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iTAP

A phase III, placebo controlled, double blind, randomized clinical trial to assess the efficacy and safety of tenofovir disoproxil fumarate given from 28 weeks' gestation until 2 months postpartum to Hepatitis B (HB) virus chronically infected, HBsAg and HBeAg positive pregnant women to prevent perinatal transmission of HBV to their infants who receive passive-active HBV immunization

Analysis Plan Version 3.0

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CONTENTS

1. Introduction

1.1 Purpose

This document describes the planned statistical analysis for the primary final 6-month report and supplemental 12-month report of the iTAP trial. Previous analysis plan documents have described the statistical analysis for the closed reports of the interim safety and efficacy reviews of the iTAP trial by the Data and Safety Monitoring Board (DSMB).

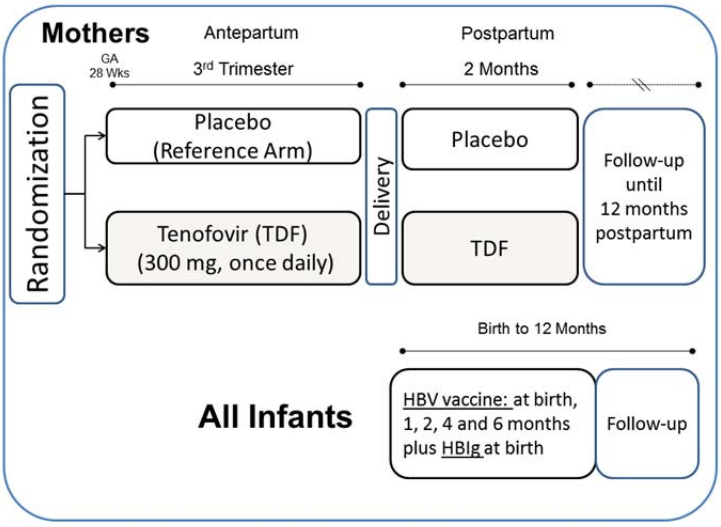
1.2 Analysis Reports

The primary analysis reports will be distributed to study team members, including the program scientists. Data summaries will be presented by randomized arms (i.e. tenofovir and placebo).

1.3 Design

iTAP is a multicenter, controlled, double blind, randomized clinical trial to assess the efficacy to prevent HBV perinatal transmission, safety and tolerance of tenofovir disoproxil fumarate (TDF) versus placebo, given from 28 weeks' gestation until 2 months post-partum to hepatitis B sAg and eAg positive mothers.

1.3.1 Overview of the Randomized Trial Design



1.3.2 Sample Size

A total of 328 pregnant women will be enrolled.

1.3.3 Population

Consenting pregnant women ≥18 years of 28 weeks (+/- 10 days) gestational age with negative HIV serology, and positive HBsAg and HBeAg tests within 6 months of enrollment. Additionally women must have ALT ≤30 U/L within 3 months of enrollment and confirmed ≤60 U/L at the pre-entry visit.

Exclusion criteria include women with a history of TDF or any other anti-HBV treatment during the current pregnancy, Cockcroft-Gault creatinine clearance <50 ml/min, confirmed dipstick proteinuria >1+ (>30 mg/dL) or normoglycemia glucosuria, positive serology for hepatitis C within 12 months prior to enrollment, pre-existing fetal anomalies incompatible with life, any concomitant condition or treatment that would contraindicate participation or concurrent participation in any other clinical trial without written agreement from the two study teams.

All infants born to mothers participating in the study will be included. Stillbirths will be excluded.

1.3.4 Randomization and Stratification

Pregnant women will be randomized 1:1 to receive TDF or placebo stratified by site using permuted blocks.

1.4 Study Objectives and Endpoints

1.4.1 Primary Objective

To assess the efficacy of TDF, versus placebo, in HBV infected HBsAg and HBeAg positive pregnant women, from 28 weeks' gestation until 2 months postpartum (5- month course) to prevent perinatal transmission of HBV to their infants who receive HBV passive-active immunization.

