutes after dosing in a minimum of 20 maternal subjects.
m End-of-Trial form should be completed at the subject's last scheduled visit or at the time of premature discontinuation.
Abbreviations: BMI=body mass index, IMP=investigational medicinal product, MoM=mother's own milk, PK=pharmacokinetic

Table 4 Trial Flow Chart – Infant-related Activities

Procedure	Screening Visit 0-144 hours of delivery	Randomization Visit 96-192 (+4) hours of delivery	Treatment			Post-treatment Follow-up	Post-trial Activities		
			Day 3 Visit[a]	Day 10 Visit[a]	Day 15[a]/ End-of-Treatment Visit	Day 18[a]/ Follow-up Visit	At infant's discharge from NICU	One month after NICU discharge	Long-term Follow-up
Exclusion criteria		X[b]							
Collecting the following data from hospital records									
Medical history	X[c]								
Body weight		X[d]	X[d]	X[d]	X[d]		X		
Length and head circumference							X		
Concomitant medications[e]	X	X	X	X	X	X	X		
Adverse events[e]	X	X	X	X	X	X	X		
Morbidity events of special interest[f]	X	X	X	X	X	X	X		
Infant enteral feeds			X[g]	X[g]	X[g]		X[h]		
Collection of additional NICU data							X[h]		
Collecting the following data by phone or other means									
Hospital re-admission and reason								X	
Administration of ASQ-3									X[i]

a Day 3, Day 10, Day 15/End-of-Treatment and Day 18/Follow-up visits can be postponed a maximum of 2 days.
b These assessments may be performed 0 to 144 hours of delivery but must be performed prior to randomization.
c Medical history for the infant refers to congenital conditions and events occurring from birth to signing of informed consent by the maternal subject. Events that occur following signing of informed consent are recorded as adverse events.
d Collected for all days from Day 1 to Day 14 as available from hospital records.
e Collected from hospital records from signing of informed consent through time of infant's discharge from NICU or until the last milk sample expressed during maternal subject's treatment with IMP is either consumed by the infant or discarded, whichever occurs last.
f Collected from hospital records from signing of informed consent through infant's discharge from NICU.
g Infant enteral feeds including volume of MoM and formula/donor milk fed to the infant as available from hospital records from Day 1 to Day 14.
h Including time to full enteral feeds, time to infant's discharge from NICU, number of days the infant requires TPN until

discharge from NICU, type of feeding (MoM and formula/donor milk) at time of infant's discharge from NICU, whether maternal subject is lactating at time of infant's discharge from NICU.

i Completion of the ASQ-3 by a primary caregiver at infants' 9 months, 18 months and 24 months of corrected gestational age.

Abbreviations: ASQ-3=Ages and Stages Questionnaire-3, MoM=mother's own milk, NICU=neonatal intensive care unit, TPN=total parenteral nutrition

6.2 Screening Period

Maternal subjects who provide informed consent for participation will enter the screening period as soon as possible following delivery. The screening period runs from the signing of informed consent to randomization and includes an observation period of a minimum of 48 hours to confirm maternal subjects' compliance with required milk expression frequency. Initial eligibility check and screening assessments for a maternal subject should be performed within 144 hours of delivery.

Subjects willing to participate in the trial will undergo the following screening procedures (performed by trial center staff unless otherwise specified):

Maternal subject-related activities at the screening visit:

- Maternal subject signs and dates the informed consent and provides parental consent for the infant
- Perform inclusion and exclusion criteria check
- Record demographic and baseline characteristics (date of birth, smoking history, race, ethnicity, and education level)
- Record medical history
- Record obstetric history, including previous pregnancy and delivery (parity) outcomes
- Record lactation history, including number and duration of lactation following previous deliveries (if any) and lactation data from the current postpartum period (number of milk expression sessions, timing of the first milk expression attempt, occurrence of skin-to-skin contact, and use of hand expression)
- Record antenatal and peripartum data from the most recent pregnancy, including gestational age, time and method of delivery, reason for preterm delivery, other pregnancy complications, presence of fetal growth restriction, birth weight, spontaneous or induced labor, use of antenatal steroids, and use of oxytocin in the postpartum period
- Record pre-pregnancy BMI
- Record concomitant medications (from 90 days before delivery to the date of signed informed consent; prohibited therapy listed in section 4.3.2)
- Collect and record AEs occurring since signing of informed consent
- Collect blood sample for safety laboratory parameters (Table 6) analysis

Prior to the observation period:

- Provide detailed and standardized lactation instructions and support
- Provide a multi-user, electric, double-pumping breast pump to maternal subject and an adequate number of containers, labels and other relevant trial supplies
- Provide training to maternal subject on how to record expression sessions
- Instruct maternal subject to express milk from both breasts with the breast pump at least 5 times every 24 hours during the observation period. Both breasts should be pumped and emptied in accordance with the instructions in the lactation manual for subjects. Milk expression may also be conducted occasionally by hand expression (as subject wishes) or exceptionally by breastfeeding (only when the infant is considered by NICU staff to be capable of being breastfed). See Section 7.1.1

At the start of the observation period:

- Have the maternal subject express milk using a breast pump under the supervision of trial center staff. The observation period (a minimum of 48 hours) will start with this milk expression session
- Instruct maternal subject to bring all the milk collected to the trial center at each scheduled visit, including the randomization visit (if it has not been brought to the trial center)

During the observation period:

- Lactation support is available to maternal subject
- Maternal subject expresses milk with a breast pump for at least 5 times every 24 hours including at least once during the night and with no more than 5 hours between any sessions
- Maternal subject collects the milk in the supplied containers and labels and stores the containers appropriately
- Maternal subject records the milk expression properly on the milk container label in accordance with instructions provided in the lactation manual for subjects

Infant-related activities at the screening visit:

Collect the following data from hospital records:

- Record medical history
- Record information on morbidity events of special interest (Section 8.4)
- Record concomitant medications after signing of informed consent
- Collect and record AEs after signing of informed consent

6.3 Randomization

Randomization of eligible maternal subjects will occur at 96 to 192 (+4) hours of delivery. Every effort should be made to randomize maternal subjects as early as possible, but not earlier than 96 hours of delivery.

Maternal subject-related activities at the randomization visit:

End of observation period

- Provide detailed and standardized lactation instructions, support, and training in how to weigh milk.
- Have maternal subject express milk at the site and record the milk expression properly on the milk container label, in accordance with instructions provided in the lactation manual
- Weigh the milk collected during the observation period, including the milk from the milk expression session just performed, in accordance with instructions provided in the milk weighing procedures manual
- Review milk expression documentation for completeness and compliance
- Perform remainder of inclusion and exclusion criteria check (prohibited therapy listed in Section 4.3.2)
- Perform physical examination
- Measure vital signs (sitting blood pressure and heart rate)
- If the maternal subject is still eligible and if the amount of available milk exceeds the needs of the infant, collect a milk sample for analysis of milk composition (Section 7.3.2). Sample should be taken from the milk expressed at the trial center prior to randomization

Randomization

- Randomly assign the trial treatment to the maternal subject through the e-CRF
- Prime and weigh each nasal spray bottle before dispensing the IMP kit
- Have maternal subject administer first dose of trial medication at the trial center, express milk, and record the milk expression properly on milk container labels in accordance with instructions provided in the lactation manual for subjects
- Instruct maternal subject to bring all the milk collected (if it has not been brought to the trial center), her nasal spray bottles, and the milk container labels with recordings of the milk expression to the trial center at the Day 3 visit
- Record concomitant medications
- Collect and record AEs

Infant-related activities at the randomization visit:

Prior to randomization

- Ensure infant exclusion criteria check is performed

Randomization

Collect the following data from hospital records:

- Record infant body weight (for the day of randomization or last recorded value as available)
- Record concomitant medications. Each concomitant medication needs to be reported in the electronic system only once (dose and frequency may be omitted), as a complete list of medications (including dose and frequency, as applicable) may be printed from the hospital records, de-identified and sent to the sponsor following discharge of the infant from the NICU only if more information is later needed.
- Collect and record AEs including information on morbidity events of special interest (Section 8.4)

6.4 Treatment Period Days 1 to 14

All maternal subjects will begin treatment as soon as they are randomized. In this trial, treatment days start from the time of randomization, with Day 1 being the first 24 hours after randomization, Day 2 being 24 to 48 hours after randomization and so on. For example, if a subject is randomized at 10 AM, her first treatment day or Day 1 is from 10 AM on that day to 10 AM on the next day. The treatment period will include 14 such consecutive intervals of 24 hours from the time of randomization, corresponding to 14 treatment days (Days 1 to 14). Trial visits can be scheduled according to calendar days without considering 24-hour periods. The maternal subjects should stop the administration of IMP as soon as having completed 14 days' treatment, rather than continue dosing until the Day 15/End-of-Treatment visit, as reminded by the trial center staff on or before Day 14.

6.4.1 All Treatment Days

Maternal subject-related activities:

- Lactation support is available to maternal subject
- Maternal subject administers the trial medication approximately 5 to 10 minutes prior to each milk expression session
- Maternal subject expresses milk 6 to 8 times every 24 hours including at least once during the night and with no more than 5 hours between sessions (Section 7.1.1)
- Maternal subject records the required details of dosing and milk expression on milk container labels in accordance with instructions provided in the lactation manual
- Maternal subject collects the milk into the supplied containers and labels and stores the containers appropriately
- Maternal subject will be contacted by the trial center staff to ensure compliance with the instructions for administration of the medication and recording of the milk expression

6.4.2 Day 3 Visit

Day 3 visit can be postponed a maximum of 2 days.

