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Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (ASPIRIN): a randomised, double-blind, placebo-controlled trial.

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Low-Dose Aspirin versus Placebo in Nulliparous Women for the Prevention of Preterm Delivery

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Abstract:

Background: Preterm birth remains a common cause of neonatal mortality with a disproportionate burden occurring in low and middle-income countries. Meta-analyses of low-dose aspirin to prevent preeclampsia suggest that the incidence of preterm birth may be decreased, particularly if initiated before 16 weeks.

Methods: We conducted a multi-country randomized, double masked trial of aspirin (81 mg) daily compared to placebo initiated between 6 weeks and 0 days of pregnancy and 13 weeks and 6 days of pregnancy in nulliparous women. Prior to randomization, ultrasound confirmed the gestational age and presence of a singleton viable pregnancy. The primary outcome was preterm birth, defined as delivery at or after 20 weeks and prior to 37 weeks gestational age.

Results: A total of 11,976 women in 6 countries (India, Guatemala, Pakistan, Kenya, Zambia, Democratic Republic of Congo) were randomly assigned to aspirin (5,990 women) or placebo (5,986 women). Preterm birth occurred in 11.6% of women randomized to aspirin and 13.1% randomized to placebo (RR, 0.89; 95% CI, 0.81 to 0.98). Women who took aspirin were also less likely to deliver before 34 weeks gestation (3.3% vs 4.0%; RR, 0.75; 95%CI, 0.61 to 0.93) or experience perinatal mortality (45.7/1000 vs 53.6/1000; RR, 0.86; 95%CI, 0.73 to 1.00). Adverse maternal events were similar between the two groups.

Conclusions: In nulliparous women with singleton pregnancies, low dose aspirin initiated between 6 weeks and 0 days and 13 weeks and 6 days results in lower rates of preterm delivery before 37 weeks and before 34 weeks.

Trial Registration: Funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; NCT ASPIRIN ClinicalTrials.gov 02409680/Clinical Trials Registry-India CTRI/2016/05/006970.

Background:

Preterm birth, defined as delivery prior to 37 weeks, remains a predominant driver of infant mortality worldwide with the greatest burden of disease occurring in low and middle-income countries[1,2]. Though improvements in neonatal care have resulted in improved survival[3], this care is often limited or unavailable in the regions with the highest burden of mortality. Beyond the newborn period, longitudinal adverse effects in health and socioeconomic outcomes have been associated with preterm delivery compared to individuals delivered at term[4–6]. Despite numerous trials of preventive and tocolytic therapies, an effective strategy for the prevention of preterm birth has proved elusive, beyond a few at-risk groups[7,8].

Meta-analyses and systematic reviews of trials of low-dose aspirin in pregnant women for the purpose of prevention of preeclampsia have suggested that women receiving aspirin have a lower occurrence of preterm birth[9–12]. This effect may be greater when low dose aspirin is begun before 16 weeks of gestation[13]. Though promising as a strategy, a large definitive trial of low-dose aspirin initiated early in pregnancy with the prevention of preterm birth as the primary outcome has not been conducted. The Aspirin (Aspirin Supplementation for Pregnancy Indicated risk Reduction In Nulliparas-ClinicalTrials.gov Identifier: NCT02409680/Clinical Trials Registry-India CTRI/2016/05/006970) trial was therefore designed to test the hypothesis that low-dose aspirin (81 mg) administered daily initiated between 6 weeks 0 days and 13 weeks 6 days reduces the incidence of preterm delivery amongst nulliparous women with a singleton pregnancy.

Trial Oversight:

We conducted a multinational, randomized double-masked, placebo-controlled trial assessing daily low- dose aspirin (81 mg) begun between 6 weeks and 0 days and 13 weeks and 6 days until 36 weeks and 0 days of pregnancy to prevent preterm birth before 37 weeks amongst nulliparous women with a singleton pregnancy. Nulliparous women were selected as they have a higher rate of preterm birth than multiparous women[14] and are unlikely to undergo treatment to prevent prematurity due to a lack of obstetrical history. The trial was conducted by the NICHD Global Network for Women's and Children's Health Research in 7 sites in 6 countries- India (2 sites), Pakistan, Zambia, Democratic Republic of Congo, Guatemala and Kenya - between March 2016 and April 2019. The trial protocol (available with the full text of this article at NEJM.org) has been previously published[15]. Prior to the initiation of the trial, the protocol was approved by the relevant ethics committees and regulatory agencies of each country as well as the ethics committees of the United States-based collaborators and that of the Research Triangle Institute (RTI) International. The trial was conducted in accordance with Good Clinical Practice Guidelines. An external independent data and safety monitoring board oversaw the conduct of the trial and monitored the occurrence of serious adverse events. No formal interim analyses were planned nor conducted.

Trial initiation, data management, safety monitoring, drug/placebo supply procurement, and supply chain management, as well as development of the statistical plan and performance of the analyses were performed by the trial's data coordinating center, RTI International. The trial protocol and the manuscript were written by the lead author, trial statisticians, and members of the steering committee (NICHD representatives, RTI International researchers and site research representatives). All authors attest to the accuracy and completeness of the data and the fidelity of the trial to the protocol.

