WHO ACTION-III TRIAL
(Antenatal CorticosTeroids for Improving Outcomes in Preterm Newborns)

A multi-country, multi-centre, three-arm, parallel group, double-blind, placebo-controlled, randomized trial of two doses of antenatal corticosteroids for women with a high probability of birth in the late preterm period in hospitals in low-resource countries to improve newborn outcomes

Statistical Analysis Plan

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List of abbreviations

ACS Antenatal corticosteroids
AE Adverse Event
CPAP Continuous Positive Airway Pressure
CRF Case Report Form
FiO_2 Fraction of Inspired Oxygen
ICD-10 International Classification of Diseases 10^{th} revision
IM Intramuscular
IMP Investigational Medical Product
ITT Intention-to-treat
LMICs Low and Middle Income Countries
NICU Neonatal Intensive Care Unit
PP Per Protocol
SAE Serious Adverse Event
SAP Statistical Analysis Plan
SCBU Special Care Baby Unit
SpO2 Oxygen saturation
SRD Severe Respiratory Distress
WHO World Health Organisation

1 BACKGROUND AND RATIONALE

1.1 Background to the trial

The global burden of preterm birth

Every year, an estimated 15 million babies are born preterm. The majority of these births occur in the late preterm period (gestation 34 to <37 weeks) and approximately 80% of all preterm births occur in South Asia and Sub Saharan Africa (Chawanpaiboon et al., 2019). Preterm birth complications are the leading cause of death among children under 5 years of age, responsible for approximately 1 million deaths in 2015. Preterm neonates are at an increased risk of a range of short- and long-term respiratory, infectious and neurological morbidities. While these risks are substantially higher in infants born at earlier gestations, late preterm infants, who account for approximately 85% of all preterm births, still experience a significantly higher rate of morbidity and mortality compared to term infants.

Efficacy of antenatal corticosteroids for preterm birth

Glucocorticoids play a very important role in normal foetal development, especially on pulmonary maturation, brain development and foetal growth. Antenatal corticosteroids (ACS) have long been regarded as a cornerstone intervention in preventing neonatal deaths and severe morbidities due to preterm birth. The recently conducted ACTION I trial has laid to rest any controversy on the benefits (and harms) of ACS for births in the early preterm period (<34 weeks gestation).

While neonatal mortality and morbidity rates are lower in late preterm infants compared to early preterm births, the number of preterm births in the late preterm period is more than three times larger than that in the early preterm period. Even if the benefits of ACS are modest (assuming no harms), overall impacts on preterm-associated morbidity, mortality and health care utilization will be significant at a population level, especially in low-resource settings, where the prevalence of preterm birth is higher, and their outcomes are generally poorer. However, the benefits of ACS in the late preterm period are less clear than the benefits in the early preterm period.

1.2 Rationale

There is currently a lack of clarity on clinical benefits of ACS use in the late preterm period, and uncertainty about the potential for harm. While the ALPS trial, conducted in the USA, suggests benefit for late preterm newborns, an increased risk of hypoglycemia in newborns (RR=1.60; 95%CI 1.37,1.67) was also observed (Gyamfi-Bannerman et al., 2016). This trial was conducted in facilities where there is a high level of care available for preterm infants and their mothers and therefore the generalizability of the reported benefits to low-resource settings is unclear. The possibility of additional benefits for mortality and morbidity reduction in settings with high mortality amongst preterm newborns has also not been explored. Furthermore, the ACT Trial, conducted in 6 low-resource countries, raised concerns that the use of ACS at lower level facilities in Low and Middle Income Countries (LMICs) may not confer benefit or could cause maternal and newborn harm (Althabe et al., 2015). The safety and efficacy of ACS in low-resource facilities in the late preterm period is thus in equipoise, and an efficacy trial is

needed. This is particularly urgent, given the high burden of preterm births, particularly late preterm birth in these settings. Preterm births are the single largest contributor to the high neonatal mortality rates seen in many LMICs. Also, recent studies indicate equipoise regarding the optimal regimen that could confer benefits while minimizing risks of harmful effects. The World Health Organisation (WHO) guidance on the use of ACS in preterm birth is currently restricted only to early preterm birth (< 34weeks of gestation). Further evidence on the efficacy and safety of ACS in late preterm birth is required before WHO recommendations on the use of ACS in late preterm period (≥34 weeks to <37 weeks gestation) can be made.

2 TRIAL AIMS AND OBJECTIVES

2.1 Trial aims

The first aim of this trial is to assess the benefits and possible harms of two regimens of ACS - dexamethasone phosphate 4x6mg intramuscular (IM) q12h (Dexa-4x6mg) and betamethasone phosphate 4x2mg IM q12h (Beta-4x2mg) - compared to placebo, when given to pregnant women in the late preterm period (gestation age of 34^{+0} to 36^{+5} weeks) when they are at risk of preterm birth.

If the two regimens of ACS are found to be superior to placebo then the second aim of the trial will be to determine whether the lower dose treatment (Beta-4x2mg) is non-inferior to the standard dose (Dexa-4x6mg).

The trial will be conducted in hospitals in low-resource countries, where the WHO ACS treatment criteria can be met.

2.2 Primary Objectives

1. To compare the effect of an ACS regimen of dexamethasone phosphate 6mg IM q12h for 4 doses or until birth, whichever is earlier (Dexa-4x6mg) to placebo on a composite outcome of stillbirth, neonatal death or use of respiratory support within 72 hours of life, when given to pregnant women with a high probability of birth in the late preterm period (34^{+0} to 36^{+5} weeks gestation) in hospitals in low resource settings.