Maternal subject-related activities:

- Weigh the milk collected since the randomization visit and record the corresponding weights for each milk expression session (this can also be performed any day when the maternal subject brings collected milk to the trial center)
- Review dosing and milk expression documentation for completeness and compliance
- Measure vital signs (sitting blood pressure and heart rate)
- If applicable, insert indwelling catheter, collect blood sample for plasma concentration of merotocin (pre-dose sample; a minimum of 3 hours after the previous dose)[b]
- Prime and weigh each nasal spray bottle before dispensing the IMP kit
- Have maternal subject administer trial medication prior to milk expression
- If applicable, collect blood sample for plasma concentration of merotocin at 5 minutes after dosing[b]
- Have maternal subject express milk at the site and record the milk expression on milk container labels in accordance with instructions provided in the lactation manual for subjects
- Collect a milk sample for analysis of merotocin concentration (Section 7.2.6) and a second milk sample for analysis of milk composition (Section 7.3.2). Samples should be taken from the milk expressed at this visit. Samples are taken only if the amount of available milk exceeds the needs of the infant at the discretion of the investigator
- If applicable, collect blood samples for plasma concentration of merotocin at 10, 20, 30, 45, and 60 minutes after dosing[b]
- Record concomitant medications
- Collect and record AEs
- Perform drug accountability, including weighing and collection of used IMP
- Instruct maternal subject to bring all the milk collected (if it has not been brought to the trial center), the milk container labels with recordings of dosing and milk expression, and her nasal spray bottles to the trial center at the Day 10 visit

[b] Blood samples for the analysis of merotocin concentration are taken in a minimum of 20 maternal subjects.

Infant-related activities:

Collect the following data from hospital records for all treatment days as available since last visit:

- Record body weight
- Record infant enteral feeds (volume of MoM and formula/donor milk fed to the infant)
- Record concomitant medications
- Collect and record AEs including information on morbidity events of special interest (Section 8.4)

6.4.3 Day 10 Visit

Day 10 visit can be postponed a maximum of 2 days.

Maternal subject-related activities:

- Weigh the milk collected since the Day 3 visit, and record corresponding weights for each milk expression session (this can also be performed any day when the maternal subject brings collected milk to the trial center)
- Review dosing and milk expression documentation for completeness and compliance
- Measure vital signs (sitting blood pressure and heart rate)
- If applicable, inset indwelling catheter, collect blood sample for plasma concentration of merotocin (pre-dose sample; a minimum of 3 hours after the previous dose)[c]
- Prime and weigh each nasal spray bottle before dispensing the IMP kit
- Have maternal subject administer the trial medication prior to milk expression
- If applicable, collect blood sample for plasma concentration of merotocin at 5 minutes after dosing[c]
- Have maternal subject express milk at the site and record the milk expression on milk container labels in accordance with instructions provided in the lactation manual for subjects
- Collect a milk sample for analysis of merotocin concentration (Section 7.2.6) and a second milk sample for analysis of milk composition (Section 7.3.2). Samples should be taken from the milk expressed at this visit. Samples are taken only if the amount of available milk exceeds the needs of the infant at the discretion of the investigator
- If applicable, collect blood samples for plasma concentration of merotocin at 10, 20, 30, 45, and 60 minutes after dosing[c]
- Record concomitant medications
- Collect and record AEs
- Perform drug accountability, including weighing and collection of used IMP

[c] Blood samples for the analysis of merotocin concentration are taken in a minimum of 20 maternal subjects.

- Instruct maternal subject to bring the milk collected (if it has not been brought to the trial center), the milk container labels with recordings of dosing and milk expression, and her nasal spray bottles to the trial center at the Day 15/End-of-Treatment visit
- Remind maternal subject to stop administer the trial medication on Day 14
- Consider if infant is expected to be discharged prior to maternal subject completion of trial and, if needed, provide scales, weighing worksheet, and training to the maternal subject for milk and infant weighing (in case of breastfeeding) prior to discharge.

Infant-related activities:

Collect the following data from hospital records for all treatment days as available since last visit:

- Record body weight
- Record infant enteral feeds (volume of MoM and formula/donor milk fed to the infant)
- Record concomitant medications
- Collect and record AEs including information on morbidity events of special interest (Section 8.4)

6.4.4 Day 15/End-of-Treatment Visit

End-of-Treatment assessments are performed on Day 15 or the day after the maternal subject's last dose of IMP in case of premature discontinuation. Day 15/End-of-Treatment visit can be postponed a maximum of 2 days.

Maternal subject-related activities:

- Weigh the milk collected since the Day 10 visit (if applicable) and record corresponding weights for each milk expression session (this can also be performed any day when the maternal subject brings collected milk to the trial center)
- Review dosing and milk expression documentation for completeness and compliance
- Perform physical examination
- Measure vital signs (sitting blood pressure and heart rate)
- Collect blood sample for safety laboratory parameters (Table 6) analysis
- Record concomitant medications
- Collect and record AEs
- Perform drug accountability, including weighing used IMP and collection of all used and unused IMP
- Instruct maternal subject that milk expression information should continue to be collected through the end of Day 17

Infant-related activities:

Collect the following data from hospital records for all treatment days as available since last visit:

- Record body weight
- Record infant enteral feeds (volume of MoM and formula/donor milk fed to the infant)
- Record concomitant medications
- Collect and record AEs including information on morbidity events of special interest (Section 8.4)

6.5 Post-Treatment Follow-up Period (Days 15 to 18)

Maternal subject-related activities:

- Lactation support is available to maternal subject
- Maternal subject expresses milk 6 to 8 times every 24 hours including at least once during the night and with no more than 5 hours between sessions (Section 7.1.1)
- Maternal subject records milk expression in accordance with instructions provided in the lactation manual. For subjects who complete the assigned treatment of Days 1 to 14, milk expression information is to be recorded through the end of Day 17
- Maternal subject collects the milk in the supplied containers and labels and stores the containers appropriately

6.5.1 Day 18/Follow-up Visit

All maternal subjects who complete the assigned treatment of Days 1 to 14 will have a Follow-up visit on Day 18 or 3 days after the End-of-Treatment visit in case of premature discontinuation. The visit can be postponed a maximum of 2 days.

Maternal subject-related activities:

- Weigh the milk collected since the Day 15/End-of-Treatment visit (if applicable) and record corresponding weights for each milk expression session from Days 15 to 17
- Collect and review milk expression documentation for completeness and compliance
- Collect scales (if applicable)
- Record concomitant medications
- Collect and record AEs
- Complete End-of-Trial form

Infant-related activities:

Record the following (from hospital records) for all days as available since last visit:

- Record concomitant medications
- Collect and record AEs including information on morbidity events of special interest (Section 8.4)

6.6 Post-trial Activities

6.6.1 Infant-related Activities at Infant's Discharge from NICU

Collect the following from hospital records for all days as available since last visit, unless otherwise noted:

- Record body weight, length, and head circumference (for the day of discharge only or last recorded values as available)
- Record information on morbidity events of special interest (Section 8.4)
- Record concomitant medications until the time of infant's discharge from NICU or until the last milk sample expressed during maternal subject's treatment with IMP is either consumed by the infant or discarded, whichever occurs last
- Collect and record AEs until the time of infant's discharge from NICU or until the last milk sample expressed during maternal subject's treatment with IMP is either consumed by the infant or discarded, whichever occurs last
- Record the date when the infant becomes tolerant to full enteral feeding, date of discharge from NICU, number of days the infant requires TPN until discharge from NICU, type of feeding (MoM and formula/donor milk) at time of infant's discharge from NICU, and whether the maternal subject is lactating (i.e., breastfeeding or breast pumping) at time of infant's discharge from NICU

6.6.2 Infant-related Activities about One Month after NICU Discharge

- Contact the maternal subject, by phone or other means, to establish whether the infant has been re-admitted to hospital since the NICU discharge and, if so, the reason for the re-admission

6.6.3 Infant-related Activities Long-term Follow-up

- Completion of the ASQ-3 by a primary caregiver at infants' 9 months of corrected gestational age
- Completion of the ASQ-3 by a primary caregiver at infants' 18 months of corrected gestational age

- Completion of the ASQ-3 by a primary caregiver at infants' 24 months of corrected gestational age

7 TRIAL ASSESSMENTS

A laboratory manual will cover all blood and milk analyses and describe sampling and shipment procedures including contact details, sampling window, storage conditions, equipment, volume, analytical method, reference range, etc. The manual will be provided to the trial centers before the start of the trial. The total blood volume collected for each maternal subject will be approximately 9 mL for safety measurements only and approximately 65 mL for both safety and PK measurements (only applicable for a subset of minimum 20 subjects).