Screening and recruitment:

Each site established a plan to screen pregnant women residing within the study communities. Nulliparous women between 6 weeks and 0 days and 13 weeks and 6 days, who were between 14 (18 when required by individual ethics boards) and 40 years of age, were identified and were individually consented for participation by trained staff. We excluded women who had any of the following by medical history: allergy or contraindication to aspirin, previously taken aspirin therapy for more than 7 days during this pregnancy, multiple gestations, history of more than two first trimester losses, or medical conditions for which low-dose aspirin therapy is currently indicated (e.g. diabetes and hypertension). Non-excluded women then underwent a medical screening for additional eligibility criteria which included: blood pressure (BP > 140/90 were excluded), hemoglobin assessment (<7.0 g/dl were excluded) and ultrasound for gestational age dating. Women were also excluded from the trial if the ultrasound demonstrated absence of a fetal heartbeat, multiple gestations, and/or presence of a fetal anomaly. The crown-rump length and last menstrual period were entered into a smartphone application to determine the gestational age in accordance with American College of Obstetrics and Gynecology (ACOG) guidance[16].

Randomization and trial regimen:

Eligible and consented women were randomly assigned in a 1:1 ratio to a daily regime of either 81 mg of aspirin or placebo. The aspirin tablets and placebo were manufactured by Morepen Laboratories in Parwanoo, Himachal Pradesh, India and Helix Pharma Limited located in Karachi, Pakistan. Packaging and distribution were handled by Bilcare Research Global Clinical Supplies. The placebo tablets were identical to the aspirin tablets in size, weight, and appearance. Certificates of analysis following USP reference standards were performed for each lot produced. Stability testing at 6, 12, 18, and 24 months for each lot was performed by high performance liquid chromatography for active ingredients and appearance by RTI International. The randomization sequence was developed for each site by the data coordinating center using a computer algorithm based on randomly permuted block design with varied block sizes. Women then received sequentially numbered pre-packaged 2-week medication allotments. These were exchanged every 2 weeks by study personnel and an assessment of compliance, side-effects, interval medical contacts, and concomitant medications were documented. Throughout the study, research staff and local health providers were masked to treatment. Blood pressure assessments were made between 16 to 20 weeks, 28 to 30 weeks and then biweekly beginning at 34 weeks until delivery. Repeat hemoglobin assessments were obtained between 26-30 weeks. Maternal and neonatal outcomes were obtained through 42 days using a previously described registry [17].

Outcomes:

The primary outcome of this study was preterm birth, which was defined as any delivery at or after 20 weeks 0 days and prior to 37 weeks and 0 days. Predefined secondary maternal outcomes were hypertensive disorders of pregnancy, preterm (<34 weeks' gestation) hypertensive disorders of pregnancy, vaginal bleeding, antepartum hemorrhage, postpartum hemorrhage, maternal mortality through 42 days postpartum, and late abortion. Secondary fetal/neonatal outcomes were perinatal mortality, preterm birth before 34 weeks, preterm birth before 28 weeks, small for gestational age as defined by the Intergrowth standard[18], birthweight <1500 gm, birthweight <2500 gm, spontaneous abortion, stillbirth (both non-macerated and total stillbirth), fetal loss (defined as birth between 16-20 weeks and perinatal mortality between 20 weeks to <7 days post-delivery), and medical termination of pregnancy. All staff were trained in the study procedures, and methods of internal quality checks were designed to ensure high quality data. Definitions of secondary outcomes are provided in the Supplementary Appendix.

Review of outcomes and data consistency was performed in a masked fashion prior to data lock and analysis. Quality assessment of the ultrasound images was performed contemporaneously on 10% of studies with feedback provided to the individual sonographer.

Statistical Analysis:

The expected incidence of the primary outcome was conservatively estimated to be 8%[1]. Assuming a 5% risk of miscarriage and a 2% rate of lost to follow up, the sample size of 11,920 participants (5,960 per arm) would provide 90% power to detect a 20% reduction in the incidence of preterm birth in women treated with low-dose aspirin assuming a two-sided type one error of 5%. Recognizing that missing data was likely to occur due to miscarriage and/or medical termination of pregnancy, we planned a priori to perform a modified intent to treat

analysis for the primary outcome including only women who achieved a pregnancy of 20 weeks and beyond (See the Supplementary Appendix). Women who were subsequently determined to be ineligible were excluded from the analysis as part of the modified intent to treat approach. We also pre-specified a sensitivity analysis within a per-protocol population, defined primarily as a participant who consumed 90% of her prescribed regimen (See the Supplementary Appendix). Analyses of all binary outcomes included a Cochran-Mantel-Haenszel test stratified by site to formally test the primary hypothesis followed by generalized linear model-based sensitivity analyses that explore the treatment by site interaction, adjustment for key demographic, and clinical variables. Analyses of secondary outcomes are exploratory in nature and therefore, p-values and confidence intervals are provided for descriptive purposes only and no adjustment for multiple comparisons were made. Serious adverse events were assessed on all women who were allocated to drug or placebo (safety population). Further description of the statistical methods is provided in the Supplementary Appendix.