2. To compare the effect of an ACS regimen of betamethasone phosphate 2mg IM q12h for 4 doses or until birth, whichever is earlier (Beta-4x2mg) to placebo on a composite outcome of stillbirth, neonatal death or use of respiratory support within 72 hours of life, when given to pregnant women with a high probability of birth in the late preterm period (34^{+0} to 36^{+5} weeks gestation) in hospitals in low resource settings.

3. To compare the effect of an ACS regimen of dexamethasone phosphate 4x6mg q12h to a regimen of betamethasone phosphate 4x2mg IM q12h, on a composite outcome of stillbirth, neonatal death or use of respiratory support within 72 hours of life, when given to pregnant

women with a high probability birth in the late preterm period (34+0 to 36+5 weeks gestation)in hospitals in low resource settings..

2.3 Secondary objectives

1. To compare the effect of dexamethasone phosphate 4x6mg IM q12h regimen to placebo on (i) newborn safety and healthcare utilisation outcomes (ii) maternal safety and healthcare utilisation outcomes, when given to pregnant women (34^{+0} to 36^{+5} weeks gestation) with a high probability of birth in the late preterm period in hospitals in low resource settings.

2. To compare the effect of betamethasone phosphate 4x2mg IM q12h regimen to placebo on (i) newborn safety and healthcare utilisation outcomes (ii) maternal safety and healthcare utilisation outcomes, when given to pregnant women (34^{+0} to 36^{+5} weeks gestation) with a high probability of birth in the late preterm period in hospitals in low resource settings.

3. To compare the effect of betamethasone phosphate 4x2mg IM q12h regimen to dexamethasone phosphate 4x6mg IM q12h regimen on (i) newborn safety and healthcare utilisation outcomes (ii) maternal safety and healthcare utilisation outcomes, when given to pregnant women (34+0 to 36+5 weeks gestation) with a high probability of birth in the late preterm period in hospitals in low resource settings.