7.1 Assessments Related to Primary Endpoint

7.1.1 Volume of MoM Produced over Days 1 to 14

In this trial, milk expression will be conducted mostly with the breast pump, occasionally by hand expression or exceptionally by breastfeeding the infant. Each milk expression session will be conducted in accordance with instructions provided in the lactation manual for subjects. In this trial, one session of milk expression is defined as one round of pumping, one round of pumping followed immediately by hand expression or one round of breastfeeding followed immediately by pumping. In case of pumping combined with either breastfeeding or hand expression, MoM expressed through pumping and through the other method will be recorded separately. However, if hand expression occurs in between pumping sessions during the observation period, this should be considered a separate session but is not included in the stated goal of milk expression frequency, i.e., at least 5 times every 24 hours. The expressed milk through pumping and through hand expression is collected into supplied containers provided by Ferring and labelled appropriately as detailed in the lactation manual for subjects. Milk weighing will be performed as instructed in the milk weighing procedures manual. If the infant is discharged to home prior to the Day 18/ Follow-up visit, two standardized scales will be offered to the maternal subject for the recording of milk expression, one for measuring the weight of the expressed milk and one for measuring the weight of the infant before and after feeds (if the subject is breastfeeding).

Instructions on different milk expression methods and milk collection are summarized in Table 5.

Table 5 Instructions on Milk Expression and Milk Collection

Milk expression method	Milk expression [a,b]		Milk collection	
	Observation period	Treatment and follow-up periods	Observation period	Treatment and follow-up periods
Milk expression using the breast pump (i.e., pumping)	At least 5 times every 24 hours including at least once during the night and with no more than 5 hours between milk expression sessions	6-8 times every 24 hours including at least once during the night and with no more than 5 hours between milk expression sessions	Milk collected into separate bottles for milk expressed from left/right breast and for each session. No milk pooling	
Hand expression	Permitted both immediately after a pumping session and in between pumping sessions. [b] Use of hand expression is at subject's own choice	Permitted only immediately after a pumping session. Use of hand expression is at subject's own choice	Milk expressed from left/right breast can be pooled into one bottle and separate bottles should be used for each hand expression session	
Breastfeeding	Only when the infant is considered by NICU staff to be capable of being breastfed and always followed by further breast pumping		Results of weighing the infant before and after breastfeeding	

[a] In this trial, one session of milk expression is defined as one round of pumping, one round of pumping followed immediately by hand expression or one round of breastfeeding followed immediately by pumping.

[b] Hand expression in between pumping sessions during observation period is to be recorded as a separate milk expression session and the volume will be included in the MoM calculation, but is not included the stated goal of milk expression frequency, i.e., at least 5 times every 24 hours.

The maternal subject will record the required information in accordance with instructions provided in the lactation manual. The milk collected at each milk expression session will be weighed in accordance with instructions provided in the milk weighing procedures manual by the trial center staff (if limited availability, the maternal subject may weigh the milk) and recorded when brought to the trial center. The recorded weight of milk expressed in grams will be converted to a volume of milk using a conversion of 1 g to 1 mL. Expressed milk will be stored for feeding to the infant after recording the milk weights.

Breastfeeding will only occur when the trial center staff consider the infant has the ability to achieve a nutritional feed through breastfeeding. It is expected that the infant will be hospitalized for the predominant or entire duration of the trial due to their prematurity. Should breastfeeding occur, the amount of breastfed milk is established by weighing the infant before and after the breastfeeding has been completed by following standardized weighing instructions and by using a standardized scale.[24] The weights before and after breastfeeding will be recorded with assistance from the NICU staff, if breastfeeding occurs at NICU. If the infant is discharged to home prior to the Day 18/Follow-up visit, the maternal subject will be provided with a standardized scale to use at home for measuring the weight of the infant before and after feeding and will record the required information for each breastfeeding session in accordance with instructions provided in the lactation

manual for subjects. After breastfeeding her infant, the maternal subject should continue to express milk using the breast pump.

The milk volume collected on each day from Days 1 to 14, including any amount given to the infant by breastfeeding, will be calculated as the total production in each treatment day. In this trial, treatment days start from the time of randomization, with Day 1 being the first 24 hours after randomization, Day 2 being 24 to 48 hours after randomization and so on. For example, if a subject is randomized at 10 AM, her first treatment day or Day 1 is from 10 AM on that day to 10 AM on the next day. The treatment period will include 14 such consecutive intervals of 24 hours from the time of randomization, corresponding to 14 treatment days (Days 1 to 14). Trial visits can be scheduled according to calendar days without considering 24-hour periods.

7.2 Assessments Related to Secondary Endpoints

7.2.1 Time to the First Occurrence of a Daily Volume of MoM ≥500 mL and ≥750 mL

The volume of MoM produced on each treatment day will be calculated by using recorded weights of expressed milk in the same method as described in Section 7.1.1. The time from randomization to the first treatment day when maternal subjects produce a daily volume of MoM ≥500 mL and ≥750 mL will be calculated.

7.2.2 Proportion of Subjects with a Daily Volume of MoM ≥500 mL and ≥750 mL

The volume of MoM produced on each treatment day will be calculated by using recorded weights of expressed milk in the same method as described in Section 7.1.1. The proportion of maternal subjects who produce a daily volume of MoM ≥500 mL and ≥750 mL will be calculated for every treatment day from Days 1 to 14.

7.2.3 Volume of MoM Produced over Days 15 to 17

Maternal subjects who complete Days 1 to 14 of assigned treatment will be asked to continue recordings of milk expression on milk container labels through the end of Day 17. The volume of MoM produced over Days 15 to 17 will be calculated by using recorded weights of expressed milk in the same way as described in Section 7.1.1.

7.2.4 Volume of MoM Fed to the Infant

The volume of MoM fed to the infant over Days 1 to 14 will be recorded from hospital records. The volume of breastfed milk over Days 1 to 14 will be recorded.

7.2.5 Volume of Formula/Donor Milk Fed to the Infant

The volume of formula or donor milk fed to the infant over Days 1 to 14 will be recorded from hospital records.

7.2.6 Merotocin Concentration in Milk

At Day 3 and Day 10 visits, a milk sample of approximately 2 mL for merotocin concentration analysis will be taken from the milk expressed at the trial center. Samples are taken only if milk production is, at the discretion of the investigator, adequate to meet the needs of the infant.

Analysis of milk concentration of merotocin will be performed by Ferring Bioanalysis Department by means of a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method using the milk samples obtained at Day 3 and Day 10 visit, if available. The personnel analyzing the milk samples for merotocin will be blinded to treatment allocation when performing the analyses.

7.2.7 Infant Body Weight

Infant body weight will be collected for the day of randomization (or last recorded measurements as available) and for all treatment days from Day 1 to Day 14 where data are available. Infant body weight may not be measured daily, so data can be missing for some treatment days.

7.2.8 Adverse Events (Maternal Subject and Infant)

Frequency and intensity of AEs will be recorded for maternal subjects and for the infant (as available from hospital records). See Section 8.2 regarding collection and recording of AEs. A search for predefined preferred terms (PTs) and reported terms will be conducted on all treatment-emergent AEs (TEAEs) for maternal subjects to identify those that can indicate nasal local tolerability issues.

7.2.9 Safety Laboratory Parameters (Maternal Subjects)

Blood samples for safety laboratory evaluations of clinical chemistry and hematology will be collected at screening and at Day 15/End-of-Treatment visit. The clinical chemistry and hematology analyses will be performed by a central laboratory. Safety laboratory parameters are listed in Table 6.

Table 6 Safety Laboratory Parameters

Clinical Chemistry	Hematology
Alanine aminotransferase	Hematocrit
Albumin	Hemoglobin
Alkaline phosphatase	Mean cellular volume
Aspartate aminotransferase	Mean corpuscular hemoglobin content
Glucose	Mean corpuscular hemoglobin concentration
Calcium	Platelet count
Chloride	Red blood cell count
Cholesterol	White blood cell count with differential count
C-reactive protein	White blood cell morphology
Creatinine	
Gamma-glutamyltransferase	
Phosphate	
Potassium	
Sodium	
Total bilirubin	
Urea (blood urea nitrogen)	

The investigator will review the laboratory results and evaluate and document whether the results are clinically significant or non-significant.

7.3 Assessments Related to Exploratory Endpoints

7.3.1 Plasma Concentration of Merotocin

Blood samples for plasma concentration of merotocin will be collected using an indwelling catheter at pre-dose and at 5, 10, 20, 30, 45, and 60 minutes after dosing at site at Day 3 and Day 10 visits. For the pre-dose sample, sampling should occur a minimum of 3 hours after the previous dose. Blood samples for the analysis of merotocin concentration will be taken in a minimum of 20 maternal subjects.

Analysis of plasma concentration of merotocin will be performed by means of a validated LC-MS/MS method.

7.3.2 Milk Composition

At randomization, Day 3, and Day 10 visits, a milk sample of approximately 4 mL for milk composition analysis will be taken from the milk expressed at the trial center. The milk sample at randomization will be taken prior to randomization. Milk composition including lipids, protein, caloric content, lactose, and Human Milk Oligosaccharides will be assessed by a central laboratory (detailed in the laboratory manual) for each of the 3 milk samples, if available. Samples are taken only if milk production is, at the discretion of the investigator, adequate to meet the needs of the

infant.

7.4 Assessments Related to Post-trial Endpoints

Additional data will be collected from the hospital records of the infant when the infant is discharged from NICU. The additional data (if available) are infant body weight, length and head circumference at time of infant's discharge from NICU, the date when the infant becomes tolerant to full enteral feeding, date of discharge from NICU, number of days the infant requires TPN until discharge from NICU, type of feeding (MoM and formula/donor milk) at time of infant's discharge from NICU, and whether the maternal subject is lactating (i.e., breastfeeding or breast pumping) at time of infant's discharge from NICU.

