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Title:	Meta-Analysis Plan for Study Number 201182, GSK1550188, SLE, Pregnancy Analysis

Compound Number: GSK1550188

Effective Date: [29-May-2015]

Description: Evaluate the outcome data for systemic lupus erythematosus (SLE) subjects who became pregnant while exposed to belimumab during phase 2 – 4 clinical trials as well as spontaneous pregnancies reported in patients who were receiving marketed belimumab, and correlate the outcomes with relevant confounders in the SLE population.

Subject: SLE pregnancy, belimumab

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ABBREVIATIONS

ACR	American College of Rheumatology
AE	adverse event
BPR	Belimumab Pregnancy Registry
CDC	Centers for Disease Control and Prevention
CEDD	corrected estimated date of delivery
CI	confidence interval
CMG	Case Management Group
EDD	estimated date of delivery
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
HCP	health care provider
LMP	last menstrual period
LTF	lost to follow-up
PGA	Physician Global Assessment
SAE	severe adverse event
SDI	SLICC/ACR Damage Index
SGA	small for gestational age
SLE	systemic lupus erythematosus
TLF	table, listing, figure
WHO	World Health Organization

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1. Introduction:

Systemic Lupus Erythematosis (SLE) is a chronic and progressive autoimmune disease typically requiring lifelong treatment. Pregnancy in women with SLE is associated with significant maternal and foetal morbidity, including spontaneous abortion, pre-eclampsia, intrauterine growth restriction, foetal death, and pre-term delivery [Molad, 2005]. More individuals with SLE are women than men; the female-to-male ratio in the childbearing years has been reported to be as high as 12:1 [Danchenko, 2006]. Individuals with SLE testing positive for anti-cardiolipin (aCL) antibodies are at the highest risk of spontaneous abortions and poor foetal outcome [Cortez Hernandez, 2002] with a reported foetal loss rate in the literature of between 15-25% [Rahman, 1998; Andrade, 2008; Yasmeen, 2001; Clowse, 2005]. The combination of high disease activity, with low complement and/or anti-ds DNA autoantibodies, during the second trimester increased the risk of fetal loss and preterm delivery pregnancy outcomes [Clowse 2011].

Belimumab is a human immunoglobulin-Gγ monoclonal antibody that inhibits the biologic activity of soluble B-lymphocyte stimulator [BLyS]. In the BLISS clinical trials, subjects with autoantibody-positive SLE were randomized to treatment with placebo or belimumab 1mg/kg or 10mg/kg, while also receiving standard SLE therapy. The SLE Responder Index (SRI) response rate at week 52 was significantly improved in patients treated with belimumab compared with placebo [Navarra 2009].

There are no adequate, well-controlled studies of the use of belimumab in pregnant women or published data reporting pregnancy outcomes for women with SLE who were exposed to belimumab in the preconception period or during pregnancy. It is known that Belimumab crosses the placenta in pregnant monkeys in concentrations that result in reversible pharmacologic activity in fetuses and newborn monkeys. Overall human IgG is known to cross the placental barrier and belimumab may cause a reduction in the number of fetal B cells. Secreted concentrations into breast milk were low in two female adult monkeys [Auyeung-Kim 2009].

Belimumab has an FDA class C pregnancy category. Human pregnancy data is available from GSK SLE phase II to III clinical trials on belimumab [Powell, 2014]. In these trials, women of childbearing potential with SLE were required to either be abstinent or use birth control and in the event of pregnancy, subjects were withdrawn from the study. Nonetheless, there were 95 pregnancies in these studies as of 14 March 2014. Of the 83 pregnancies whose outcome was known, 24% underwent elective termination of pregnancy (none due to anomaly), 28% had spontaneous miscarriage, 2.4% had stillbirth, and 42% had live birth without congenital anomaly. Three (3.6%) of the live births resulted in a congenital anomaly. The long-term effects, if any, on infants exposed in to belimumab in utero are unknown. Healthcare providers and patients need belimumab pregnancy-related data to make informed decisions regarding reproductive health. In the published pregnancy outcomes to date, belimumab treatment was discontinued when the pregnancy was recognized. However, in some ongoing clinical trials, it is no longer

mandatory to discontinue belimumab treatment in pregnancy. The decision is left to the discretion of the treating physician.