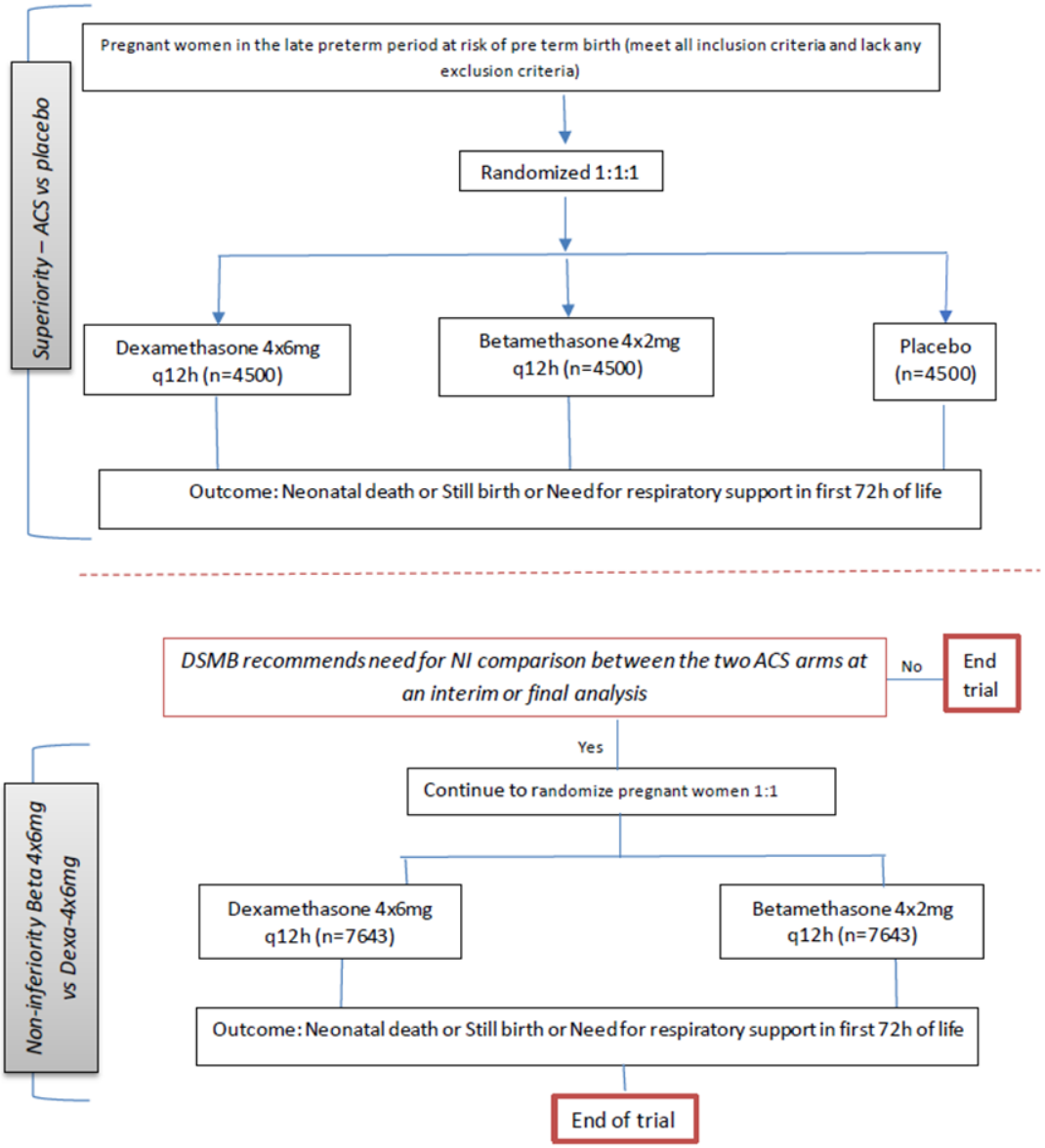
3 TRIAL DESIGN

ACTION III will be a multi-country, multi-centre, parallel group, three-arm, individually randomized, double-blind, placebo-controlled randomised trial, of two ACS regimens (dexamethasone phosphate 6mg IM q12h and betamethasone phosphate 2mg IM q12h – each for 4 doses or until birth, whichever is earlier), given to women with a high probability of birth in the late preterm period (34^{+0} to 36^{+5} weeks gestation).

The trial will be performed in 34 hospitals across seven sites in 5 countries, Bangladesh, India (Belgaum & New-Delhi), Kenya, Nigeria (Ibadan & Ile lfe) and Pakistan, where the WHO ACS treatment criteria can reasonably be met. Trial activities will be facility-based, with community follow up of recruited women and newborns to 28 completed days of life.

The trial will comprise of two phases: The first phase will focus on a superiority comparison of ACS (Beta-4x2mg or Dexa-4x6mg) over placebo with randomisation in a 1:1:1 allocation (figure 1). If both active treatment arms are shown to be superior to placebo and based on a benefit-risk assessment, a second phase to perform a non-inferiority comparison of Beta-4x2mg with Dexa-4x6mg with randomisation in a 1:1 ratio will be conducted to investigate whether the lower dose regimen is non-inferior to the standard regimen.

Figure 1: Overall trial design



In November 2024 the DSMB reviewed the findings from a blinded interim analysis and after unblinding one of the three arms recommended cessation of the placbo arm and that the trial should continue as a two arm trial to assess whether betamethasone phosphate 4x2mg IM q12h (Beta-4x2mg) is non-inferior to dexamethasone phosphate 4x6mg intramuscular (IM) q12h (Dexa-4x6mg). At a subsequent meeting the DSMB decided that they did not need to see an interim analysis during the second non-inferiority phase of the trial.

3.1 Study population

The population of interest is women with a singleton or multiple pregnancy at 34+0 weeks to 36+5 weeks and a high probability of late preterm birth (which extends up to 36+6 weeks), defined as birth expected between 12 hours and 7 days.

3.2 Investigational Medical Product (IMP)

3.2.1 Administration

The Investigational Medical Product (IMP) regimens will be as follow:

- Dexamethasone phosphate 4x6mg q12h (Dexa-4x6mg) regimen: A single course of 6mg IM dexamethasone sodium phosphate administered every 12 hours, to a total of four doses (starting immediately after randomisation at time points 0 hours, 12 hours, 24 hours and 36 hours) or until birth occurs, whichever comes first. If the full regimen is completed, the woman would have received a total of 24mg of dexamethasone in divided doses;
- Betamethasone phosphate 4x2mg IM q12h (Beta-4x2mg) regimen: A single course of 2mg IM betamethasone phosphate administered every 12 hours, to a total of four doses (starting immediately after randomisation at time points 0 hours, 12 hours, 24 hours and 36 hours) or until birth occurs, whichever comes first. If the full regimen is completed, the woman would have received a total of 8 mg betamethasone phosphate in divided doses

Identical placebo, given in exactly the same schedule as above, i.e. administered every 12 hours, to a total of four doses (time points 0 hours, 12 hours, 24 hours and 36 hours) or until birth occurs, whichever comes first.

Packaging, appearance, labelling and volumes administered allow complete blinding of the three arms.

3.2.2 Per protocol treatment

Treatment as per protocol is defined as the receipt of the appropriate number of doses at appropriate time points between randomisation and delivery. The first dose should be administered immediately after randomisation at time point 0 hours and up to 3 more doses should be administered before birth at time points 12 hours $\pm$1 hour, 24 hours $\pm$1 hour and 36 hours $\pm$1 hour, or until birth occurs, whichever comes first. If the interval from randomisation to delivery is less than 36h, the full regimen of 4 doses will not be completed. The woman may have received 1 dose (<12h interval), 2 doses (>12h but <24h interval) or 3 doses (>24h but <36h interval), but if the expected number of doses for the interval from randomisation to delivery have been received, she will be considered as having received the treatment as per protocol. See Section 4.1.1 for details of which women and their babies will be included in per protocol population.

3.3 Outcomes

3.3.1 Primary outcome

Stillbirth (post randomization) OR neonatal death within 72 hours of birth OR use of respiratory support within 72 hours of birth or until discharge from hospital, whichever is earlier.