Concomitant medications and AEs will be collected from hospital records through time of infant's discharge from NICU or until the last milk sample expressed during maternal subject's treatment with IMP is either consumed by the infant or discarded, whichever occurs last. Information on infant's morbidity events of special interest occurring prior to the infant's discharge from NICU, including NEC, intra-ventricular hemorrhage, BPD, RDS, late-onset sepsis, ROP, and hemodynamically significant patent *ductus arteriosus*, are recorded at the time of infant's discharge from NICU based on hospital records. The trial is not powered to draw conclusions on the incidences of these events, but they are collected in order to capture any trends on the impact of feeding patterns on their incidences.

From the follow-up contact about one month after the infant's NICU discharge, the date of any hospital re-admission of the infant occurring since NICU discharge, and the reason for the re-admission will be recorded. Investigators should assess the causal relationship between the reason for such re-admissions and the IMP.

For long-term follow-up, the ASQ-3 will be provided for all infants at 9 months, 18 months and 24 months of corrected gestational age. A primary caregiver of the infant will answer the questionnaire that consists of approximately 30 questions covering five domains of development, including communication, gross motor, fine motor, problem-solving, and personal-social skills. It takes about 15-30 minutes to complete the questionnaire. If a score falls into the black zone of any domain on the scoring summary sheet, standard referral procedures should be followed.

Data from post-trial activities will be provided in an addendum to the clinical trial report.

7.5 Other Assessments

7.5.1 Vital Signs (Maternal Subject)

Vital signs include blood pressure and heart rate. Systolic and diastolic blood pressure and heart rate will be measured for maternal subjects at randomization, Day 3, Day 10 and Day 15/

End-of-Treatment visits. Vital signs will be measured while maternal subject is in sitting position after resting for at least 3 minutes. Vital signs should always be measured before blood sampling.

All recordings will be performed using validated standard equipment. Vital sign assessments may be repeated for quality reasons and the repeat will be used for analysis.

7.5.2 Physical Examination (Maternal Subject)

A full physical examination of the maternal subject will be performed at randomization and at Day 15/End-of-Treatment visit. The physical examination of the maternal subject comprises examination of general appearance, central and peripheral nervous system, head and neck (including ears, eyes, nose, mouth, and throat), cardiovascular system, respiratory system, gastrointestinal system, lymphatic system, urinary system, breasts, skin, and musculoskeletal system.

7.6 Handling of Biological Samples

A detailed description of all sample collections and shipment procedures will be included in a separate laboratory manual.

All biological samples will be analyzed at central laboratories and will be maintained in storage after the end of the trial. Destruction will take place within 2 years after reporting of the trial. For all biological samples collected in the trial, it applies that analyses beyond those described in the protocol can only be performed after obtaining the required approvals. The processes related to handling of biological samples will be described in the informed consent forms (ICFs), and biobank/data protection legislation including local legislation will be adhered to.

8 ADVERSE EVENTS

8.1 Adverse Event Definition

An AE is any untoward medical occurrence in a subject participating in a clinical trial. It includes:

- Any unfavorable and unintended sign, symptom or disease temporally associated with the use of the IMP, whether or not considered to be caused by the IMP
- AEs commonly observed and AEs anticipated based on the pharmacological effect of the IMP
- Any laboratory abnormality, vital sign or finding from physical examination assessed as clinically significant by the investigator [note: findings from assessments and examinations done during screening are not AEs but are recorded as medical history]
- Accidental injuries, reasons for any change in medication (drug and/or dose), reasons for any medical, nursing or pharmacy consultation or reasons for admission to hospital or surgical procedures

Overdoses, medication errors and technical malfunctions of IMP will be captured by the e-CRF and will be reviewed by Ferring Pharmacovigilance on an ongoing basis.

Pre-treatment Adverse Event for Maternal Subjects

A pre-treatment AE for a maternal subject is any untoward medical occurrence arising or observed between informed consent and administration of the IMP.

Treatment-emergent Adverse Event for Maternal Subjects

A TEAE for a maternal subject is any AE occurring after start of the IMP and before the Day 15/End-of-Treatment visit. A pre-treatment AE or pre-existing medical condition that worsens in intensity after start of IMP and before the Day 15/End-of-Treatment visit is also considered treatment emergent.

Pre-treatment Adverse Event for Infants

A pre-treatment AE for an infant is any untoward medical occurrence arising or observed between the signing of the parental informed consent and the infant's first exposure to MoM expressed during maternal subject's treatment period.

Treatment-emergent Adverse Event for Infants

A TEAE for an infant is any AE occurring from the infant's first exposure to MoM expressed during maternal subject's treatment period until the infant's last exposure to MoM expressed during maternal subject's treatment period (i.e., the last milk sample expressed during maternal subject's treatment with IMP is either consumed by the infant or discarded). A pre-treatment AE or pre-existing medical condition that worsens in intensity during the interval stated above is also considered treatment emergent.

8.2 Collection and Recording of Adverse Events

8.2.1 Collection of Adverse Events

The sources of AEs cover:

- The subject's response to questions about her health (a standard non-leading question such as 'How have you been feeling since your last visit?' is asked at each visit). (This is only applicable to maternal subjects)
- Symptoms spontaneously reported by the subject. (This is only applicable to maternal subjects)
- Investigations and examinations where the findings are assessed by the investigator to be clinically significant changes or abnormalities
- Other information relating to the subject's health becoming known to the investigator (e.g., hospitalization)

8.2.2 Recording of Adverse Events

The investigator must record all AEs in the Adverse Event Log provided in each subject's e-CRF with information about:

- Adverse event
- Date and time of onset (time can be omitted, if applicable)
- Intensity
- Causal relationship to IMP
- Action taken to IMP
- Other action taken
- Date and time of outcome (time can be omitted, if applicable)
- Outcome
- Seriousness

Each of the items in the Adverse Event Log is described in detail in the following sections.

Adverse Events

AEs should be recorded as diagnoses, if available. If not, separate signs and symptoms should be recorded. One diagnosis/symptom should be entered per record.

If a subject suffers from the same AE more than once and the subject recovers in between the events, the AEs should be recorded separately. If an AE changes in intensity, a worst-case approach should be used when recording the event, i.e., the highest intensity and the longest duration of the event.

However, if an AE with onset before the first IMP administration (i.e., a pre-treatment AE) changes in intensity, this must be recorded as 2 separate events. The initial AE should be recorded with outcome 'not recovered' and the date and time of outcome is when the intensity changed. The second AE should be recorded with date and time of onset when the intensity changed.

Note the following: A procedure is not an AE; the reason for conducting the procedure is. Hospitalization is not an AE; the reason for hospitalization is. Death is not an AE, but the cause of death is (an exception is sudden death of unknown cause, which is an AE).

Date and Time of Onset

The date of onset is the date when the first sign(s) or symptom(s) was first noted. If the AE is an abnormal clinically significant laboratory test or outcome of an examination, the onset date is the date the sample was taken or the examination was performed.

Intensity

The intensity of an AE must be classified using the following 3-point scale:

Mild: Awareness of signs or symptoms, but no disruption of usual activity

Moderate: Event sufficient to affect usual activity (disturbing)

Severe: Inability to work or perform usual activities (unacceptable)

Causal Relationship to IMP

The possibility of whether the IMP caused the AE must be classified as one of the following:

Reasonable possibility: There is evidence or argument to suggest a causal relationship between the IMP and the AE. The AE may occur as part of the pharmacological action of the IMP or may be unpredictable in its occurrence

Examples:

- AEs that are uncommon but are known to be strongly associated with IMP exposure
- AEs that are not commonly associated with IMP exposure, but the event occurs in association with other factors strongly suggesting causation, such as a strong temporal association with the IMP or the event recurs on rechallenge with the IMP

No reasonable possibility: There is no reasonable evidence or argument to suggest a causal relationship between the IMP and the AE

Examples:

- Known consequences of the underlying disease or condition under investigation
- AEs common in the trial population, which are also anticipated to occur with some frequency during the course of the trial, regardless of IMP exposure

Action Taken to IMP

The action taken to the IMP in response to an AE must be classified as one of the following:

- No change (medication schedule maintained or no action taken)
- Discontinued
- Interrupted
- Dose reduced

Other Action Taken

AEs requiring therapy must be treated with recognized standards of medical care to protect the health and well-being of the maternal subject.

If medication is administered to treat the AE, this medication should be entered in the Concomitant Medication Log. Infant concomitant medication needs to be reported in the electronic system only once (dose and frequency may be omitted), as a complete list of medications (including dose and frequency, as applicable) may be printed from the hospital records (de-identified) and sent to the sponsor following discharge of the infant from the NICU if more information is later needed.

Date and Time of Outcome

The date and time the subject recovered or died.

Outcome

The outcome of an AE must be classified as one of the following:

- Recovered (fully recovered or the condition has returned to the level observed at initiation of trial treatment)
- Recovered with sequelae (resulted in persistent or significant disability/incapacity)
- Recovering
- Not yet recovered
- Fatal

8.2.3 Collection and Recording of Adverse Events for Maternal Subjects

Events that occur in maternal subjects following the signing of informed consent are to be collected as AEs. Data regarding these AEs are to be recorded in the e-CRF. Maternal subject AEs will be collected and recorded from the time of signing ICF through the Day 18/Follow-up visit.