Results:

Characteristics of the participants:

From March 2016 through June 2018, a total of 14361 women underwent screening for eligibility after providing informed consent. A total of 2385 women were excluded or declined randomization and the remaining 11976 consented and were randomized: 5990 were assigned to low-dose aspirin and 5986 were allocated to placebo (Figure 1). The low-dose aspirin group had 5787 women who were in the modified intent to treat (MITT) population and the placebo group contained 5771. Baseline characteristics and site of delivery were similar between the two groups (Table 1). Overall adherence to medication or placebo defined as taking $\geq$ 90% of the prescribed medications was high (MITT population overall 84.9%: aspirin 85.3% vs placebo 84.4%). The quality of the drug was evaluated upon manufacture and episodic assessments of stability by a masked third party demonstrated appropriate potency throughout the duration of the study (See the Supplementary Appendix).

Primary outcome

The primary outcome of preterm delivery before 37 weeks occurred in 11.6% of women receiving aspirin and 13.1% of women in the placebo group (RR, 0.89; 95%CI, 0.81 to 0.98). To prevent one preterm delivery, 66 women (NNT) would need to be prescribed aspirin. In the per protocol population, the primary outcome occurred in 10.9% of women receiving aspirin and 12.3% of women in the placebo group (RR, 0.89; 95% CI, 0.80 to 0.99). No interaction between the study site and the primary outcome was seen in either of these analyses. The intent to treat outcomes are noted to be similar to the modified intent to treat analyses and are provided in the Supplementary Appendix.

Secondary outcomes

Preterm delivery before 34 weeks was reduced in women who were randomized to aspirin compared to those randomized to placebo (3.3% vs. 4.0%; RR, 0.75; 95%CI, 0.61 to 0.93). Preterm delivery before 28 weeks trended lower in women who received aspirin compared to

placebo but did not achieve statistical significance (0.9% vs. 1.3%; RR, 0.72; 95%CI, 0.51 to 1.02). Perinatal mortality occurred less frequently among women randomized to aspirin compared to those who received placebo (aspirin 45.7/1000 vs placebo 53.6/1000; RR, 0.86; 95%CI, 0.73 to 1.00). The incidence of overall hypertensive disorders of pregnancy was not different between women randomized to aspirin (6.1%) and those who received placebo (5.6%) (RR, 1.08; 95%CI, 0.94 to 1.25); however, the incidence of women who were delivered before 34 weeks with hypertensive disorders of pregnancy was significantly lower in women randomized to aspirin (0.1%) compared to women randomized to placebo (0.4%)(RR, 0.38; 95%CI, 0.17 to 0.85). No differences in the occurrence of fetal growth abnormalities defined as a birthweight <2500 gm or <1500 gm were noted between the two groups (Table 2). Fetal loss (Stillbirth and abortion at or after 16 weeks) was also lower among women randomized to aspirin (52.1/1000) compared to women who received placebo (60.8/1000)(RR, 0.86; 95% CI, 0.74 to 1.00) Other maternal and fetal/neonatal outcomes were similar between the two groups.

Maternal and Fetal/Neonatal Serious Adverse Events

Overall serious adverse events were similar between the groups (aspirin 14.0% vs placebo 14.4%- RR, 0.94; 95%CI, 0.84 to 1.05). Broad categories of adverse events are compared between groups and are shown in table 3A (maternal) and 3B (fetal/neonatal). No differences in maternal bleeding complications (antepartum hemorrhage, postpartum hemorrhage, or upper gastrointestinal bleeding) were detected between the groups. The proportion of women who had a second hemoglobin $\leq$ 7.0 g/dl or had a 3.5 g/dl drop also did not differ between groups. Maternal mortality was high (176/100000) compared to high-income countries, though no observable differences were seen between groups. Fetal/neonatal serious adverse events did not differ between women who received aspirin and those who received placebo. No differences were seen in the rates of overall anomalies, gastroschisis or neonatal death.

Discussion

In this randomized double masked controlled trial, nulliparous women with a singleton pregnancy who were allocated to low-dose aspirin between 6 weeks and 0 days and 13 weeks and 6 days until 36 weeks gestation were 11% less likely to deliver before 37 weeks. Similarly, the risk of preterm delivery prior to 34 weeks was lowered by 25% and perinatal mortality was decreased by 16%. Importantly, we saw no increase in either maternal or fetal serious adverse events between women prescribed low-dose aspirin compared to women who received placebo.

These outcomes are consistent with several meta-analyses which had demonstrated similar levels of reduction of preterm birth and perinatal mortality [9,19,20] . Because of the large sample size, this trial was able to demonstrate these benefits definitively in a diverse group of women in six low and middle- income countries. The simple eligibility criteria used as part of this trial allows this intervention to potentially be applied to diverse groups of pregnant women in multiple settings and may be particularly relevant in low- and middle-income countries. The low cost and demonstrated tolerability of aspirin in this population suggests that this intervention can be readily and safely adopted across a span of clinical sites.

Several limitations should be noted. First the applicability of this intervention to other groups of women beyond nulliparas with singleton gestations remains unclear. Secondly, prior meta-analyses have suggested that higher doses of aspirin (>100 mg) may further lower the incidence of preeclampsia[10]. The optimal dose and time of initiation for the prevention of preterm birth remains unclear. Finally, though aspirin has been endorsed for the prevention of preeclampsia at term, we were only able to demonstrate a decrease in the incidence of preterm (<34 weeks) hypertensive disorders of pregnancy. This failure to demonstrate a difference in term preeclampsia may be related to both our definition of hypertensive disorders of pregnancy and the settings in which we performed this study. The diagnosis of preeclampsia most commonly occurs at the time of the birth admission. In the care settings for this trial, measurement of blood pressure and assessment of proteinuria does not routinely occur, potentially leading to an ascertainment bias. Recognizing this challenge in our care settings, we chose to use an expansive diagnosis of hypertensive disorders (See the Supplementary Appendix) that may have led to imprecision in this outcome. Nonetheless, our trial of aspirin in pregnancy is similar to other large trials that have likewise failed to demonstrate a benefit in the decreasing in the incidence of preeclampsia at term but noted effects earlier in pregnancy[21–23] .