3.3.2 Neonatal secondary efficacy outcomes

1. Stillbirth (post randomization);
2. Neonatal death within 72 hours, 7 days, 28 days of birth;
3. Resuscitation at birth (among live births in ACTION study and non study hospitals, excluding home births): use of positive pressure ventilation for > 1 minute (with Bag & Mask, T piece) (assumed to be > 1 minute in non-study hospital);
4. Severe respiratory distress (SRD) within 72 hours after birth or until discharge from hospital, whichever is earlier (among babies born in ACTION study hospitals): any of the following clinical signs present at two or more consecutive 6 hourly assessments (i) respiratory rate ≥ 70/min; (ii) chest indrawing; (iii) grunting; or (iv) Oxygen saturation SpO2 < 90%; or deaths within 72 hours with cause of death of SRD;
5. Respiratory support within 72 hours of birth or until discharge from hospital, whichever is earlier (among all live births): use of any of the following respiratory support: (i) any mechanical ventilation; (ii) continuous use of CPAP for 12 hours or more with an FiO_2 ≥ 0.4 at any time; (iii) continuous use of supplementary oxygen for 24 hours or more with an FiO_2 ≥ 0.4 at any time;
6. Death or mechanical ventilation or very high settings for CPAP within 72 hours of birth: stillbirth or neonatal death within 72 hours or mechanical ventilation within 72 hours or need for very high CPAP settings (≥ 8 cm water pressure and ≥ 0.7 FiO_2) within 72 hours;
7. Cause specific mortality.

3.3.3 Neonatal secondary safety outcomes

1. Clinically suspected neonatal sepsis within 7 days of life or until discharge from hospital, whichever is earlier (among babies admitted within 7 days of life in ACTION study hospital): onset of at least two (or more) of the following signs at 6, 12, 24, 36, 42, 48, 54, 60, 66, 72, 96, 120, 144 or 168 hours (the two signs need to be present at the same time point, but can appear at different time): (i) stopped feeding well; (ii) severe chest indrawing (or rise of respiratory support after 24 hours); (iii) fever (body temperature ≥ 38°C); (iv) hypothermia (body temperature < 35.5°C); (v) movement only when stimulated or no movement at all; (vi) convulsions; or deaths within 7 days with cause of death of neonatal sepsis.
2. Neonatal hypoglycaemia within 36 hours of life or until discharge from hospital, whichever is earlier (among babies admitted within 36 hours of life in ACTION study hospital): blood glucose by point of care glucometer or laboratory value < 45 mg/dL at 6, 12, 24 or 36 hours, or detected anytime < 36 hours based on a test because of clinical suspicion, requiring correction by IV fluids; or deaths within 36 hours with cause of death of neonatal hypoglycaemia.

3.3.4 Neonatal secondary health service utilization outcomes

1. Admission to Neonatal Intensive Care Unit (NICU) or Neonatal Special Care Unit (NSCU) within 72 hours of birth (among all live births);
2. Duration of birth hospitalization: total number of days of hospitalisation from birth to first discharge/ transfer to another facility/ LAMA or death if it occurs at hospital before first discharge (among live births in ACTION study and non study hospitals, excluding home births);
3. Parenteral antibiotic use within 7 days of life (among all live births).

Denominators for neonatal outcomes	DSMB reports	Interim analysis
Primary outcome	All births	All births
Stillbirths	All births	All births
Neonatal deaths	All live births	All live births
Resuscitation at birth		Live births in ACTION study & non study hospitals (excluding home births)
Severe respiratory distress within 72 hours of life		Live births in ACTION study hospitals (excluding births in non study hospital & home births)
Use of respiratory support within 72 hours of life	All live births, excluding neonatal deaths within 2 hours of life	All live births
Death or mechanical ventilation or very high settings for CPAP within 72 hours of birth	All births	All births
Neonatal sepsis within 7 days of life	Live births admitted within 7 days of life in an ACTION study hospital*, excluding neonatal deaths within 6 hours of life	Live births admitted within 7 days of life in an ACTION study hospital*
Neonatal hypoglycaemia within 36 hours of life	Live births admitted within 36 hours of life in an ACTION study hospital*, excluding neonatal deaths within 6 hours of life	Live births admitted within 36 hours of life in an ACTION study hospital*
Admission to NICU/NSCU within 72 hours of life		All live births
Parenteral antibiotic use within 7 days of life		All live births

* Therefore, babies born in non-study hospitals or at home are excluded when they were not admitted in ACTION hospitals within 7 days of iife

3.3.5 Maternal secondary safety outcomes

1. Possible maternal bacterial infection: maternal fever (body temperature ≥ 38°C), or clinically suspected or confirmed infection (obstetric or non-obstetric), assessed by an obstetric care physician and for which therapeutic antibiotics were used during any hospital admission from randomization to 28 days postpartum;
2. Post-partum chorioamnionitis: suspected or confirmed chorioamnionitis assessed by an obstetric care physician during any hospital admission from randomization to 28 days postpartum;

3. Post-partum endometritis: suspected or confirmed post-partum endometritis assessed by an obstetric care physician during any hospital admission from delivery to 28 days postpartum;
4. Maternal death: Any maternal death from randomization to 28 completed days postpartum.

3.3.6 Maternal secondary health service utilization outcomes

1. Duration of birth hospitalization: total number of days of hospitalization from delivery to first discharge (home births excluded);
2. Therapeutic antibiotic use within 28 completed days postpartum;
3. Antibiotic use within 28 completed days postpartum.

3.4 Sample size

3.4.1 Superiority phase

For the superiority phase, assuming an incidence of the primary outcome of between 9% and 12% in placebo arm and a loss to follow-up of 2.5%, a sample size of 4500 women recruited per trial arm (total number = 13,500) will enable us to detect a minimum 20% relative reduction in the ACS arm (Dexa-4x6mg or Beta-4x2mg) compared to placebo with a power of 80% or more (α at 0.027 to account for multiple comparisons).