8.2.4 Collection and Recording of Adverse Events for Infants

Events that occur in infants following the signing of parental consent are to be collected as AEs. Data regarding these AEs are to be recorded in the e-CRF using information obtained from the infant's hospital records (as available). Infant AEs will be collected and recorded from the time informed consent is obtained through the Day 18/Follow-up visit during the trial. As part of post-trial activities after the Day18/Follow-up visit, infant AEs will also be collected and recorded through time of infant's discharge from NICU or until the last milk sample expressed during maternal subject's treatment with IMP is either consumed by the infant or discarded, whichever occurs last. These AEs will be reported separately from those collected through the Day 18/Follow-up visit.

About one month after the infant's NICU discharge, the maternal subject will be contacted (by phone or other means) to inquire about any hospital re-admission and the reason for such.

8.3 Adverse Events Requiring Special Handling for Maternal Subject

8.3.1 Uterine Contraction

As uterine contraction during postpartum is considered a physiological phenomenon, uterine contraction is not to be reported as AEs unless it requires active management, e.g., analgesic use.

8.4 Morbidity Events of Special Interest for Infants

Infants' morbidity events of special interest are events of special interest because there is support or indications in the literature that their incidences and severities are associated with the degree to which premature infants are fed with mother's milk or inversely with formula based on cow-milk. The incidences of these events are therefore included in the trial design as a post-trial exploratory endpoint. These morbidities are not identified as safety parameters in the sense that there is any rationale why merotocin should have a causative effect upon them. The following infant events are regarded as morbidity events of special interest and will be followed until they are resolved or until the medical condition is stable. Additional information on NEC, intra-ventricular hemorrhage, BPD, RDS, late-onset sepsis, ROP, and hemodynamically significant patent *ductus arteriosus* will be collected in the e-CRF.

8.5 Serious Adverse Events

8.5.1 Serious Adverse Event Definition

Serious Adverse Events (SAEs) during the Trial

An event is defined a SAE if it:	Guidance
Results in **death**	Any event resulting in a fatal outcome must be fully documented and reported, including deaths occurring within 4 weeks after the treatment ends and irrespective of the causal relationship to the IMP. The death of a subject enrolled in a trial is *per se* not an event but an outcome.
Is **life threatening**	The term life threatening refers to an AE in which the subject was at immediate risk of death at the time of the event. It does not refer to an event that may have caused death if it were more severe.
Requires in-patient **hospitalization** or prolongation of existing hospitalization	The term hospitalization means that the subject was admitted to hospital or that existing hospitalization was extended as a result of an event. Hospitalization describes a period of at least 24 hours. Overnight stay for observation, stay at emergency room or treatment on an outpatient basis do not constitute a hospitalization. However, medical judgement must always be exercised and when in doubt the case should be considered serious (i.e., if case fulfils the criterion for a medically important event). Hospitalizations for administrative or social purposes do not constitute an SAE. Hospital admissions and/or surgical operations planned before trial inclusion are not considered AEs, if the illness or disease existed before the subject was enrolled in the trial, provided that the condition did not deteriorate during the trial.
Results in persistent or signify-cant **disability/incapacity**	Disability/incapacity means a substantial disruption of a person's ability to conduct normal life functions. In doubt, the decision should be left to medical judgement by the investigator.
Is a **congenital anomaly/birth defect**	Congenital anomaly/birth defect observed in any offspring of the subject conceived during treatment with the IMP.
Is an **important medical event**	Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. 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.

8.5.2 Collection, Recording and Reporting of Serious Adverse Events

SAE Reporting by the Investigator

All SAEs must be reported **immediately** to Ferring Pharmacovigilance as soon as it becomes known to the investigator and not later than within 24 hours of their knowledge of the occurrence of an SAE.

The investigator is responsible for submitting the completed SAE Report Form with the fullest possible details **within 3 calendar days** of his/her knowledge of the SAE.

The SAE Report Form is included in the e-CRF system, and must be completed and submitted according to the instructions provided on the form. In case the e-CRF cannot be accessed and hence the SAE Report Form cannot be filled in within the e-CRF system, a paper SAE Report Form should be used and sent to Ferring Pharmacovigilance using the contact details below.

Ferring Pharmacovigilance
E-mail: [redacted]
Fax: [redacted]

Completion of the Demographics, Adverse Event Log, Medical History Log and Concomitant Medication Log are mandatory for initial reports and for follow-up reports if any relevant changes have been made since the initial report. Data entries must have been made in the e-CRF for Ferring Pharmacovigilance to access the information.

Additional information relevant to the SAE such as hospital records, results from investigations, e.g., laboratory parameters (that are not already uploaded in the e-CRF), invasive procedures, scans and X-rays and autopsy results can be faxed or scanned and e-mailed to Ferring Pharmacovigilance using the contact details in the section above. In any case this information must be supplied by the investigator upon request from Ferring. On any copies provided, details such as maternal subject's name, address and hospital ID number should be concealed and instead maternal subject number should be provided.

The investigator will supply Ferring and the IRBs with any additional requested information such as results of post-mortem examinations and hospital records.

Ferring will report all SAEs according to local regulations.

8.6 Follow-up of Adverse Events and Serious Adverse Events

8.6.1 Follow-up of Adverse Events with Onset during the Trial

During the trial, the investigator must follow-up on each AE, maternal or infant, until it is resolved or until the medical condition is stable.

After the Day 18/Follow-up visit, the investigator must follow-up on any AE classified as serious or considered to have a reasonable possible causality to the IMP until it is resolved or until the medical condition is stable. All such relevant follow-up information must be reported to Ferring. If the event is a chronic condition, the investigator and Ferring may agree that further follow-up is not required.

8.6.2 Collection of Serious Adverse Events with Onset after Last Trial Visit

If an investigator becomes aware of an SAE of the maternal subject after the Day 18/Follow-up visit, and he/she assesses the SAE to have a reasonable possible causality to the IMP, the case will have to be reported to Ferring, regardless of how long after the end of the trial this takes place.

If an investigator is informed of a hospital re-admission of the infant from the follow-up call about one month after infant' discharge from NICU, and he/she assesses the reason for the re-admission to have a reasonable possible causality to the IMP, the case will be reported as an SAE to Ferring. Similarly, if an investigator becomes aware of an SAE of the infant during the infant's long-term follow-up, and he/she assesses the SAE to have a reasonable possible causality to the IMP, the case will have to be reported to Ferring. The SAE will be followed up until the event is resolved or until the medical condition is stable.

9 STATISTICAL METHODS

The Ferring Global Biometrics Department will be responsible for the statistical analyses of the primary, secondary and exploratory endpoints. This section details the planned statistical analyses for the primary endpoint and outlines the planned statistical analyses for the secondary and exploratory endpoints. All analyses and further descriptions of the statistical methodology for the primary, secondary and exploratory endpoints will be included in the Statistical Analysis Plan (SAP) available before breaking the blind of the trial. A separate SAP will be prepared to cover the post-trial information.

9.1 Determination of Sample Size

The primary objective of this trial is to evaluate the effect of merotocin on increasing milk production in women with preterm delivery. The comparison is based on the primary endpoint of the volume of MoM produced over Days 1 to 14.

Since neither the onset nor the duration of effect of merotocin is known, the initial sample size calculation is based on a comparison of the time-averaged difference between the merotocin group and the placebo group over Days 1 to 14. A sample size of 100 maternal subjects, allocated equally to each treatment group, will provide roughly 80% power to detect a 50% increase in the volume of MoM produced over Days 1 to 14, compared to placebo.

The primary analysis of the volume of MoM obtained over Days 1 to 14 will be based on a repeated measures ANCOVA. For a given sample size, the power is a function of the assumed (constant) treatment effect and the assumed correlation of observations within subjects. The power for a sample size of 100 maternal subjects equally distributed between the two treatment groups for various combinations of correlation and treatment effect is shown in Table 7. As shown in the table, a sample size of 100 subjects has approximately 80% power to detect a 50% increase in the volume of MoM produced, unless the within subject correlation is greater than 0.8.

Table 7 Power for Various Combinations of Correlation and Treatment Effect

Correlation	Treatment effect [a] (merotocin relative to placebo)		
	30% increase	40% increase	50% increase
0.6	64.2 %	81.1 %	92.3 %
0.7	57.2 %	74.4 %	86.1 %
0.8	52.1 %	66.5 %	80.2 %

a Assuming 100 subjects will be equally distributed between the two groups, with a uniform 30% drop-out rate in the trial.

The results presented in Table 7 are based on simulations. For each scenario, 1,000 datasets with 100 subjects equally distributed between the 2 treatment groups were generated. In each simulation, 14 observations from a multivariate log-normal distribution were generated for each subject. The means and variances of the multivariate log-normal distribution used to draw samples from, were based on external data received by Ferring. The correlation between the volume of MoM expressed

on any two given days by the same individual was assumed to be constant and is provided in Table 7 for each scenario. To account for subjects not completing the trial, a 30% drop-out rate over the duration of the trial was built into each simulation. It is estimated that approximately 250 maternal subjects will need to be screened.

9.2 Subject Disposition

The number of maternal subjects screened will be presented, and the number of maternal subjects randomly assigned to receive trial treatment, completing the treatment period and completing the trial will be summarized by treatment group and analysis sets. The number of subjects providing data in the full analysis set (FAS) will be tabulated by treatment day. Reasons for discontinuation will be summarized by treatment group.