Hypothesis: an anti-HBV agent, TDF administered from the beginning of the last trimester of pregnancy to two months postpartum to HBV infected, HBeAg-positive, pregnant women with ALT ≤30 U/L will reduce the risk of *in utero, intrapartum* and early *postpartum* transmission of their infants from 12% to 3% or less.

1.4.2 Secondary Objectives

- To assess the safety of TDF administered for 5 months perinatally in HBsAg and HBeAg positive women with ALT ≤30 U/L, and their in utero exposed infants.
- To compare the risk of acute exacerbation or flare (ALT >300 U/L) up to 12 months postpartum, following planned discontinuation of study treatment, in HBeAg positive women randomized to TDF or placebo.

1.4.3 Primary Endpoint

Infant's HBV infection status, defined as HBsAg positive confirmed by HBV DNA, at 6 months of age.

1.4.4 Secondary Endpoints

- Occurrence of maternal and infant adverse events (AE), including International Conference on Harmonisation (ICH) Serious Adverse Events (SAEs) and Division of AIDS (DAIDS) grade 3/4 signs and symptoms, regardless of their relatedness to the study treatment.
- Occurrence of acute exacerbation or flare of hepatitis B, following planned discontinuation of study treatment up to 12 months postpartum. The acute exacerbation of flare of hepatitis B is defined as ALT >300 U/L regardless of baseline values.
- Infant's HBV infection status, defined as HBsAg positive confirmed by HBV DNA, at or after 6 months through 12 months of age.
- Infant growth related outcomes, including Z-scores of weight, height and head circumference (HC) at 6 and 12 months of age.

1.5 Maternal Follow-up

Eligibility and pre-enrolment tests should be performed within 3 months prior to enrollment. After enrollment, maternal visits will be performed at 28, 32, 36 weeks' gestation, delivery, and at 1, 2, 3, 4, 6 and 12 months postpartum. All effort is made to strictly follow the visit schedule but occasional departures of no more than one week will be considered acceptable.

Maternal assessments	**Antepartum**					**Delivery**		**Postpartum (months)**					
	Screening	**Pre-entry**	**Enrollment 28 wks**	**32 wks**	**36 wks**		**Before discharge**	**1**	**2[1]**	**3**	**4**	**6**	**12[2]**
			Study Treatment										
Counseling and Questionnaire	X	X	X	X	X	X		X	X	X	X	X	X
Physical/Obstetric exam	X	X		X	X	X		X	X	X	X	X	X
Study treatment dispensation, return of used study treatment bottles/adherence assessment			X	X	X	X		X	X				
Record results of HBsAg, HIV serology and Ultra sound	X												
SGPT/ALT	X	X		X	X	X		X	X	X	X	X	X
HBeAg test (if negative during postpartum period, anti-HBeAb will be tested)		X							X				X
Complete Blood Count[3]		X				X			X				
Serum SGOT/AST, bilirubin (direct& conjugated), alkaline phosphatases, and albumin		X											X
Hepatitis C serology		X											
Serum creatinine[4]		X		X	X	X	X	X	X		X[5]		
Serum phosphorus		X		X	X	X		X	X		X		
Dipstick glycosuria and proteinuria		X		X		X			X				
Urine sample collection[8]			X	X					X				X
HBV DNA load (retrospective)			X			X[6]		X[6]					
Tenofovir plasma level						X							
Plasma/serum storage	X	X	X	X	X	X	X	X	X	X	X	X	X
RNA storage			X	X	X			X	X	X	X		
PBMC isolation[7]			X	X	X			X	X	X	X		
Total blood volume (mL)	5	16	3	8	8	10	4	8	13	8	8	8	10
Total blood volume for PBMC (mL)[7]			30	30	30			30	30	30	30		
Cord blood volume (mL)						15							

[1] Or early study treatment discontinuation
[2] Or early study discontinuation (if subject consents)
[3] Including platelet count
[4] Calculate creatinine clearance using the Cockcroft-Gault formula. Online calculation at http://nephron.com/cgi-bin/CGSI.cgi).
[5] In case of Grade 1 or higher creatinine at 2 months postpartum
[6] Funding will be sought to retrospectively measure HBV DNA load.
[7] For women enrolled in sites with PBMC isolation capacity (flares sub-studies).
[8] If possible, 10 ml will be collected. After centrifugation, 10 aliquots will be stored frozen

If ALT is >60 U/L it will be repeated within 3 days. If ALT is confirmed between 60 and 150 U/L, a new ALT test will be scheduled 2 weeks later. If ALT >150 U/L is confirmed immediately or if ALT is confirmed between 60 and 150 U/L 2 weeks later, the site will contact PHPT and re-introduction of double blind study treatment will be considered.