Incidence in Placebo arm	20% reduction in ACS arm	Sample size per arm, 90% power, α=0.027, 2.5% LFU	Sample size per arm, 85% power, α=0.027, 2.5% LFU	Sample size per arm, 80% power, α=0.027, 2.5%LFU
12%	9.6%	4257	3700	3280
11%	8.8%	4700	4078	3613
10%	8%	5222	4529	4014
9%	7.2%	5858	5081	4500

3.4.2 Non-inferiority phase

The interim analysis reviewed by the DSMB in November 2024 was based on the first 8100 women randomised (about 2700 women per arm). Following the DSMB meeting the trial was paused briefly to allow removal of the placebo. In total, 9467 women were randomised before the placebo was withdrawn (superiority phase, about 3156 women per arm).

Following the interim analysis the DSMB provided WHO with information to enable sample size calculations to be performed. The incidence of the primary outcome in the two ACS combined arms was 8.2%. Based on this information and our knowledge that the incidence of the primary outcome across all 3 arms combined was 9.4% we estimate that incidence in the placebo arm was about 11.8%.

In January WHO convened a meeting of neonatologists and obstetricians with expertise in the area of ACS to consider what would be an appropriate non-inferiority margin in the light of this information. While there were varying opinions on the most appropriate non-inferiority margin, ranging between

1.5% and 1.8% on the risk difference scale, the group agreed that a non-inferiority margin of 1.7% was acceptable.

A non-inferiority analysis is based on comparing the upper confidence bound for the risk difference between the two treatments and comparing this with the non-inferiority margin. If the upper confidence limit is below the non-inferiority margin then non-inferiority is considered to have been demonstrated. For the purposes of this analysis we plan to use a 90% confidence interval which will maintain a type 1 error rate of 5%. Assuming an overall incidence of 8.2% across the two arms, a non-inferiority margin of 1.7% and requiring a power of 85%, the table below shows the sample size required for various assumptions about the true incidence in each arm.

True incidence in Dexa-4x6mg arm	True incidence in Beta-4x2mg arm	True difference between the two arms	Sample size (babies) required per arm* assuming independent observations and no losses to follow up	Sample size (women) assuming a twinning rate of 7%, a design effect of 1.04 and 2% losses to follow-up
8.2%	8.2%	0%	3880	3848
8.075%	8.325%	0.25%	5306	5262
8.05%	8.35%	0.3%	5686	5639
8.025%	8.375%	0.35%	6109	6059
8.0%	8.4%	0.4%	6581	6527

* calculated using the artbin command in Stata

The trial randomises women rather than individual babies and the number of babies is greater than the number of women enrolled (7% greater at the interim analysis). This however raises the possibility of correlated outcomes with twin pairs. The estimated design effect at the interim analysis was 1.04. Taking this into account and allowing for 2% losses to follow-up results in the numbers in the last column of the table which represent the number of women that would need to be recruited into each arm for each scenario. (Loss to follow-up at the interim analysis was less than 0.5% with only 10 out of 8669 babies lost to follow-up/withdrawn).

Based on these calculations and the funding available we plan to recruit 6059 women into each arm which will provide 85% power to demonstrate non-inferiority (1.7% margin) if the true difference between the two arms is less than or equal to 0.35%.

3.5 Timeline

Recruitment scheduled to begin: July 2022
Recruitment for the superiority phasehalted: Dec 2024
NI phase commenced – Dec 2024/Jan 2025
Follow-up of last patient scheduled to be completed: Mar 2026

4 DATA ANALYSIS

4.1 Analysis populations

4.1.1 Women

Screened population: all women screened.

Randomised population: all randomised women.

Intention-to-treat (ITT) population: all randomised women according to randomised treatment assignment, excluding those who withdraw their consent after randomisation for their data to be used (will be considered as lost to follow-up). However, if consent is withdrawn only for continuing participation in the study, but consent is not withdrawn for using already collected data, then data available from these participants will be included in the analysis.

In the ITT strategy of analysis, any participants with protocol violations or deviations will be analysed in the arm to which they were allocated. If randomized twice (protocol violation), women will be included in the arm to which they were allocated first.

Pregnant women included in the ITT population are denoted as trial participants.

Per Protocol (PP) population: all women in the ITT population, excluding those with protocol violations or deviations which reflect a failure to follow the protocol with respect to the delivery of treatment (see Section 3.2.2 for details of the treatment schedule)**.** This includes:

- **Protocol violations at randomisation:**

    1. Study participant randomised, but did not meet eligibility criteria
    2. Study participant randomised twice, i.e. received at least one dose from each of two treatments (both allocations excluded from PP population)

- **Protocol violations and deviations during treatment:**

    1. Study participant did not receive any of the four doses
    2. Study participant did not receive one or more scheduled doses due to an oversight, study ampoule(s) broken or found to be empty
    3. Study participant received an incorrect study pack for any dose
    4. Study participant received concurrent administration of parenteral corticosteroids
    5. Study participant received a scheduled dose earlier (<1h) or later (>1h) than planned
    6. Study participant received an incorrect dosing

Analysis populations for women's secondary outcomes will include all women from the ITT or PP population with non-missing values for each outcome after imputation, whenever possible, of missing information required to meet the outcome definition (see section 4.3 on operational definition of outcomes).

4.1.2 Babies

Randomized population: all babies born to women in the randomised population during the study period, excluding fetal deaths prior to randomisation in case of multiple pregnancies.