Purpose

To evaluate maternal, fetal and infant outcome data for subjects with systemic lupus erythematosus (SLE) who were exposed to belimumab during pregnancy

2.1. Objective(s)

The primary objective is to determine if there is an increase in birth defects in infants born to women with SLE who were exposed to belimumab during pregnancy. A full listing of trials appears in Section 11.1.

Secondary outcomes include adverse maternal and infant outcomes, e.g. spontaneous miscarriage, preterm birth and still birth.

2.2. Endpoint(s)

2.2.1. The primary endpoint is:

The overall frequency (n, %) of birth defects per live births for unblinded reports in women with SLE who received belimumb during pregnancy.

2.2.2. Secondary endpoints include:

- The study population will include all subjects from unblinded clinical studies, spontaneous events and open-label or observational post marketing studies who had a pregnancy reported while receiving belimumab
- Types of birth defects among live births: Chromosomal, cardiovascular, musculoskeletal to include limb defects, urogenital, neural tube defects, gastrointestinal, and other structural defects (including cleft lip and cleft palate)
- Pregnancy outcomes(per all pregnancies)
    - Rates of spontaneous miscarriage
    - Rates of births including live term and pre-term births as well as rates of stillbirths
    - Rates of elective pregnancy termination

3. RELATIONSHIP BETWEEN SUBGROUPS AND DESCRIBED OUTCOMES.DATA SOURCES/STUDIES INCLUDED

Data will come from the following sources:

- GSK safety reporting database (OCEANS/ Argus) including data fields and narrative comments.

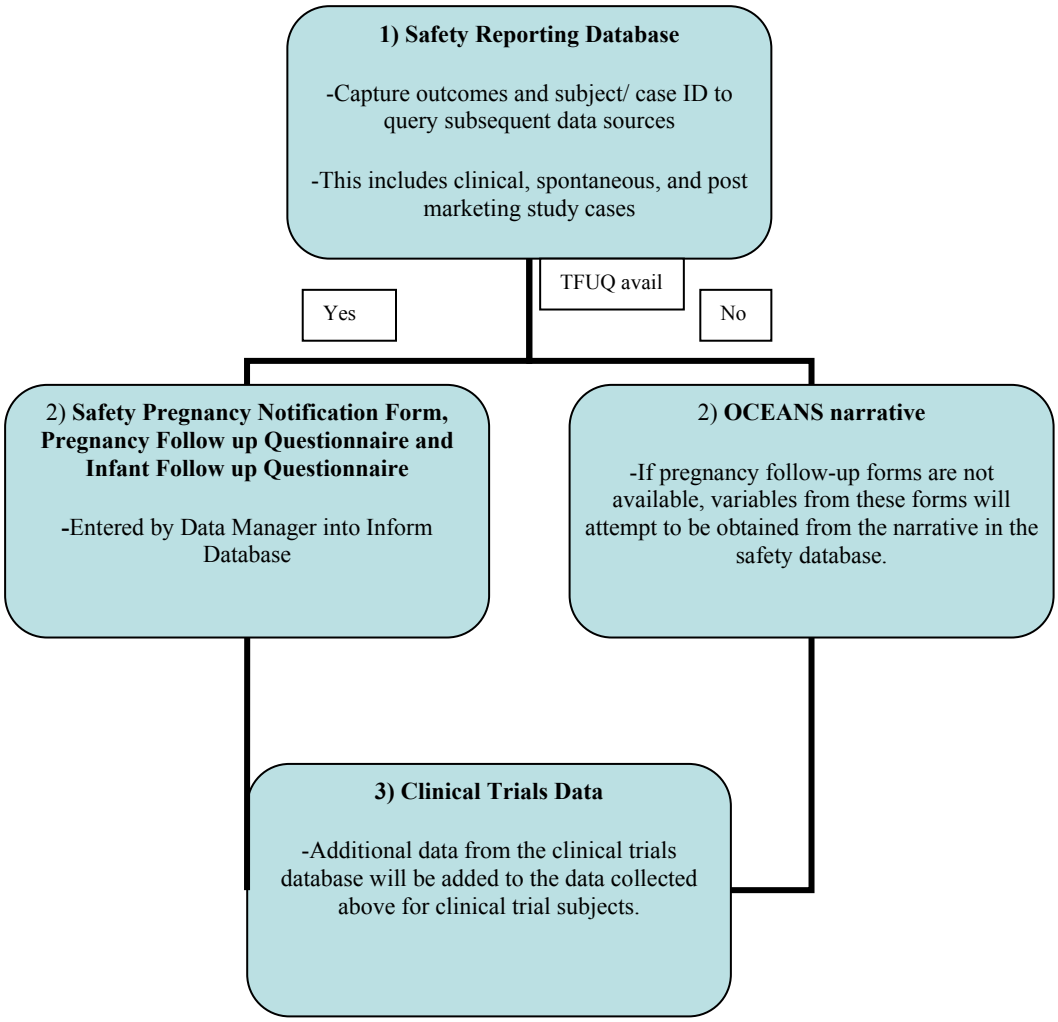
- Pregnancy Notification Form, Pregnancy Follow up Questionnaire and Infant Follow up Questionnaire.