9.3 Protocol Deviations

Protocol deviations will be rated as either minor or major. Protocol deviations impacting the primary endpoint will be rated as major. Maternal subjects will be excluded from the per protocol (PP) analysis set from the day where the first major protocol deviations occurred and onwards. Data will not be excluded from the PP analysis set in case of minor protocol deviations. Major protocol deviations include but are not limited to the following:

- For a given treatment day:
  - Less than 5 milk expression attempts
  - Less than 80% compliance with intra-nasal administration of assigned treatment prior to milk expression

The Ferring clinical team will perform a blinded review of protocol deviations before declaration of clean file and lock of database. If the blinded review identifies serious unforeseen deviations deemed to impact the primary endpoint and affect the conclusions of the trial, these will also be rated as major deviations. A comprehensive list of major protocol deviations will be detailed and documented in the clean file document prior to database release. Major protocol deviations will be tabulated by treatment day and treatment group.

9.4 Analysis Sets

Analysis sets' definitions are based on the randomized maternal subject but will apply accordingly to the infant as well.

9.4.1 Intention-to-Treat Analysis Dataset

The Intention-to-Treat (ITT) analysis set is defined as all randomized maternal subjects.

9.4.2 Full Analysis Set

The FAS is defined as all randomized and exposed maternal subjects providing data on volume of MoM produced for at least 1 day after dosing initiation. Since this is a PoC trial, subjects will be analyzed according to actual treatment received.

9.4.3 Per Protocol Analysis Set

The PP analysis set will consist of data from all maternal subjects in the FAS without major protocol deviations (Section 9.3). Since this is a PoC trial, subjects will be analyzed according to actual treatment received.

9.4.4 Safety Analysis Set

The safety analysis set comprises all treated maternal subjects and infants and is analyzed according to the actual treatment received.

9.5 Trial Population

9.5.1 Demographics and Other Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all randomized maternal subjects by treatment group.

9.5.2 Medical History, Concomitant Medication and Other Safety Evaluations

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by treatment group. Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and will be summarized by Anatomical Therapeutic Chemical Classification System (ATC) classification 1st level (alphabetically), ATC classification 2nd level (in decreasing order of frequency) and treatment group.

Reporting of other safety data prior to randomization and start of treatment is detailed together with reporting of safety data after randomization and start of treatment in Section 9.8.

9.6 Endpoint Assessments

9.6.1 General Considerations

Statistical analysis will be performed using SAS software Version 9.2 or later (SAS Institute, Inc, Cary, North Carolina) unless stated otherwise.

Analysis and Presentation of Primary and Secondary Endpoints

Results for the primary endpoint and secondary efficacy endpoints will be presented for both the FAS and the PP analysis sets. The primary endpoint and selected secondary efficacy endpoints will also be presented by gestational age group (<27 weeks and ≥27 weeks).

Continuous variables will be summarized using the mean, standard deviation, median, minimum value and maximum value. Categorical variables will be summarized using frequency counts and percentages. All primary and secondary efficacy endpoints will be presented in data listings.

Treatment differences will (where appropriate) be presented with 95% two-sided confidence intervals and p-values corresponding to the statistical test of the hypothesis 'equal effect' against the alternative 'different effect'. All statistical tests will be performed using a two-sided test at a 5% significance level, unless otherwise stated.

Multiplicity

Concerning the secondary efficacy endpoints, no formal adjustment for multiplicity will be utilized. Statistical significant results will be interpreted cautiously.

Missing Data

Missing data on the primary endpoint will not be imputed for the primary analysis. As this is a PoC trial, the interest is in assessing the difference in the amount of MoM expressed during treatment adherence. Furthermore, the repeated measures ANCOVA model is robust against dropouts under the assumption that the drop-out is not related to treatment. The reason for premature discontinuation will be compared between treatment groups. Sensitivity analyses examining the robustness of the primary analysis results with respect to the above missing data assumption will be carried out by imputing missing data under a missing-not-at-random (MNAR) assumption. The imputation will be carried out using the pattern mixture model with control based pattern imputation.[32]

Missing values for the secondary endpoints will not be imputed.

9.6.2 Primary Endpoint

Primary Endpoint: Primary Analysis

The primary objective of this PoC trial is to evaluate the effect of merotocin on increasing milk production in women with preterm delivery. The primary endpoint of the trial is the volume of MoM produced over Days 1 to 14.

Repeated Measures ANCOVA Model:
The primary endpoint will be analyzed using a repeated measures ANCOVA with a general (unstructured) covariance matrix. The daily volume of MoM produced will be the dependent

variable. The model will include the baseline volume of MoM produced as covariate, with treatment group, treatment day, treatment-by-day interaction, and gestational age group (<27 weeks and ≥27 weeks) as factors. The baseline volume of MoM produced is defined as the volume obtained at the 24-hour interval for eligibility during the observation period. The average treatment effect across treatment days and the within-day treatment effect will be reported along with the corresponding two-sided 95% confidence intervals and p-values.

The analyses based on the FAS will be considered the primary, while the analyses based on the PP analysis set will be considered supportive. PoC will be considered to be established if the repeated measures ANCOVA model results in a significant positive average treatment effect of merotocin compared to placebo across the treatment period in the FAS.

Primary Endpoint: Sensitivity/Supportive Analyses

The Safety Committee may choose to reduce the dose in case of any safety concerns. In that case, the analyses will be performed both by combining the merotocin dose groups into one and by using the actual merotocin dose groups separately.

Sensitivity analyses exploring the impact of the missing data assumption on the results of the primary analysis will be performed for the FAS and PP analysis sets. Missing data will be imputed under a MNAR assumption using the pattern-mixture model with control-based pattern imputation.

The sensitivity of the results with respect to choice of the covariance structure will be investigated using more restrictive covariance structures (compound symmetry, Toeplitz, separate compound symmetry for each treatment group, and separate Toeplitz pattern for each treatment group). Nested models will be compared using the likelihood ratio test. In addition, interactions of treatment and gestational age group will be tested in the model with a general covariance structure.

Although the randomization will be stratified by site, it will not be included in the model for the primary analysis because issues may arise when adjusting for a large number of small centers (with respect to the number of randomized subjects). Additionally, common methods, such as pooling small centers together to form one large center, lack scientific justification. To ensure that the trial conclusions are not substantially affected by this exclusion, sensitivity analyses will examine the relationship between the effect of treatment and center. This will be carried out by including center and the center*treatment interaction as factors in the repeated measures ANCOVA model specified for the primary endpoint.

Sensitivity analyses will be performed to assess the relationship between the time of randomization from delivery and the effect of treatment on the volume of MoM produced over Days 1 to 14. This will be carried out by including the time of randomization from delivery and the time of randomization from delivery by treatment interaction in the repeated measures ANCOVA model specified for the primary endpoint.

The above primary analysis will be repeated to examine the consistency of the relationship between treatment and the volume of MoM produced over Days 1 to 14 after having adjusted for additional covariates (age of maternal subject, ethnicity, presence of fetal growth restriction, birth weight, caesarean section, primipara versus multipara, use of antenatal steroids and pre-pregnancy BMI). Each covariate will be added to the model one by one and tested at a two-sided significance level of 20%. In case two or more covariates are significant at the 20% level, a forward selection process will be applied with a threshold for adding effects at a two-sided significance level of 20% to identify the final model.

9.6.3 Secondary Endpoints

Secondary efficacy endpoints will be analyzed using the FAS and the PP analysis set, whereas secondary safety endpoints will be reported using the safety analysis set.

The time from randomization to the first occurrence of a daily volume of MoM ≥500 mL and ≥750 mL will be analyzed by fitting a discrete time survival model adjusted for gestational age group, as well as the baseline volume of MoM.

The proportion of maternal subjects producing at least 500 mL and 750 mL of MoM over Days 1 to 14 will be analyzed by repeated logistic regression adjusted for treatment day, treatment-by-day interaction and gestational age group.

The volume of MoM produced over Days 15 to 17 will be compared between treatment groups using a repeated measures ANCOVA model adjusting for the volume of MoM produced on Day 14.

Volume of MoM fed to the infant over Days 1 to 14 and volume of formula/donor milk fed to the infant over Days 1 to 14 will be analyzed and presented using an ANCOVA approach similar to the one used for the primary endpoint but gestational age will be adjusted for as a continuous covariate.

The proportion of subjects with quantifiable amount of merotocin in the milk will be summarized for the merotocin group.

Infant body weight will be summarized by treatment day, treatment group and gestational age measured in weeks, together with change from baseline values.

Maternal subject TEAEs will be summarized by treatment group, including separate summaries by intensity. All infant AEs will be summarized by treatment group, again including separate summaries by intensity. Further details are provided in Section 9.8.2.

Routine safety laboratory parameters of maternal subjects will be summarized by time point and treatment group, together with change from baseline values. For each laboratory parameter, a summary table will be prepared displaying the proportion of maternal subjects who have at least one markedly abnormal value. Markedly abnormal criteria for the safety laboratory parameters will

be specified in the SAP.

9.6.4 Exploratory Endpoints

A population PK model will be developed describing merotocin concentrations in plasma and the relationship between merotocin exposure and milk volume will be explored. The analysis methods will be described in detail in a separate modelling analysis plan prepared by Ferring's Translational Medicine Department. This analysis plan will be available before breaking the blind of the trial and results of the analysis will be reported separately.