Intention-to-treat (ITT) population: all babies born to women in the ITT population during the study period, excluding fetal deaths prior to randomisation in case of multiple pregnancies.

Per Protocol (PP) population: all babies born to women in the PP population, excluding fetal deaths prior to randomisation in case of multiple pregnancies.

Analysis populations for babies' primary and secondary outcomes will include all babies from the ITT or PP population with non-missing values for each outcome after imputation, whenever possible, of missing information required to meet the outcome definition (see section 4.3 on operational definition of outcomes).

4.2 Overview of statistical methods

The primary analyses for both the superiority phase and the non-inferiority phase will be performed on an ITT basis on all participants (babies of randomized mothers, mothers) with outcome data available.

For the superiority phase analysis, the 9467 women recruited before the withdrawal of the placebo arm and their babies will be included in the ITT analysis. For the non-inferiority analysis all women (and their babies) randomized to one of the ACS arms at any time during the trial will be included in the ITT analysis.

In one hospital (KLE Hospital, Belgaum) at the start of the trial all women who underwent C-section received ACS outside of the trial as per hospital policy prior to the trial. This issue was identified late 2023 and after discussions with the hospital this practice ceased to be routine. To address this issue we will also perform ITT analyses of the primary outcome for both trial phases which exclude all women recruited at KLE Hospital on or before 6th December2023.

For both trial phases baseline characteristics will be compared between study arms, by visual inspection, to detect important imbalances in prognostic variables that could bias the results. However, given the large sample size for the trial, we expect the randomization to render important imbalances unlikely.

For the superiority phase analysis, comparative analyses between trial arms will consider multiplicity as both ACS arms use the same placebo arm as a comparator: confidence intervals for the intervention

effect (e.g. risk ratios) will be computed to have a joint 95% coverage probability using Dunnett's method (Dunnett et al., 1964). This involves computing the (joint) 95% confidence intervals using ±2.21xSE rather than ±1.96xSE.

The primary outcome and most other study outcomes are binary variables. For this type of variable, each intervention arm will be compared against the placebo arm using risk differences. For continuous outcomes (duration of birth hospitalization for the mothers and the babies), each ACS dose arm will be compared against the placebo arm using mean differences. The median duration and Kaplan Meier curves will also be reported by arm.

Effect modification across pre- and post-randomisation subgroups will be investigated for the primary endpoint. Subgroup analyses will be pre-defined and not data driven and statistical tests for effect modification will be treated as hypothesis generating rather than hypothesis testing.

For the non-inferiority analysis we will compute the risk difference for the primary outcome (risk in Beta-4x2mg arm minus risk in Dexa-4x6mg arm) and a 90% confidence interval for the risk difference. The upper bound of this confidence interval will be compared with the non-inferiority margin (1.7%) to assess whether Beta-4x2mg arm is non-inferior to Dexa-4x6mg arm. If the 90% confidence interval does not include a risk difference of zero we will also report the 95% confidence limits and a P-value (2-sided) for the test of the null hypothesis that the true risk difference is zero versus the alternative that it is not.

For secondary outcomes in the non-inferiority phase we will report 95% confidence intervals and 2-sided P-values.

4.3 Operational definitions of outcomes

Operational definitions and measurements (Case Report Form (CRF) and variables) related to primary and secondary outcome can be found in appendix 1.

Different scenarios where information required to meet outcome definitions is missing have also been anticipated. With respect to the primary outcome (appendix 2a), information on respiratory support within 72 hours of birth will not be collected for the full time period for babies born at home or discharged before 72 hours of birth. When babies born at home do not seek care or when babies are discharged well before 72 hours of birth, it will be assumed that had the baby spent all 72 hours in hospital, respiratory support would not have been provided during the period when they were actually not in hospital. When babies born in hospital are discharged while on respiratory support against medical advice before 72 hours of birth, respiratory support if they had stayed at hospital will be assumed either to have continued when babies are deceased at 72 hours after birth, or to not have continued when babies are alive at 72 hours after birth.

Furthermore, for babies born in ACTION hospital, signs of respiratory distress and respiratory support will be monitored every 6 hours within 72 hours of birth (or until discharge from hospital, whichever is earlier). Severe respiratory distress was defined as any of the following clinical signs, tachypnea, chest indrawing, grunting or oxygen saturation < 90%, present at two or more consecutive 6 hourly

assessments within 72 hours of life, and will therefore require 2 consecutive time points to meet outcome definition. Similarly, continuous use of CPAP for 12 hours or more with an $FiO_2 \geq 0.4$ at any time will also require 2 consecutive time points to meet outcome definition, and continuous use of supplementary oxygen for 24 hours or more with an $FiO_2 \geq 0.4$ at any time 4 consecutive time points. Whenever one time point is missing, signs of respiratory distress and respiratory support will be assumed to have been continued only if provided at both the previous and the following time points.

Other scenarios with respect to missing information for defining secondary outcomes can be found in appendix 2b.