1.6 Infant Follow-up

Infant visits will be performed at birth, 1, 2, 4, 6, 9 and 12 months.

Infant assessments	Birth	1 month	2 months	4 months	6 months	9 months	12 months[1]
Physical examination including length, weight and head circumference[2]	X	X	X	X	X	X	X
Mitochondrial dysfunction check list[3]					X		X
Counseling and Questionnaire	X	X	X	X	X	X	X
Record date and time of HB Immune globulin (HBIg) injection[4]	X						
Record date and time of HB immunization	X	X	X	X	X		
Complete Blood Count	X						X
Serum creatinine	X						
Serum phosphorus/calcium	X						
HBsAg[1,5]	X	X[5]	X[5]	X[5]	X[5]	X	X
HBV DNA[1]	X				X[6]	X	X[6]
SGPT/ALT	X						X[6]
Anti-HBsAb			X	X	X	X	X[7]
HBeAg and anti-HBeAb if positive HBsAg							X
Plasma storage	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X
Total blood volume (mL)	3	3	2	2	3	3	4

Additional investigations if HBsAg+ (except at birth): retrospective HBV DNA loads, HBeAg
[1]Or early discontinuation, with mother's/guardian's/parents' consent.
[2]Including Ballard Score at birth.
[3]Assessment for possible mitochondrial dysfunction: see list of major and minor neurological and other organ signs in Appendix 3.
[4]InjectHBIg at a site different from HBV vaccine.
[5]Draw blood before injection of HBIg and vaccine.
[6] If HBsAg positive at this time point
[7] If anti-HBs < 10 IU/L (and HBsAg/HBV DNA negative), the pediatrician in charge will be encourage to consider revaccination.

A check list of signs and conditions suggesting possible mitochondrial dysfunction that may trigger other investigations will be completed at the 6 and 12 month visit.

2. Analysis Principles

Throughout this document, unless otherwise noted, analyses will be performed and results presented by randomized arm. Women (and their infants) randomized and later found ineligible as indicated on the 'Protocol Deviation for mother' case report form (CRF) will be included or excluded from all analyses at the discretion of the study chair without reference to the data prior to freezing the database for the 6-month report. All included participants will be analyzed as randomized (i.e. intention-to-treat analyses). Analysis will not be stratified by site.

The following abbreviations and visit week windows will be used:

Maternal visits:

SC: screening	≤3 months prior to date of enrollment and prior to pre-entry
PE: pre-entry	≤3 months prior to date of enrollment, after screening and prior to the M1 visit
M1: 28 weeks gestation	≤3 months prior to date of enrollment to 1 day after (28 weeks gestation +/- 10 days)
M2: 32 weeks gestation	estimated 32 weeks gestation +/-14 days
M3: 36 weeks gestation	estimated 36 weeks gestation +/-14 days
LD: Labor and delivery	date of delivery, -5/+14 days
MPP1: 1 month post-partum	date of delivery + 1 month, +/-15 days
MPP2: 2 months post-partum	date of delivery + 2 months, +/-15 days
MPP3: 3 months post-partum	date of delivery + 3 months, +/-15 days
MPP4: 4 months post-partum	date of delivery + 4 months, -15/+30 days
MPP6: 6 months post-partum	date of delivery + 6 months, -30/+45 days
MPP12: 12 months post-partum	date of delivery + 12 months, +/-45 days

Infant visits:

C0: date of birth	date of birth, -0/+5 days
C1: 1 month of age	date of birth + 1 month, +/-15 days
C2: 2 months of age	date of birth + 2 months, -15/+30 days
C4: 4 months of age	date of birth + 4 months, +/-30 days
C6: 6 months of age	date of birth + 6 months, -30/+45 days
C9: 9 months of age	date of birth + 9 months, +/-45 days
C12: 12 months of age	date of birth + 12 months, +/-45 days

In the event of multiple evaluations in one visit window, prior to enrollment the evaluation closest to enrollment will be used, and after enrollment the evaluation closest in absolute value to the target visit time will be used. If two evaluations are equidistant from the target visit time, the earlier evaluation will be used.