In conclusion, this trial demonstrates that the administration of aspirin at a dose of 81 mg beginning between 6 weeks 0 days and 13 weeks 6 days through 36 weeks resulted in a significantly lower incidence of preterm birth amongst women with a singleton pregnancy in low and middle-income countries.

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Figure 1. Randomization and Follow-up in the ASPIRIN Trial

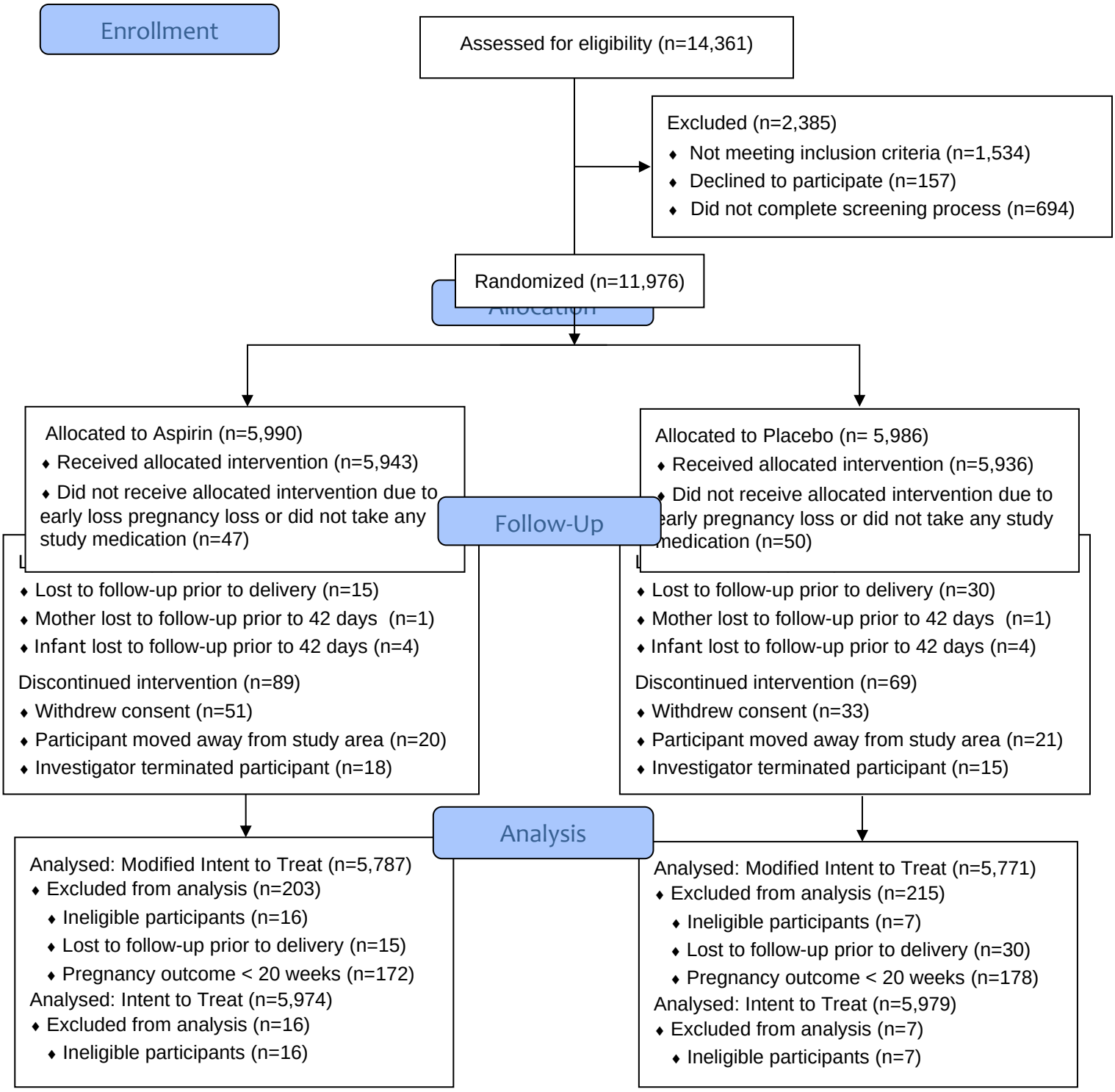

Table 1. Baseline and Site of Delivery Characteristics (Intent to Treat Population)