4.4 Dummy tables and figures

4.4.1 Screening, eligibility and randomisation

4.4.1.1 Table SR 1a: Screening, eligibility and randomization of pregnant women per site and at all sites
4.4.1.2 Figure 1: CONSORT Participant flow diagram
4.4.1.3 Table SR 1b: Clinical assessment of high probability of late preterm birth (up to 36+6 weeks) per trial arm (all sites)
4.4.1.4 Table SR 1c: Clinical assessment of high probability of late preterm birth (up to 36+6 weeks) per site and at all sites
4.4.1.5 Table SR 2: Reasons for non randomisation per site and at all sites
4.4.1.6 Table SR 3a: Analysis populations per trial arm (all sites)
4.4.1.7 Table SR 3b: Analysis populations per site and at all sites

Screening and eligibility information will be presented overall and by study site: eligibility status of screened women, reasons for non-eligibility (table SR 1a), and among women recruited but not randomised, reasons for not being randomised (table SR 2).

Randomised, ITT and PP populations will be shown by trial arm (table SR 3a), by study site and overall (table SR 3b).

4.4.2 Baseline characteristics

4.4.2.1 Table BC 1a: Baseline demographic characteristics of randomized pregnant women per trial arm (all sites)
4.4.2.2 Table BC 1b: Baseline demographic characteristics of randomized pregnant women per site and at all sites
4.4.2.3 Table BC 2a: Baseline clinical characteristics of randomized pregnant women per trial arm (all sites)
4.4.2.4 Table BC 2b: Baseline clinical characteristics of randomized pregnant women per site and at all sites
4.4.2.5 Table BC 3a: Characteristics of the pregnancy at trial entry per trial arm (all sites)

4.4.2.6 Table BC 3b: Characteristics of the pregnancy at trial entry per site and all sites

Although randomization combined with a large sample size is likely to prevent any important imbalances between arms, baseline characteristics will be compared between trial arms, by visual inspection, to detect important imbalances in prognostic variables that could bias the results. The following baseline characteristics will be tabulated overall, by site and by trial arm: women demographics (tables BC 1a & 1b), women clinical characteristics, i.e. obstetric history, BMI and medical conditions (tables BC 2a & 2b) and characteristics of the pregnancy at trial entry (tables BC 3a & 3b).

4.4.3 Treatment administration and per protocol treatment

4.4.3.1 Table TA 1a: Number and timing of Investigational Medical Product (IMP) doses received per trial arm (all sites)

4.4.3.2 Table TA 1b: Number and timing of Investigational Medical Product (IMP) doses received per site and at all sites

4.4.3.3 Table TA 2a: Reasons for non-administration of scheduled doses per trial arm (all sites)

4.4.3.4 Table TA 2b: Reasons for non-administration of scheduled doses per site and at all sites

Number and timing of IMP doses, as well as the proportion of randomized women who received the appropriate number of doses will be reported by trial arm (table TA 1a), by site and overall (table TA 1b). Reasons for non-administration of scheduled doses, including reasons for which the woman has still received the treatment as per protocol or not, will be shown by trial arm (table TA 2a), by site and overall (table TA 2b).

4.4.4 Labour and childbirth

4.4.4.1 Table LC 1a: Characteristics of the delivery per trial arm (all sites)

4.4.4.2 Table LC 1b: Characteristics of the delivery per site and at all sites

4.4.4.3 Table LC 2a: Characteristics of newborns at birth per trial arm (all sites)

4.4.4.4 Table LC 2b: Characteristics of newborns at birth per site and at all sites

4.4.4.5 Table LC 3a: Caesarean: Primary indication per trial arm (all sites)

4.4.4.6 Table LC 3b: Caesarean: Primary indication per site and at all sites

Key characteristics related to the delivery and the newborn will be presented by trial arm (tables LC 1a & 2a), by site and overall (tables LC 1b & 2b).

4.4.5 Neonatal outcomes

4.4.5.1 Table NO 1a: Neonatal primary composite outcome per trial arm (all sites, ITT analysis)

4.4.5.2 Table NO 1b: Neonatal primary composite outcome per site and trial arm (ITT analysis)

4.4.5.3 Figures 2: Forest plots for Risk Ratios across sites (ITT analysis)

4.4.5.4 Table NO 2: Neonatal secondary efficacy & safety outcomes per trial arm (all sites, ITT analysis)

4.4.5.5 Table NO 3: Causes of perinatal death per trial arm (all sites, ITT analysis)

For binary outcomes, the total number of observations, number of missing values and percentages will be reported per arm. For continuous outcomes, the total number of observations, number of missing values and minimum, maximum, means and standard deviations, median and interquartile range will be reported per arm.

Binary neonatal outcomes will be compared between arms using risk differences estimated by binomial generalised estimating equations with identity links and robust standard errors to account for clustering among babies born to the same mother. The primary analysis will include arm and site as fixed covariates (tables NO 1a & 1b, NO 2), and a secondary analysis will also adjust for any baseline covariates for which there is considered to be an important imbalance at baseline.

Duration of birth hospitalisation (continuous neonatal outcome) for all babies and among babies discharged alive only will be compared between arms using mean differences estimated using mixed linear models, including a maternal random effect to account for clustering among babies born to the same mother. The primary analysis will include arm and site as fixed covariates, and a secondary analysis will also adjust for any important prognostic variables (regardless of any baseline difference between arms) in order to increase precision of treatment effect estimates. The median duration of birth hospitalization will also be reported by arm and Kaplan Meier curves will be plotted by arm treating deaths as censored observations. The proportion of babies still hospitalized at day 29 will be also reported.

In order to account for multiple comparisons of treatments in the superiority phase, confidence intervals for risk differences and mean differences will be computed to have a joint 95% coverage probability using Dunnett's method.

Cause specific mortality data will be presented descriptively with no statistical comparison between trial arms (table NO 3).