The date of enrollment will be taken from the enrollment date on the 'Declaration of New Enrollment' CRF. This CRF is completed at the M1 visit when the next available Study Identifier (BMxxxx) at site is assigned. The assigning of this identifier indicates randomization.

The date of delivery and date of birth will be taken from the delivered date on the 'Declaration of Delivery/Birth' CRF.

Premature study discontinuation will be categorized as death, loss to follow-up or withdrawn consent from the 'End of Study for Woman' and the 'End of Study for Child' CRFs.

For study visit compliance, the target number of women/infants at each scheduled visit will be calculated as the number of women/infants on-study that have passed the expected visit date given above by 7 days before 4 months post-partum/of age and by 14 days thereafter. For women, the LD visit will be expected if 40 weeks gestation has passed by 7 days before the woman discontinues the study. Woman delivering prior to 37 weeks will not be expected to have a 36 weeks gestational age (M3) visit.

Premature study treatment discontinuation will be defined as discontinuing study treatment >7 days before 60 days post-partum or discontinuing the study >7 days prior to 60 days post-partum if treatment discontinuation date is unknown. The analysis of severe hepatic disease exacerbation or flare defined as SGPT/ALT >300 U/L from study treatment discontinuation will only include women with an SGPT/ALT measurement after study treatment discontinuation.

With the exception of ALT/SGPT, where graded categories for event severity are specified they will be calculated as normal, grade 1, grade 2, grade 3 and grade 4 according to the DAIDS table for grading the severity of adult and pediatric adverse events, version 1.0, December 2004, clarification August 2009. ALT/SGPT will be categorized as >60 to ≤150, >150 to ≤300, and >300 U/L, and >150 to ≤300 U/L will be considered grade 3 and >300 U/L grade 4. Adverse event (AE) analyses will include ICH SAEs and Grade 3/4 adverse events.

The secondary endpoints of occurrence of AEs and severe hepatic disease exacerbation or flare will employ the analysis method specified in the protocol based on the exact binomial distribution and Fisher's exact test as well as sensitivity analysis of time to first occurrence using Kaplan-Meier methods and the log-rank test. For the AE endpoint, time will start at enrollment for women and birth for infants and for women/infants event time will be at their first AE occurrence or censored at their last study visit if no AE occurs. For the severe hepatic disease exacerbation or flare endpoint, time will start at study treatment discontinuation date and event time will be at first flare occurrence or censored at the last SGPT/ALT measurement if no flare occurs.

Version 1 of the C0 visit CRF only required a Ballard score for infants born <37 weeks gestational age based on the best estimate by site clinician or weighing <2500 grams. Therefore, the analysis of premature birth (<37 weeks gestational age) by Ballard score will assume infants ≥37 weeks gestational age based on the best estimate by site clinician and weighing ≥2500 grams completing CRF version 1 are not <37 weeks gestational age by Ballard score.

Z-scores-for-age will be calculated according to WHO standards.

At the 6-month analysis, HBsAg will be tested on infants at 6 months of age, and if positive confirmed by a HBV DNA test. Infants who discontinue the study before 6 months of age will be tested for HBsAg at their last available sample, and if

positive confirmed by a HBV DNA test. At the 12-month analysis, HBsAg will be tested on infants at 9 and 12 months of age in addition, and if positive at 12 months confirmed by a HBV DNA test at 12 months. All infants will be routinely tested for HBV DNA at 9 months of age.