- Clinical Trial Data in which pregnancy occurred.

A full list of the clinical trials is given in Section 11.1. This list may be updated as additional pregnancies occur. Variables to be extracted from each specified data source are listed in Section X.

Individual pregnancies will be identified from the safety reporting data base, and appropriate data will be collected as outlined in Figure 1. Clinical trial data are collected from all of these specified data sources while spontaneous and post marketing data will come only from the safety database and follow up questionnaires.

Figure 1 Summary of Data Sources



4. PLANNED ANALYSES

All data will be summarized using descriptive statistics. Continuous variables will be summarized by number of participants, mean, standard deviation (SD), median, lower quartile, upper quartile, minimum and maximum unless otherwise stated. Categorical variables will be summarized by number and percentage in each category. Missing data will be displayed as a separate category where appropriate. The denominator for all percentages will reflect the number of participants within the cohort, unless otherwise stated (e.g. excluding lost to follow-up (LTF)). Section 11.1 lists all planned summaries for the study. All data analyses and reporting will be performed using SAS Version 9.3 [SAS Institute Inc., 2011].

Missing Dates

Partial or missing dates for exposures or medical conditions of interest will be presented in listing format unaltered with the missing information displayed as reported. The frequency of birth defects based on timing of belimumab exposure is of interest. As a conservative estimate of birth defects, a missing date will be imputed to correspond to the first trimester of exposure.

Estimating last menstrual period (LMP) or conception date is integral in understanding pregnancy exposure and calculating the duration of drug exposure into pregnancy. LMP will be calculated with priority given to Estimated Date of Delivery (EDD – 280). If EDD is unavailable from the safety database field, safety database narrative, or Pregnancy Notification Form, then LMP will be extrapolated from the most relevant data available in the narrative by an appropriate healthcare professional. If an inconsistent value is given from the three compared sources, an executive decision will be made by Medical Monitor, SERM physician or appropriate healthcare professional by applying medical judgment to the available data. If date of conception or LMP is given in month/ year format, day will be imputed as the midpoint of the specific month. For example an estimated LMP of June 2010 will be imputed as June, 15 2010.

If maternal date if birth (DOB) is given as birth year, birth date will be imputed as 1-Jan-YEAR. In the interest of understanding advanced maternal age, this is a conservative estimate to estimate advance maternal age.