Characteristic	Aspirin	Placebo
Modified Intent to Treat Population	5,974	5,979
Maternal age (years), n (%)		
< 20	2,320 (38.8)	2,357 (39.4)
20 – 29	3,523 (59.0)	3,487 (58.3)
> 29	131 (2.2)	135 (2.3)
Projected gestational age at enrollment (weeks), Median (P25, P75)	10.0 (8.6, 12.0)	10.1 (8.6, 12.0)
Maternal education, n (%)		
No formal schooling	875 (14.6)	872 (14.6)
1-6 years of schooling	876 (14.7)	888 (14.9)
7-12 years of schooling	3,574 (59.8)	3,567 (59.7)
≥ 13 years of schooling	648 (10.8)	651 (10.9)
Maternal height (cm), Mean (StdDev)	153.2 (6.9)	153.1 (7.0)
Maternal weight (Kg), Mean (StdDev)	49.3 (9.0)	49.2 (8.7)
Maternal BMI (Kg/m^2), Mean (StdDev)	21.1 (3.8)	21.0 (3.7)
Antenatal care visits, Median (P25, P75)	5 (4, 6)	5 (4, 6)
Delivery attendant, n (%)		
Physician	2,990 (50.2)	2,962 (49.8)
Nurse/Nurse midwife	2,284 (38.4)	2,277 (38.3)

Characteristic	Aspirin	Placebo
Traditional birth attendant	472 (7.9)	476 (8.0)
Family/Self/Other	208 (3.5)	229 (3.9)
Delivery location, n (%)		
Hospital	3,541 (59.5)	3,554 (59.8)
Clinic/Health center	1,854 (31.1)	1,798 (30.2)
Home/Other	561 (9.4)	594 (10.0)
Delivery mode, n (%)		
Vaginal	4,278 (71.8)	4,348 (73.1)
C-Section	1,523 (25.6)	1,441 (24.2)
Miscarriage	114 (1.9)	131 (2.2)
MTP	41 (0.7)	26 (0.4)

Characteristics were compared between study arms using chi-square tests for categorical measures, t-tests for continuous data, and Wilcoxon rank sum tests for ordinal data. All p-values comparing treatment groups were greater than 0.05.

Table 2. Primary, Secondary, and Other Outcomes

Outcome	Aspirin	Placebo	p-Value[4]	RR (95% CI)[5]
Primary Outcome				
Preterm delivery[1], n/N (%)	668/5,780 (11.6)	754/5,764 (13.1)	0.012	0.89 (0.81, 0.98)
Secondary Efficacy Outcomes				
Hypertensive disorders[1], n/N (%)	352/5,780 (6.1)	325/5,764 (5.6)	0.30	1.08 (0.94, 1.25)
Small for gestational age[1], n/N (%)	1,506/5,492 (27.4)	1,564/5,467 (28.6)	0.17	0.95 (0.90, 1.01)
Perinatal mortality[1], n/N (Rate/1000)	264/5,779 (45.7)	309/5,763 (53.6)	0.048	0.86 (0.73, 1.00)
Other Maternal Outcomes of Interest				
Vaginal bleeding[2], n/N (%)	214/5,933 (3.6)	246/5,940 (4.1)	0.13	0.87 (0.73, 1.04)
Antepartum hemorrhage[1, 6], n/N (%)	26/5,761 (0.5)	25/5,746 (0.4)	0.90	1.03 (0.60, 1.79)
Postpartum hemorrhage[3, 6], n/N (%)	54/5,928 (0.9)	43/5,907 (0.7)	0.27	1.25 (0.84, 1.86)
Maternal mortality through 42 days[2, 6], n/N (Rate/100,000 deliveries)	9/5,958 (151)	12/5,948 (202)	0.51	0.75 (0.32, 1.78)
Late abortion[2], n/N (Rate/1000)	23/5,819 (4.0)	30/5,808 (5.2)	0.33	0.77 (0.45, 1.31)
Preterm and hypertensive disorders[1, 6], n/N (%)	8/5,780 (0.1)	21/5,764 (0.4)	0.015	0.38 (0.17, 0.85)
Other Fetal Outcomes of Interest				
Preterm < 34 weeks of pregnancy[1], n/N (%)	189/5,780 (3.3)	230/5,764 (4.0)	0.039	0.75 (0.61, 0.93)

Outcome	Aspirin	Placebo	p-Value[4]	RR (95% CI)[5]
Preterm < 28 weeks of pregnancy[1], n/N (%)	54/5,780 (0.9)	75/5,764 (1.3)	0.06	0.72 (0.51, 1.02)
Measured birth weight < 2500g[1], n/N (%)	1,078/5,628 (19.2)	1,153/5,624 (20.5)	0.07	0.93 (0.87, 1.01)
Birth weight < 2500g[1, 7], n/N (%)	1,101/5,671 (19.4)	1,178/5,671 (20.8)	0.07	0.94 (0.87, 1.01)
Measured birth weight < 1500g[1, 7], n/N (%)	78/5,628 (1.4)	101/5,624 (1.8)	0.08	0.87 (0.57, 1.33)
Birth weight < 1500g[1], n/N (%)	97/5,671 (1.7)	118/5,671 (2.1)	0.15	0.79 (0.58, 1.07)
Fetal loss[2,8], n/N (Rate/1000)	303/5,818 (52.1)	353/5,807 (60.8)	0.039	0.86 (0.74, 1.00)
Spontaneous abortion[2], n/N (Rate/1000)	134/5,956 (22.5)	152/5,946 (25.6)	0.26	0.88 (0.70, 1.10)
Stillbirth (macerated excluded)[1], n/N (Rate/1000)	105/5,744 (18.3)	119/5,717 (20.8)	0.32	0.88 (0.68, 1.14)
All Stillbirth[1], n/N (Rate/1000)	141/5,780 (24.4)	166/5,764 (28.8)	0.14	0.85 (0.68, 1.06)
Medical termination of pregnancy (MTP) [2, 6], n/N (Rate/1000)	42/5,956 (7.1)	30/5,946 (5.0)	0.16	1.40 (0.88, 2.23)

Note: The following superscripts indicate the analysis population for each outcome variables:[1] Modified intent to treat (mITT), [2] Intent to treat (ITT) and [3] Safety.