Due to the trial's group sequential design, the primary endpoint will be considered significant if the one-sided p-value is <0.049. The primary analysis will be conducted as a complete case analysis excluding infants without a 6 month endpoint and including infants whose 6 month endpoint is available in their original randomized group, regardless of the duration of study treatment the mother actually received if at least one dose was taken. The visit window for the infants' 6 month HBsAg and HBV DNA measurements will be extended to ≥30 days prior to 6 months to 90 days after (i.e. at <9 months). HBV positive at 6 months of age will be defined as a positive HBsAg test confirmed by detectable HBV DNA. Infants with a negative HBsAg test or positive HBsAg test but undetectable HBV DNA will be considered as HBV negative. HBV DNA detectable will be defined as a quantifiable HBV DNA level above the limit of detection of the assay or a detected but un-quantifiable HBV DNA level below than the limit of detection. The limit of detection will be calculated as the standard detection limit of the assay (e.g. 15 IU/mL) multiplied by the dilution factor. The HBV DNA test may be missing due to, for example, insufficient sample volume, test failure or an error (concomitant HBV antibodies). If the HBV DNA test is missing for any reason other than an error, an infant will be considered HBV positive if the HBsAg test is positive. The primary complete case analysis will be independently programmed by another statistician to verify the result using the HBsAg results dataset (wshep), HBV DNA dataset (hepvl), and the dataset containing enrollment and delivery/birth date (itap_enrolled).

As stated in the protocol, transmission to one or more offspring of a multiple pregnancy will be considered as only one transmission, i.e. infants born from multiple pregnancies will be included in the denominator as representing one (one mother-infant(s) pair) and if one or more are HBV infected it will count as an event. This approach will also be taken for other dichotomous infant endpoints, counting the first event in any infant from a multiple pregnancy. However, descriptions of the infant population, study conduct and continuous infant endpoints (e.g. Z-scores-for-age at 6 and 12 months) will analyze infants from multiple pregnancies separately.

The following sensitivity/secondary supportive analyses on the primary endpoint will be performed:

1. Considering infants from multiple pregnancies separately.
2. Imputing infants' last available HBV infection status as their 6 months status for infants lost to follow-up prior to 6 months.
3. Considering women lost to follow-up prior to delivery and live born infants with missing results at 6 months as failures (i.e. HBV positive).
4. In the complete case population, considering any infant that is HBsAg positive confirmed by detectable HBV DNA at 6, 9 or 12 months as having a HBV infection (12-month analysis only).
5. If there is a baseline imbalance of ≥1 $\log_{10}$ IU in HBV DNA load between randomized arms, exact logistic regression to compare HBV infection status at 6 months of age in the complete-case population between randomized arms with and without adjustment for HBV DNA load will be performed.

Limited validation by code review occurs for the iTAP clinical trial (see CBAR SOP exemption #28705 for details).

3. Pregnant Women/Mothers

3.1 Accrual and Eligibility Violations

Table: Number of pregnant women enrolled, by month and by site.

List or Text: Description of pregnant women randomized out of sequence order.

List: Description of women (and their infants) randomized and later found ineligible as indicated on the 'Protocol Deviation for mother' CRF, and inclusion/exclusion from the analysis following blind review by the study chair.

3.2 Baseline Characteristics

Table: median, 25th and 75th percentiles, min, max, categories if given: age at enrollment (years) (categories: <25, ≥25-<35, ≥35), sonogram information available (categories: results available, not available, not performed), best estimate of gestational age at enrollment by site clinician based on last menstrual period (LMP) and sonogram (weeks), height (cm),

weight (kg) pre-pregnancy and at enrollment, BMI pre-pregnancy (<18.5, 18.5-24.9, 25-29.9, ≥30), HBV DNA load (log_{10} IU) (below limit of detection, limit of detection to ≤5, >5 - ≤7, >7).

3.3 Study Status

Table: Number (%): Women discontinuing the study before delivery, between delivery and 2 months postpartum visit, between 2 and 6 months postpartum visit, women discontinuing the study and on-study between 6 and 12 months post-partum visits, and woman who have reached 12 month postpartum visit (completed study). Sub-categories death, loss to follow-up and withdrawn consent will be given for women prematurely discontinuing the study, and those still on-study between 6 and 12 months will be given for the 6-month analysis.

List: Reasons for death, loss to follow-up or withdrawn consent

Table: median, 10^{th}, 25^{th}, 75^{th}, 90^{th} percentiles, min, max: weeks from M1 visit to last study visit (for women on-study or completed study).