Milk composition variables will be summarized by time point and treatment group.

9.6.5 Post-trial Endpoints

Post-trial endpoints will be presented in summary tables.

9.7 Extent of Dosing and Treatment Compliance

Extent of actual dosing is defined as the number of intra-nasal trial treatment spray administrations and also as the number of days receiving trial treatment. Both variables will be summarized by treatment group.

Compliance is defined in terms of the number of milk expression attempts and the use of the nasal spray. For women attempting less than 6 milk expressions on a given day, their daily compliance is calculated as number of IMP administrations divided by 5 (the minimum number of milk expression attempts stated in the protocol). For women who perform 6-8 milk expression attempts, compliance is calculated as the number of IMP administrations divided by number of milk expressions. For women expressing milk more than 8 time per day, compliance is calculated as the number of IMP administrations divided by 8 (the maximum number of IMP administrations specified in the protocol). This will be done for both the overall treatment period and each treatment day. Compliance over Days 1 to 14 will be summarized by treatment group as the number of maternal subjects with at least 80% compliance.

Drug dosing will be evaluated by weighing each nasal spray bottle before dispensing and after return to the site taking into account the number of doses administered as reported by the maternal subject.

9.8 Safety

9.8.1 General Considerations

Safety parameters will be evaluated for the safety analysis set.

9.8.2 Adverse Events

All AEs recorded for maternal subjects and infants will be coded using MedDRA. Maternal subject TEAEs will be tabulated by System Organ Class (SOC) and PT, and separately all infant TEAEs will also be tabulated by SOC and PT. The total number of maternal subjects reporting a TEAE, the percentage of maternal subjects (%) with a TEAE and the number of events reported will be presented.

Summary tables will be prepared for:

- All TEAEs
- TEAEs by causality (related/unrelated)
- TEAEs leading to death
- TEAEs by intensity
- Treatment-emergent adverse drug reactions by intensity
- Treatment-emergent SAEs
- TEAEs leading to withdrawal

Separate data listings will be provided for AEs for maternal subjects and infants. Pre-treatment AEs will be flagged.

9.8.3 Other Safety Variables

Physical examination data will be presented as shift tables from baseline by treatment group. Maternal subject blood pressure and heart rate will be summarized in shift tables by treatment group.

9.9 Interim Analysis

An unblinded interim analysis for futility assessment is planned once approximately 50% of the planned 100 subjects have completed assigned treatment period of Days 1 to 14 of the trial. The primary endpoint, volume of MoM produced over Days 1 to 14, will be evaluated for futility. Stopping the trial due to lack of merotocin benefit (i.e., futility) could be considered if the conditional power is lower than 10%.

The futility analysis has an impact on the overall power of the trial. A simulation study was performed to assess the power of the trial when including the proposed futility analysis. Under an alternative hypothesis of treatment effect (i.e., 50% increase), the overall power of the trial with inclusion of futility analysis is 77.2% and 91.1% and the probability of declaring futility during the interim analysis is 4.6% and 1.1% when the within subject correlation is 0.8 and 0.6, respectively. Assuming no treatment effect, the probability of declaring futility during the interim analysis is

37.0% and 31.0% when the within subject correlation is 0.8 and 0.6, respectively. In this simulation study, the conditional power was evaluated with an assumption that the future data after the interim analysis would be generated under the treatment effect of 50% increase for merotocin relative to placebo.

The interim analysis will be performed by the DMC (see Section 3.4) based on cleaned data, and the recruitment will continue at the time of interim analysis unless otherwise notified. The DMC will review unblinded interim data and make a recommendation on whether the trial should be terminated early due to the futility (non-binding).

There is no planned interim analysis with the intention to stop the trial early due to overwhelming efficacy.

10 DATA HANDLING

10.1 Source Data and Source Documents

Source Data - International Conference on Harmonisation Definition

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents - International Conference on Harmonisation Definition

Source documents are defined as original documents, data and records (e.g., hospital records, clinical and office records, laboratory notes, memoranda, maternal subjects' evaluation checklists, milk container labels and weighing worksheet, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, maternal subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Trial-specific Source Data Requirements

Source documents need to be preserved for the maximum period of time required by local requirements. For each subject screened, the investigator will indicate as a minimum in the source documents that informed consent is obtained and the reason for screening failure if applicable. For each subject randomized, the investigator will indicate in the source documents that the subject participates in this trial, and will record at least the following information, if applicable:

- Existence of subject (e.g., date of birth)
- Confirmation of participation in trial (trial ID, subject ID)
- Informed consent(s) (date and time of obtaining written informed consent(s))
- Eligibility for participation in the trial (documenting all inclusion/exclusion criteria)
- Relevant medical history
- Visit dates
- Records of MoM weights
- Dispensing of IMP
- Dates and doses of concomitant medications
- Adverse events (description as well as start/stop date and time)
- Reason for discontinuation
- Event of unblinding, including the reason for unblinding

The source data for analytical parameters of blood samples will be available at the central laboratory.

10.2 e-CRF

An e-CRF system provided by an independent third-party contract research organization (CRO) will be used for data capture. The system is validated, and access at all levels to the system is granted/revoked following Ferring and vendor procedures, in accordance with regulatory and system requirements.

Trial data should be entered into the e-CRF in a timely manner.

The investigator will approve/authorize the e-CRF entries for each maternal subject and infant with an electronic signature which is equivalent to a handwritten signature.

The e-CRF system and the database will be hosted at the independent third party CRO. After the trial database is declared clean and released to the statistician, a final copy of the database will be stored at Ferring. The investigator will also receive a copy of the trial center's final and locked data (including audit trail, electronic signature and queries) as write-protected PDF-files produced by the independent third party CRO. The PDF-files will be stored in an electronic format and will be provided to the investigator before access to the e-CRF is revoked.

Entry errors occurring in the e-CRF will be corrected electronically. Such corrections/modifications will be automatically tracked by an audit trail detailing the date and time of the correction and the name of the person making the correction.

10.3 Data Management

All data management activities will be specified in a data management plan prepared under the responsibility of the Global Biometrics Department of Ferring. The data management plan will be issued before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning and validation. The data management plan will also include information about the intended use of computerized systems, a description of the security measures employed to protect the data and a description of the electronic data flow.

10.4 Provision of Additional Information

On request, the investigator will provide Ferring with additional data relating to the trial, duly anonymized and protected in accordance with applicable requirements.

11 MONITORING PROCEDURES

11.1 Periodic Monitoring

The monitor will contact and visit the investigator periodically to ensure adherence to the protocol, International Conference on Harmonisation-Good Clinical Practice (ICH-GCP), standard operating procedures and applicable regulatory requirements, maintenance of trial-related source records, completeness, accuracy and verifiability of e-CRF entries compared to source data, verification of drug accountability and compliance to safety reporting instructions.

The investigator will permit the monitor direct access to all source data, including electronic medical records, and/or documents in order to facilitate data verification. The investigator will co-operate with the monitor to ensure that any discrepancies that may be identified are resolved. The investigator is expected to be able to meet the monitor during these visits. When the first subject is randomized at the trial site, a monitoring visit will take place shortly afterwards. For this trial, the frequency of the monitoring visits per site will be determined through a risk-based approach depending on recruitment rate, observed data quality and overall site performance.

The monitoring procedures are described in further detail in the monitoring plan for this trial.

11.2 Audit and Inspection

The investigator will make all the trial-related source data and records available at any time to quality assurance auditor(s) mandated by Ferring, or to domestic/foreign regulatory inspectors or representatives from IRBs who may audit/inspect the trial.

The main purposes of an audit or inspection are to assess compliance with the trial protocol and the principles of ICH-GCP including the Declaration of Helsinki[33] and all other relevant regulations.

The maternal subjects must be informed by the investigator and in the ICFs that authorized Ferring representatives and representatives from regulatory authorities and IRBs may wish to inspect their medical records. During audits/inspections the auditors/inspectors may copy relevant parts of the medical records. No personal identification apart from the screening/randomization number will appear on these copies.

The investigator should notify Ferring without any delay of any inspection by a regulatory authority or IRB.

11.3 Confidentiality of Subject Data

The investigator will ensure that the confidentiality of the maternal subjects' and infants' data will be preserved. In the e-CRF and any other documents submitted to Ferring, the maternal subjects and infants will not be identified by their names, but by an identification system, which consists of an assigned number in the trial. Documents that are not for submission to Ferring, e.g., the confidential maternal subject identification code and the signed ICFs, will be maintained by the investigator in strict confidence.

12 CHANGES IN THE CONDUCT OF THE TRIAL

12.1 Protocol Amendments

Any change to this protocol will be documented in a protocol amendment, issued by Ferring, and agreed upon by the investigator and Ferring prior to its implementation. Amendments may be submitted for consideration to the approving IRB(s) and regulatory authorities, in accordance with local regulations. Changes to the protocol to eliminate immediate hazard(s) to maternal subjects may be implemented prior to IRB's approval/favorable opinion.

12.2 Deviations from the Protocol

If deviations from the protocol occur, the investigator must inform the monitor, and the implications of the deviation must be reviewed and discussed. Any deviation must be documented, either as answer to a query in the e-CRF, in a protocol deviation report or a combination of both. A log of protocol deviation reports will be maintained by Ferring. Protocol deviation reports and supporting documentation must be kept in the Investigator's File and in the Trial Master File.