[4] P-values from Cochran-Mantel-Haenszel tests stratified by site.

[5] P-values for treatment by site interaction obtained from binomial models with a log link adjusting for site, treatment and site by treatment interaction. If treatment by site interaction term is significant ($p < 0.05$), then the relative risk and 95% confidence interval are obtained from a binomial model with a log link adjusting for site, treatment and site by treatment interaction and is based on the average effect across sites. If the interaction term is not significant then the relative risk and 95% confidence interval are obtained from a binomial model with a log link adjusting for site and treatment.

[6] Antepartum hemorrhage, postpartum hemorrhage, maternal mortality < 42 days, preterm and hypertensive disorders and MTP have low or zero cell counts for at least one site and treatment combination. For these outcomes the relative risks are from models adjusting for site and treatment.

[7] Data from women with Birth weight missing (N=26) or measured after 4 days are excluded (N=84). 90 babies have only estimated weight and 76% of stillbirths have measured birth weight.

[8] Fetal loss is defined as any death of an infant greater than 16 weeks GA and prior to 7 days post-delivery. Any fetal loss (including termination of pregnancy or miscarriage) that occurs prior to 16 weeks is excluded.

Table 3. Serious Adverse Events

Events	Aspirin	Placebo	RR (95% CI)[1]	p-Value[1]
Safety population, N	5,943	5,936		
Participants with at least one SAE, n (%)	832 (14.0)	857 (14.4)	0.94 (0.84, 1.05)	0.25
At least one other SAE, n (%)	495 (8.3)	514 (8.7)	0.97 (0.86, 1.09)	0.58
3A Maternal Events				
Maternal death, n (%)	9 (0.2)	12 (0.2)	0.75 (0.32, 1.78)	0.51
Vaginal spotting/Bleeding/Leaking pv[2], N (%)	10 (0.2)	10 (0.2)	1.00 (0.42, 2.39)	1.0
Antepartum hemorrhage, n (%)	35 (0.6)	33 (0.6)	1.06 (0.66, 1.70)	0.82
Postpartum hemorrhage, n (%)	50 (0.8)	43 (0.7)	1.24 (0.42, 3.63)	0.70
Anemia/Drop in Hb > 3.5 g/dl[2], n (%)	24 (0.4)	23 (0.4)	1.04 (0.59, 1.84)	0.89
Preeclampsia/Eclampsia, n (%)	150 (2.5)	141 (2.4)	1.06 (0.85, 1.33)	0.59
Preterm labor/Preterm birth evaluation prior to delivery[2], n (%)	45 (0.8)	56 (0.9)	0.80 (0.54, 1.19)	0.27
Hypertension admission/Medical visit prior to delivery[3], n (%)	120 (2.0)	106 (1.8)	1.14 (0.88, 1.47)	0.33
Fever/Infection[2], n (%)	54 (0.9)	46 (0.8)	1.18 (0.80, 1.73)	0.42
Other[2], n (%)	57 (1.0)	57 (1.0)	1.00 (0.70, 1.44)	0.99
3B Fetal/Infant Events				

Events	Aspirin	Placebo	RR (95% CI)[1]	p-Value[1]
Fetal loss after 20 weeks, n (%)	142 (2.4)	162 (2.7)	0.88 (0.70, 1.09)	0.25
Neonatal death, n (%)	163 (2.7)	190 (3.2)	0.86 (0.70, 1.05)	0.14
Miscarriage/Abortion/MTP (medical termination of pregnancy), n (%)	51 (0.9)	54 (0.9)	0.95 (0.65, 1.38)	0.77
Other fetal anomaly[2], n (%)	32 (0.5)	36 (0.6)	0.89 (0.55, 1.43)	0.63
Gastroschisis[2], n (%)	2 (0.0)	1 (0.0)	2.01 (0.18, 22.11)	0.60

Note: The denominator for each serious adverse event is any participant included in the safety population and the numerator is participants with at least one SAE form indicating the specified serious adverse event.

[1] P-values for treatment by site interaction obtained from binomial models with a log link adjusting for site, treatment and site by treatment interaction, If treatment by site interaction term is significant ($p < 0.05$), then the relative risk and p-value are obtained from a binomial model with a log link adjusting for site, treatment and site by treatment interaction and is based on the average effect across sites. If the interaction term is not significant then the relative risk and p-value are obtained from a binomial model with a log link adjusting for site and treatment.

[2] Serious adverse events with cell counts of zero for at least one site and treatment combination. For these SAEs the relative risks and p-values are from models adjusting for site and treatment.

[3] Serious adverse events with cell counts of zero for many sites so the models did not converge.