3.4 Compliance to Follow-up

Table: target number of on-study women at each scheduled follow-up visits, actual number (%) of women with scheduled follow-up visit strictly within the visit window defined in section 2, actual gestational age at scheduled follow-up visits

3.5 Delivery Characteristics

Table: Number (%): births (single, multiple), delivery outcome (live-birth, stillbirth intrapartum, stillbirth antepartum), mode of delivery (vaginal, C-section), premature according to WHO definition (<37 weeks after LMP), C-section before labor (yes, no)

Table: median, 25th and 75th percentiles, min, max, categories: best estimate of gestational age at delivery by the site clinician based on last menstrual period (LMP) and sonogram (≥32-<35, ≥35-<37, ≥37), time from onset of labor to delivery (hours) (<3, 3-<6, 6-<9, 9-<12, ≥12), time from rupture of membranes to delivery (hours) (<3, 3-<6, 6-<9, 9-<12, ≥12)

3.6 Study Treatment Summaries

Table: Number (%): Days from enrollment to study treatment dispensation (0, 1, 2, 3, >3 with reasons), percentage compliance to study treatment from pill count at scheduled visits (<80% poor, 80-95% good, >95% excellent).

Table: median, 25th and 75th percentiles, min, max, categories: dispensed study treatment (weeks) (<4, 4-<8, 8-<12, 12-<16, 16-<20, ≥20), dispensed study treatment during pregnancy (weeks) (<4, 4-<8, 8-<12, ≥12), duration of study treatment at completion (weeks) (<4, 4-<8, 8-<12, 12-<16, 16-<20, ≥20), duration of study treatment post-partum (weeks) (<4, 4-<8, 8-<12, ≥12).

Table: Number (%): Women completed study treatment and prematurely discontinued study treatment. Sub-categories for women with ALT measurements after study treatment discontinuation will be given.

List or Text: Description of randomized study treatment un-blinding and dispensation errors.

3.7 Safety Analysis

3.7.1 ALT and Severe Hepatic Disease Exacerbations or Flare

Table: Number (%) with SGPT/ALT ever >60 U/L at a scheduled visit, first schedule visit >60 U/L, number of occurrences >60 U/L, all scheduled visits with SGPT/ALT >60 U/L, SGPT/ALT >60-≤150, >150-≤300, >300 U/L at initial rise, number (%) with confirmation test within 3 days categories (≤60, ≥60-≤150, >150-≤300, >300 U/L), number (%) with re-test 2 weeks later and categories (≤60, ≥60-≤150, >150-≤300, >300 U/L) by confirmed ≥60-≤150 or >150 U/L, number of women that might have considered re-start of study treatment based on protocol criteria

Figure: SGPT/ALT over time for women with severe hepatic disease exacerbation or flare defined as SGPT/ALT >300 U/L at any time during the study.

Table: Number (%), 95% exact binomial confidence interval in each arm: severe hepatic disease exacerbation or flare defined as ALT >300 U/L from study treatment discontinuation up to 6 months postpartum at the 6-month analysis and 12 months postpartum at the 12-month analysis. Comparison between treatment arms by Fisher's exact test (p-value).

Figure: Kaplan-Meier curve of time to first ALT >300 U/L from study treatment discontinuation including follow-up to 6 months for the 6-month analysis and 12 months for the 12-month analysis. Comparison between treatment arms by the Log-rank test (p-value).

3.7.2 Adverse Events

Table: Number (%) of women with any AE prior/at to 6 months for the 6-month analysis and up to 12 months for the 12-month analysis, 95% exact binomial confidence interval in each arm, and comparison between arms by the Fisher's exact test (p-value). MedDRA primary system organ class with sub-categorization by preferred term will be used to describe AEs.

Figure: Kaplan-Meier curve of time to first AE from enrollment to 6 months for the 6-month analysis and 12 months for the 12-month analysis. Comparison between treatment arms by the Log-rank test (p-value).

List: AEs with text description, grade, outcome, study week, MedDRA primary system organ class, MedDRA preferred term, if SAE: report type, other clinically significant event. This list will be reviewed for any data discrepancies by the study chair blinded to randomized arm prior to freezing the database for the 6-month report.