4.4.6 Maternal outcomes

4.4.6.1 Table MO 1: Maternal secondary outcomes per trial arm (all sites, ITT analysis)

For binary outcomes, the total number of observations, number of missing values and percentages will be reported per arm. For continuous outcomes, the total number of observations, number of missing values and minimum, maximum, means and standard deviations, median and interquartile range will be reported per arm.

Binary maternal outcomes will be compared between arms using risk differences estimated by binomial models with identity links. The primary analysis will include arm and site as fixed covariates (table MO 1), and a secondary analysis will also adjust for any baseline covariates for which there is considered to be an important imbalance at baseline.

Duration of birth hospitalization (continuous maternal outcome) will be compared between arms using mean differences estimated by linear regression. The primary analysis will include arm and site as fixed covariates, and a secondary analysis will also adjust for any important prognostic variables (regardless of any baseline difference between arms) in order to increase precision of treatment effect estimates. The median duration of birth hospitalization will also be reported by arm and Kaplan Meier curves will be plotted by arms.

In order to account for multiple comparisons of treatments in the superiority phase of the trial, confidence intervals for risk differences and mean differences will be computed to have a joint 95% coverage probability using Dunnett's method.

4.4.7 Stratified analyses

4.4.7.1 Table SA 1: Effect modification by pre-randomisation characteristics of ACS regimens on the primary composite outcome (all sites, ITT analysis)

4.4.7.2 Tables SA 2: Effect modification by post-randomisation characteristics of ACS regimens on the primary composite outcome (all sites, ITT analysis)

For the superiority phase, subgroup analyses comparing each ACS arm with placebo will be conducted for the primary outcome and statistical tests for effect modification by the stratifying variable will be performed. For the non-inferiority phase subgroup analyses will only be performed if there is evidence that one of the treatments is superior to the other ($P<0.05$).

The following subgroup analyses are pre-defined (not data driven) and treated as hypothesis generating rather than hypothesis testing:

Pre-randomization subgroups (table SA 1):

- Indication for enrolment i.e. rupture of membranes, preterm labour (intact membranes), planned termination
- Gestational age at enrolment: <34+ 6 weeks, 35+0 to 35+6 weeks, ≥36+0 weeks
- Site
- Single and multiple births

Post randomization subgroups (table SA 2):

- Gestational age at birth: preterm (<37 weeks), not preterm (≥37weeks)
- Interval from time of IMP administration (i.e. first dose) to birth: 0-12hours, >12-24 hours, >24 hours.

- Use of tocolytics (post randomisation)
- Appropriate size for gestational age versus small for gestational age
- Mode of births: Vaginal or caesarean section

Post-randomization subgroup analyses are at risk of bias and are advised against by some authors. However, in the current trial we believe there are good scientific reasons to investigate the post-randomisation subgroups defined a-priori above as there are plausible reasons why the effects treatment could be different in the different subgroups. Before conducting these post-randomization subgroup analyses, we will first examine whether the intervention has an effect on the stratifying variable.

Statistical tests for effect modification by the factors mentioned above will be performed. Note that all of the above subgroup analyses will be treated as hypothesis generating rather than hypothesis testing. It is also important to note that these subgroup analyses are all are pre-defined and not data driven.

4.4.8 Adverse events

4.4.8.1 Table AE 1a: Neonatal adverse events per trial arm (all sites)
4.4.8.2 Table AE 1b: Neonatal adverse events per site and all sites
4.4.8.3 Table AE 2a: Maternal adverse events per trial arm (all sites)
4.4.8.4 Table AE 2b: Maternal adverse events per site and at all sites
4.4.8.5 Tables AE 3a: Line listing of Serious Adverse Events (SAE) in babies born to randomised women
4.4.8.6 Tables AE 3b: Line listing of Serious Adverse Events (SAE) in randomised women

Maternal and neonatal adverse events (AE) and serious adverse events (SAE) that are certainly, probably or possibly related to the intervention will be shown by trial arm, by site and overall in babies born to randomized women (tables AE 1a & 1b) and in randomized women (tables AE 2a & 2b).

All SAE in babies born to randomized women (table AE 3a) and in randomized women (table AE 3b) will be listed and described using the description of symptoms, the International Classification of Diseases 10th revision (ICD-10) classification, the severity, the relatedness to the intervention and the outcome of the event, as recorded in the AE/SAE form, including those occurring between informed consent and treatment administration.

4.4.9 Protocol violations and deviations

4.4.9.1 Table PV 1:Protocol violations and deviations during screening per site and at all sites
4.4.9.2 Table PV 2a: Protocol violations and deviations during randomization and treatment per trial arm (all sites)

4.4.9.3 Table PV 2b: Protocol violations and deviations during randomization and treatment per site and at all sites

4.4.9.4 Table PV 3a: Lost to follow-up per trial arm (all sites)

4.4.9.5 Table PV 3b: Lost to follow-up per site and at all sites

4.4.9.6 Table PV 4: Baseline characteristics of women lost to follow-up per trial arm (all sites)

Protocol violations and deviations during screening will be shown by site and overall (table PV 1). Those during randomization and treatment will be shown by trial arm (table PV 2a), by site and overall (table PV 2b).

Lost to follow-up will also be reported by trial arm (table PV 3a), by site and overall (table PV 3b). In addition, numbers and baseline characteristics of women lost to follow-up will also be compared between study arms to detect any imbalances (table PV 4).

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