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Definitions of Secondary outcomes

Hypertensive disorders	Any of the following are included as evidence of hypertensive disease: o Any reported SAE of preeclampsia or eclampsia. o MNH registry report of hypertensive disease, preeclampsia or eclampsia. o Reports of elevated blood pressures that meet criteria based on the ACOG 2013 "Hypertension in Pregnancy" Task Force Report at any point after 20 weeks GA. The only case that will programmatically qualify for evidence of hypertension is: Any individual with 2 consecutive timepoints with ≥140 mm Hg systolic or ≥90 mm Hg diastolic where those timepoints occur more than a week (7 days) apart. The criteria (e.g. elevated systolic or elevated diastolic) must be consistent for the two consecutive visits. For individuals that do meet the above criteria: o If they have less no reports of elevated blood pressure or a single report of elevated blood pressure that is followed by a normal value, they will not be considered to have evidence of hypertensive disease. o If they have any other reports of elevated blood pressure, their outcome classification were adjudicated in a masked manner by clinical experts.
Small for gestational age	Defined is any newborn with weight below the 10th percentile for gestational age. Note that growth curves are based on Intergrowth standards to define the expected gestational age distribution for each site.
Perinatal mortality	This include stillbirths and deaths in the first week of life; the perinatal period commences at 20 completed weeks (154 days) of gestation and ends seven completed days after birth. Pregnancies terminated prior to 20 completed weeks of gestation are treated as missing for this outcome.
Vaginal bleeding	Bleeding during pregnancy (i.e., the WHO generally defines as 'light' or 'heavy' bleeding based on clinical symptoms) based on self-report during the bi-weekly visits during the study period.
Antepartum hemorrhage	Bleeding from the genital tract at any time after the 22nd week of pregnancy and before the birth of the baby. There are two main causes of antepartum hemorrhage, placenta previa and abruption placentae." This outcome will be defined based on Question A8b from Form MN02 from the MNH Registry. The event is defined as follows in the MNH Registry Manual of Operations: "Defined as blood loss of > 1000 cc of blood prior to delivery."
Postpartum hemorrhage	Blood loss of 1000 ml or more from the genital tract after delivery and up to six weeks post-delivery.
Maternal mortality through 42 days	The death of a woman during pregnancy (i.e. conception to delivery) and the puerperium (i.e. up to 42 days after delivery).
Late abortion	Spontaneous fetal loss ≥ 16 weeks and prior to 20 weeks gestation (or <500 g).
Preterm and hypertensive disorders	Live birth or stillbirth before 34 0/7 weeks of pregnancy are completed and those with any evidence of hypertensive disorder

Fetal loss	Any death of an infant greater than 16 weeks GA and prior to 7 days post-delivery. Any fetal loss (including termination of pregnancy or miscarriage) that occurs prior to 16 weeks will be excluded.
Spontaneous abortion	Premature expulsion of a non-viable fetus from the uterus at < 20 weeks gestation.
Stillbirth (macerated excluded)	Death of an infant prior to delivery, for a pregnancy that occurs at 20 weeks gestational age or greater; including only non-macerated still birth or stillbirths with maceration status unknown.
All Stillbirth	Death of an infant which occurs prior delivery, for a pregnancy that occurs at 20 weeks gestation or greater
Medical termination of pregnancy	An operation or other procedure to terminate pregnancy before the fetus is viable.

Statistical Plan Definitions

Safety (SAF) Population

The safety population comprises all randomized participants who received any study treatment grouped by actual treatment received, irrespective of amount or duration of treatment received.

Modified Intention to Treat (mITT) Population

The primary analysis population is the modified intention to treat population, which includes all eligible randomized participants who provided any post-baseline outcome data and who delivered at 20 weeks gestational age or greater. All participants were assigned to the arm to which they were randomized irrespective of treatment received. This population is also used for many of the secondary analyses. Note that this population represents a change from the protocol, which indicates that the ITT population will be used for the primary analyses.

Intention to Treat (ITT) Population

The intention to treat population includes all eligible, randomized participants. All participants were assigned to the arm to which they were randomized irrespective of treatment received. This population will be used to conduct sensitivity analyses for the primary outcome and will be used as the main population for some secondary analyses.

Per Protocol (PP) Population

This population excludes all or part of the data obtained from any eligible, randomized participants who deliver at 20 weeks gestational age or greater that did not receive at least 90% of the full amount of intended randomized study therapy or are considered to have substantially deviated from the protocol in a manner that may impact study outcome or treatment receipt. The population also excludes individuals who were randomized after 10 weeks, 6 days gestational age. Participants are grouped by actual treatment received. Treatment receipt reasons for exclusion and substantial deviations include:

- Documented receipt of aspirin while on study outside of assigned study drug as identified by a reported protocol deviation
- Not receiving treatment after randomization
- Receipt of less than 90% of planned total doses after randomization where the number of planned doses will be calculated as those expected between randomization and the earliest of end of pregnancy and 36 0/7 weeks GA irrespective of if study drug administration was prematurely discontinued for any reason prior to that point

For all analysis populations, data were analyzed as available with no imputation for missing outcomes except where specified for sensitivity analyses.