3.7.3 Hematology and Biochemistry at Scheduled Visits

Figures: jitter plots with median, 25th and 75th percentiles and grade 3 and 4 (if specified) indicated: hemoglobin (g/dL) (graded), hematocrit (%), white blood cells (cells/mm^3) (graded), absolute neutrophils (cells/mm^3) (graded), platelets (per mm^3) (graded), serum creatinine (mg/dL) (graded), Cockcroft-Gault creatinine clearance (ml/min), phosphorus (mg/dL) (graded), SGPT/ALT (U/L) (graded), total bilirubin (mg/dL) (graded), SGOT (U/L) (graded), alkaline phospatase (IU/L) (graded), albumin (g/dL) (graded)

Figures: Categories with number (%) indicated: glycosuria (≤1+, 2-3+, 4+), proteinuria (graded)

4. Children

4.1 Delivery Characteristics

Table: Number (%): sex (male/female), APGAR score at 1, 5 and 10 minutes (0-3, 4-6, 7-10), any congenital malformation (no, yes)

Table: median, 25th and 75th percentiles, min, max, categories if given: gestational age at birth according to Ballard exam (weeks) (<32, 32-<37, ≥37).

Table: Number (%) of mother-infant(s) pairs and 95% exact binomial confidence interval in each arm: premature deliveries (birth before 37 weeks of gestational age assessed by Ballard Score) and comparison between arms by Fisher's exact test (p-value).

4.2 Study Status

Table: Number (%): total births (multiple birth details), infants prematurely discontinuing the study before 6 months of age, infants between 6 and 12 months of age, reached 12 months of age (completed study). Sub-categories death, loss to follow-up and withdrawn consent will be given for infants prematurely discontinuing the study, and those still on-study between 6 and 12 months of age will be given at the 6-month analysis.

List: Reasons for death, loss to follow-up or withdrawn consent

Table: median, 10^{th}, 25^{th}, 75^{th}, 90^{th} percentiles, min, max: weeks from C0 visit (immediately after birth) to last study visit (infants on-study or completed study)

4.3 Compliance to Follow-up

Table: target number of on-study infants at each scheduled follow-up visit, actual number (%) of infants with scheduled follow-up visit strictly within the visit window defined in section 2, actual age at scheduled follow-up visits

4.4 HBV Vaccine and HB Immunoglobulin (HBIg)

Table: median, 25th and 75th percentiles, min, max, categories: duration from birth to HBV vaccine dosing (hours) (<1, 1-2, 2-3, 3-4, >4), duration from birth to HBIg dosing (hours) (<1, 1-2, 2-3, 3-4, >4)

Table: Compliance to HBIg and HBV vaccine, target number of infants at each visit, actual number (%) of infants at scheduled visits, number (%) with (<3, 3, 4, 5, >5) HBV vaccines.

4.5 Safety Analysis

4.5.1 Growth

Figures: jitter plots with median, 25th and 75th percentiles indicated: height (cm), weight (grams) and HC (cm) at scheduled visits up to 6 months for the 6-month analysis and up to 12 months for the 12-month analysis.

Figures: jitter plots with mean and 95% confidence interval using the t-distribution indicated: WHO Z-scores-for-age of weight, height and HC at scheduled visits, comparison between arms by the two sample t-test (p-value) at 6 months for the 6-months analysis and at 6 and 12 months for the 12-month analysis.

4.5.2 Assessment of Mitochondrial Dysfunction at 6 and 12 months

Table: neurological signs, other organ signs: number (%) major, minor according to the 'Mitochondrial dysfunction check list' CRF at 6 months for the 6-months analysis and at 6 and 12 months for the 12-month analysis.

4.5.3 Adverse Events

Table: Number (%) of mother-infant(s) pairs with any AE prior/at to 6 months for the 6-month analysis and up to 12 months for the 12-month analysis, 95% exact binomial confidence interval in each arm, and comparison between arms by the Fisher's exact test (p-value). MedDRA primary system organ class with sub-categorization by preferred term will be used to describe AEs.

Figure: Kaplan-Meier curve of time to first AE from birth including follow-up to 6 months for the 6-month analysis and to 12 months for the 12-month analysis. Comparison between treatment arms by the Log-rank test (p-value).