12.3 Premature Trial Termination

Both the investigator (with regard to his/her participation) and Ferring reserve the right to terminate the trial at any time. Should this become necessary, the procedures will be agreed upon after consultation between the two parties. In terminating the trial, Ferring and the investigator will ensure that adequate consideration is given to the protection of the best interests of the subjects. Regulatory authorities and IRB(s) will be informed.

In addition, Ferring reserves the right to terminate the participation of individual trial centers. Conditions that may warrant termination include, but are not limited to, insufficient adherence to protocol requirements and failure to enter maternal subjects at an acceptable rate.

13 REPORTING AND PUBLICATION

13.1 Clinical Trial Report

The data and information collected during this trial will be reported in a clinical trial report prepared by Ferring and submitted for comments and signature to the signatory investigator.

The additional data collected from the infant hospital records when the infant is discharged from the NICU will be reported in an addendum to the clinical trial report.

13.2 Confidentiality and Ownership of Trial Data

Any confidential information relating to the IMP or the trial, including any data and results from the trial will be the exclusive property of Ferring. The investigator and any other persons involved in the trial will protect the confidentiality of this proprietary information belonging to Ferring.

13.3 Publications and Public Disclosure

13.3.1 Publication Policy

At the end of the trial, one or more manuscripts for joint publication may be prepared in collaboration between the investigator(s) offered authorship and Ferring. In a multicenter trial based on the collaboration of many trial centers, any publication of results must acknowledge all trial centers. Results from multicenter trials must be reported in entirety in a responsible and coherent manner and results from subsets should not be published in advance or without clear reference to the primary publication of the entire trial.

Authorship is granted based on the International Committee of Medical Journal Editors (ICMJE) criteria (refer to current official version: www.ICMJE.org).[34] The total number of authors is based on the guideline from the relevant journal or congress. In the event of any disagreement in the content of a publication, both the investigators' and Ferring's opinion will be fairly and sufficiently represented in the publication.

Any external CRO or laboratory involved in the conduct of this trial has no publication rights regarding this trial.

If the investigator wishes to independently publish/present any results from the trial, the draft manuscript/presentation must be submitted in writing to Ferring for comment prior to submission. Comments will be given within 4 weeks from receipt of the draft manuscript. This statement does not give Ferring any editorial rights over the content of a publication, other than to restrict the disclosure of Ferring's intellectual property. If the matter considered for publication is deemed patentable by Ferring, scientific publication will not be allowed until after a filed patent application is published. Under such conditions the publication will be modified or delayed at the investigator's

discretion, to allow sufficient time for Ferring to seek patent protection of the invention.

13.3.2 Public Disclosure Policy

The ICMJE member journals have adopted a trial-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public, clinical trials registry. Thus, it is the responsibility of Ferring to register the trial in an appropriate registry, i.e., www.ClinicalTrials.gov, a website maintained by the National Library of Medicine at National Institutes of Health in the United States. Trial registration may occur in other registries in accordance with local regulatory requirements. A summary of the trial results is made publicly available in accordance with applicable regulatory requirements.

14 ETHICAL AND REGULATORY ASPECTS

14.1 Institutional Review Boards (IRBs)

An IRB will review the protocol and any amendments and advertisements used for recruitment. The IRB will review the ICFs, their updates (if any), and any written materials given to the maternal subjects. A list of all IRBs to which the protocol has been submitted and the name of the IRB chairmen will be included in the clinical trial report.

14.2 Regulatory Authority Approval

The regulatory permission to perform the trial will be obtained in accordance with applicable regulatory requirements. All ethical and regulatory approvals must be available before a maternal subject is exposed to any trial-related procedure, including screening tests for eligibility.

14.3 End-of-Trial and End-of-Trial Notification

At the end of the trial, i.e., when the last subject completes the Day 18/Follow-up visit, Ferring will notify the appropriate regulatory authority and the IRB about the trial completion in accordance with the local requirements of the country where the trial is conducted.

In case of early termination for safety reasons, Ferring must notify the end of the trial to the national regulatory authority and the IRB in accordance with national/local regulations.

In addition, results of the trial will be provided to the relevant regulatory authority when available and within one year of the trial completion (last maternal subject last visit).

14.4 Ethical Conduct of the Trial

This trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki,[33] in compliance with the approved protocol, ICH-GCP and applicable regulatory requirements.

14.5 Subject Information and Consent

Informed Consent Forms Regarding Participation in the Trial – Maternal Subject

The investigator (or the person delegated by the investigator) will obtain a freely given written consent from each maternal subject after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards and any other aspects of the trial which are relevant to the maternal subject's decision to participate. Maternal subjects are also informed of the importance of providing their infants with MoM according to written and oral instructions. The maternal subject must be given ample time to consider participation in the trial, before the consent is obtained. The ICF must be signed and dated by the maternal subject and the investigator who has provided

information to the maternal subject regarding the trial before the maternal subject is exposed to any trial-related procedure, including screening tests for eligibility. Subjects must be given the option of being informed about the general outcome and the results of the trial.

The investigator (or the person delegated by the investigator) will explain that the maternal subject is completely free to refuse to enter the trial or to withdraw from it at any time, without any consequences for her further care and without the need to justify her decision.

The maternal subject will receive a copy of the ICF.

If new information becomes available that may be relevant to the maternal subject's willingness to continue participation in the trial, a new ICF will be forwarded to the IRB(s) (and regulatory authority, if required). The maternal subjects will be informed about this new information and re-consent will be obtained.

Each maternal subject will be informed that the monitor(s), quality assurance auditor(s) mandated by Ferring, IRB representatives, or regulatory authority inspector(s), in accordance with applicable regulatory requirements, may review her source records and data. Data protection will be handled in compliance with national/local regulations.

Informed Consent Forms Regarding Data Collection on the Infant – Parental

If a separate information and informed consent form is required to collect data on the infant, the investigator (or the person delegated by the investigator) will obtain a freely given written consent from the parent participant, i.e., the maternal subject. Paternal consent of the infant will be obtained, if required according to local regulations. The parent participant must be given ample time before the consent is obtained. The ICF must be signed and dated by the parent participant and the investigator who has provided information to the parent participant. Written consent by the parent participant regarding collection of data on the infant must be obtained before the subject is randomized and preferably at the time of obtaining written consent by the maternal subject regarding participation on the trial.

The investigator (or the person delegated by the investigator) will explain that the parent participants are completely free to refuse to consent to this data collection or to withdraw consent at any time, without any consequences and without the need to justify their decision.

The parent participant will receive a copy of the ICF.

The parent participant will be informed that the monitor(s), quality assurance auditor(s) mandated by Ferring, IRB representatives or regulatory authority inspector(s), in accordance with applicable regulatory requirements, may review the source records and data of the infant. Data protection will be handled in compliance with national/local regulations.

14.6 Subject Participation Card

The maternal subject will be provided with a Subject Participation Card bearing the following information:

- That she is participating in a clinical trial
- That she is treated with merotocin (an oxytocin receptor agonist) or placebo (treatment allocation must not be revealed on the Subject Participation Card)
- The name and phone number of the investigator
- Name and address of Ferring (if required by local regulations)

The maternal subject will be asked to return the Subject Participation Card at the last trial visit, if applicable.

Additionally, each subject's primary care physician will be notified of their participation in the trial by the investigator, if the subject agrees and if applicable.

14.7 Compliance Reference Documents

The Helsinki Declaration, the consolidated ICH-GCP, and other national law(s) in the country where the trial will be conducted shall constitute the main reference guidelines for ethical and regulatory conduct.

15 LIABILITIES AND INSURANCE

15.1 ICH-GCP Responsibilities

The responsibilities of Ferring, the monitor and the investigator are defined in the ICH-GCP consolidated guideline, and applicable regulatory requirements in the country where the trial will be conducted. The investigator is responsible for adhering to the ICH-GCP responsibilities of investigators, for dispensing the IMP in accordance with the approved protocol or an approved amendment, and for its secure storage and safe handling throughout the trial.

15.2 Liabilities and Insurance

Ferring is, as sponsor, responsible for ensuring appropriate general/product liability insurance and, as required in accordance with applicable laws and regulations, country-specific liability insurance coverage for claims made by a trial subject for injury arising from the subject's participation in the trial.

16 ARCHIVING

16.1 Investigator File

The investigator is responsible for maintaining all the records, which enable the conduct of the trial at the trial center to be fully understood, in compliance with ICH-GCP. The trial documentation including all the relevant correspondence should be kept by the investigator for at least 15 years or longer if so required by local law after the completion or discontinuation of the trial, if no further instructions are given by Ferring.

The investigator is responsible for the completion and maintenance of the confidential maternal subject identification code which provides the sole link between named maternal subject source records and anonymous e-CRF data for Ferring. The investigator must arrange for the retention of this Subject Identification Log and signed Informed Consent Forms for at least 15 years or longer if so required by local law after the completion or discontinuation of the trial.

No trial center document may be destroyed without prior written agreement between the investigator and Ferring. Should the investigator elect to assign the trial documents to another party, or move them to another location, Ferring must be notified. If the investigator retires and the documents no longer can be archived by the trial center, Ferring can arrange having the documents archived at an external archive.

16.2 Trial Master File

Ferring will archive the trial master file in accordance with ICH-GCP and applicable regulatory requirements.

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