Drug Potency and Stability Information: Summary of stability analytical reports

Morepen Laboratories Ltd. - Parwanoo

Summary of Stability Analytical Reports

Real Time Stability Studies ($30^0C \pm 2^0C$ / RH 65% ± 5% RH)

Lot: 1 (1) Mfg. date: 09/2015	Appearance	Identification	Dissolution	Free Salicylic Acid (%)	Assay (%)
6 months	Complies	Complies	Complies	1.27	100.59
12 months	Complies	Complies	Complies	1.59	99.85
18 months	Complies	Complies	Complies	1.93	98.79
24 months	Complies	Complies	Complies	2.12	98.23
Note: Accelerated studies ($40^0C \pm 2^oC$ / RH 75% ± 5% RH) were also performed but results not presented here.					
Remarks: The sample is tested and found in compliance with the specification for the parameters tested under stability program.					

Real Time Stability Studies ($30^0C \pm 2^0C$ / RH 65% ± 5% RH)

Lot: 2 Mfg. date: 12/2016	Appearance	Identification	Dissolution	Free Salicylic Acid (%)	Assay (%)
6 months	Complies	Complies	Complies	0.19	98.44
12 months	Complies	Complies	Complies	0.27	97.03
18 months	Complies	Complies	Complies	0.34	96.55
24 months	Complies	Complies	Complies	0.43	96.05
Note: Accelerated studies ($40^0C \pm 2^oC$ / RH 75% ± 5% RH) were also performed but results not presented here.					
Remarks: The sample is tested and found in compliance with the specification for the parameters tested under stability program.					

Real Time Stability Studies ($30^0C \pm 2^0C$ / RH 65% ± 5% RH)

Lot: 3 Mfg. date: 10/2017	Appearance	Identification	Dissolution	Free Salicylic Acid (%)	Assay (%)
6 months	Complies	Complies	Complies	0.14	101.32
12 months	Complies	Complies	Complies	0.39	100.26
18 months	Complies	Complies	Complies	0.76	99.10
24 months					
Note: Accelerated studies ($40^0C \pm 2^oC$ / RH 75% ± 5% RH) were also performed but results not presented here.					
Remarks: The sample is tested and found in compliance with the specification for the parameters tested under stability program.					

HELIX Pharma (Pvt.) Ltd. Quality Control Department

Summary of Stability Analytical Reports

Real Time Stability Studies ($30^0C \pm 2^0C$ / RH 65% ± 5% RH)

Lot: 1 Mfg. date: 11/2016	Appearance	Identification	Disintegration	Dissolution	Free Salicylic Acid (%)	Assay (%)
6 months	Complies	Positive	Complies	Complies	0.78	98.15
12 months	Complies	Positive	Complies	Complies	1.21	99.47
18 months	Complies	Positive	Complies	Complies	1.36	98.43
24 months	Complies	Positive	Complies	Complies	1.38	98.14
Note: Accelerated studies ($40^0C \pm 2^oC$ / RH 75% ± 5% RH) were also performed but results not presented here.						
Discussion: The 24 months stability reveals that all parameters are with in shelf life specification and no significant changes has been observed. Hence the stability at $30^0C \pm 2^0C$ / RH 65% ± 5% RH and $40^0C \pm 2^oC$ / RH 75% ± 5% RH is satisfactory.						

Real Time Stability Studies ($30^0C \pm 2^0C$ / RH 65% ± 5% RH)

Lot: 2 Mfg. date: 08/2017	Appearance	Identification	Disintegration	Dissolution	Free Salicylic Acid (%)	Assay (%)
6 months	Complies	Positive	Complies	Complies	0.96	101.69
12 months	Complies	Positive	Complies	Complies	1.07	101.03
18 months	Complies	Positive	Complies	Complies	0.98	100.95
Note: Accelerated studies ($40^0C \pm 2^oC$ / RH 75% ± 5% RH) were also performed but results not presented here.						
Discussion: The 24 months stability reveals that all parameters are with in shelf life specification and no significant changes has been observed. Hence the stability at $30^0C \pm 2^0C$ / RH 65% ± 5% RH and $40^0C \pm 2^oC$ / RH 75% ± 5% RH is satisfactory.						

Sensitivity Analyses for Primary Outcome

Preterm delivery, n/N (%)	Aspirin	Placebo	p-Value	RR (95% CI)
Analysis with inverse probability weighting[1]	-	-	<0.001	0.88 (0.82, 0.94)
ITT Population with multiple imputation[2]	-	-	-	0.87 (0.78, 0.96)
Per-Protocol Population[3]	537/4,927 (10.9)	600/4,861 (12.3)	0.020	0.89 (0.80, 0.99)

[1] Relative risks, 95% confidence intervals and p-values are obtained from a binomial model with a log link adjusting for site, treatment and site by treatment interaction with inverse probability weighting. Includes negative outcomes for pregnancies excluded from primary analysis due to pregnancy outcome < 20 weeks (n=350), medically terminated pregnancy ≥20 weeks (n=5), or otherwise missing outcomes ≥20 weeks (n=9).

[2] Relative risks and 95% confidence intervals are obtained from a binomial model with a log link adjusting for site, treatment and site by treatment interaction for all randomized population with preterm status determined by gestational age for all pregnancies and multiple imputation for pregnancies with missing gestational age (n=45).

[3] P-values from Cochran-Mantel-Haenszel tests stratified by site. Relative risk and 95% confidence interval are obtained from a binomial model with a log link adjusting for site and treatment.