List: AEs with text description, grade, outcome, study week, MedDRA primary system organ class, MedDRA preferred term, if SAE: report type, other clinically significant event. This list will be reviewed for any data discrepancies by the study chair blinded to randomized arm prior to freezing the database for the 6-month report.

4.5.4 Hematology and Biochemistry at Scheduled Visits

Figures: jitter plots with median, 25th and 75th percentiles and grade 3 and 4 (if specified) indicated: hemoglobin (g/dL) (graded), hematocrit (%), white blood cells (cells/mm^3) (graded), absolute neutrophils (cells/mm^3) (graded), absolute lymphocytes (cells/mm^3), platelets (per mm^3) (graded), serum creatinine (mg/dL) (graded), phosphorus (mg/dL) (graded), SGPT/ALT (U/L) (graded), calcium (mg/dL) (graded)

4.6 HBV infection

4.6.1 HBV Infection Status

Table: Number with HBsAg test at 6 months of age, number (%) and description of multiple pregnancies counted as one mother-infant(s) pair, number (%) HBsAg (positive negative), number with HBV DNA test at 6 months of age, number (%) HBV DNA (detectable, undetectable), number (%) limit of HBV DNA detection (e.g. 15, 15x2, 15x3 IU/mL), number with HBV infection status at 6 months of age, number (%) HBV (positive, negative), 95% confidence interval in each arm based on exact binomial distribution, and comparison between arms with a one-sided Fisher's exact test (p-value).

Table: Number of infants with HBV infection status at 6 months of age counting infants from multiple pregnancies separately, number (%) HBV (positive, negative), 95% confidence interval in each arm based on the exact binomial distribution, and comparison between arms with a one-sided Fisher's exact test (p-value).

Table: Number of infants with HBV infection status at 6 months of age or prior to 6 months if prematurely discontinued the study, number (%) HBV (positive, negative) imputing the last available HBV infection status as their 6 months status for those who prematurely discontinued the study prior to 6 months, 95% confidence interval in each arm based on the exact binomial distribution, and comparison between arms with a one-sided Fisher's exact test (p-value).

Table: Number of infants expected to have HBV infection status at 6 months of age based on the women's enrollment date (excluding stillbirths), number (%) HBV (positive, negative) imputing missing results as failures (i.e. HBV positive), 95% confidence interval in each arm based on the exact binomial distribution, and comparison between arms with a one-sided Fisher's exact test (p-value).

Table: Number of infants HBsAg positive confirmed by detectable HBV DNA result at 6, 9 or 12 months of age, 95% confidence interval in each arm based on the exact binomial distribution, and comparison between arms with a one-sided Fisher's exact test (p-value) (12-month analysis only)

Table: Number of infants with detectable HBV DNA result at 9 months of age, 95% confidence interval in each arm based on the exact binomial distribution, and comparison between arms with a one-sided Fisher's exact test (p-value) (12-month analysis only)

Table: Number of infants with sero-protection (anti-HBs antibodies >10 IU/L) at 6 months of age, 95% confidence interval in each arm based on the exact binomial distribution, and comparison between arms with a one-sided Fisher's exact test (p-value). Number of infants with sero-protection (anti-HBs antibodies >10 IU/L) at 2, 4, 9 and 12 months will also be summarized (2 and 4 months at the 6-month analysis, and 9 and 12 months as the 12-month analysis only).

Table: If a baseline imbalance of ≥1 $\log_{10}$ IU in HBV DNA load between randomized arms exists, the odds ratio, 95% confidence interval and p-value for difference between arms for HBV infection status at 6 months of age from the exact logistic regression models unadjusted and adjusted for HBV DNA load will be given.

Table: Median, 25th and 75th percentiles, min, max, mean, standard deviation, categories: HBV DNA load at delivery ($\log_{10}$ IU) (below limit of detection, limit of detection to ≤5, >5 - ≤7, >7). Comparison between arms by the two-sample t-test (p-value) if ≤10% of the values in both arms are below the limit of detection, and by the Wilcoxon rank-sum test (p-value) if >10% of the values in either arm are below the limit of detection.