5. ANALYSIS POPULATION

The primary population will include all subjects from belimumab clinical trials who had an adverse event (AE) of pregnancy while receiving study drug plus standard SLE care. A full listing of clinical trials is given in Section 11.1.

The secondary population will include the primary population as well as all post-marketing spontaneous reports of pregnancy while the subject was receiving commercial belimumab.

6. TREATMENT COMPARISONS

For unblinded clinical studies, spontaneous events and open-label or observational post marketing studies the primary treatment comparison will be across belimumab exposure groups based on the last dose received prior to or during pregnancy. Timing of exposure will be calculated by adding 100 days (five elimination half-lives of belimumab) to the last belimumab dose. Comparison groups will be defined by cumulative exposure (e.g., if she was $29^{6/7}$ weeks at the last belimumab dose + 100 days, the pregnancy will be in the category of ≥27 weeks) as prior to pregnancy, 0 - $12^{6/7}$ weeks gestation, $13^{0/7}$ - $26^{6/7}$ weeks gestation, ≥$27^{0/7}$ weeks gestation. If a patient is started on belimumab during pregnancy such that a cumulative exposure is not applicable, a subgroup will be incorporated as needed. Analyses will be pooled and conducted across dosage and method of drug exposure (intravenous (IV), subcutaneous (SC)).

7. DATA HANDLING CONVENTIONS

7.1. Premature Withdrawal and Missing Data

Subjects who do not have documented pregnancy outcomes and are considered lost to follow up (LTF) will not be included in analyses, but will be documented in descriptive reporting.

7.2. Derived and Transformed Data

Gestational Age will be calculated based on LMP specification and date of delivery or outcome. (Date of delivery – LMP)/7 will be used as calculation and will be reconciled with gestation age reported in the OCEANS Narrative or Pregnancy Notification Form

Exposure Trimester will be calculated using LMP and defined calendar cut points based on standard definition of trimester. As previously noted, timing of exposure will be assessed as 100 days after last exposure. Comparison groups will be defined by cumulative exposure as prior to pregnancy, 0- - $12^{6/7}$ weeks gestation, $13^{0/7}$ - $26^{6/7}$ weeks gestation, ≥ $27^{0/7}$ weeks gestation. From this categorization trimester of exposure will be defined as 0 (prior to pregnancy), 1st trimester (0 $^{1/7}$ – $12^{6/7}$ weeks gestation), 2nd trimester ($13^{0/7}$ - $26^{6/7}$ weeks gestation), and 3rd trimester (≥ $27^{0/7}$ weeks gestation).

8. ANALYSES

8.1. Analyses will be conducted on unblinded clinical studies, spontaneous events and open-label or observational post marketing studies.Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively. Demographic variables of interest include: participant age, geographic region of study and baseline disease severity. Age will also be summarized categorically using by less

than 35 years or ≥ 35 years of age based on age at estimated LMP. For available obstetrical history information, outcomes will be summarized with frequencies of previous pregnancy-related conditions. Counts and percentages of the subgroup responses will be displayed in the demographics and baseline characteristic tables for gravidity, parity, number of term and preterm live births, still births, elective terminations and spontaneous miscarriages.

8.2. Belimumab Dose

For all clinical trial cases, the level of exposure will be categorized as 1mg/kg IV, 4mg/kg IV, 10mg/kg IV or SC by the dose most proximal to the pregnancy onset.

8.3. SLE History at Baseline

SLE diagnosis details will be displayed in a summary table for all baseline assessments, e.g. age at diagnosis, number of the ACR criteria met, Physician Global Assessment (PGA) score, SLICC/ACR Damage Index (SDI) score, and laboratory parameters.

8.4. Medical History

Medical history will be summarized. For each condition, the count and percentage will be provided overall and 1) at baseline (prior to conception); 2) at the time the pregnancy is initially reported and 3) ongoing during pregnancy.

8.5. SLE Related Outcomes

Laboratory parameters, including autoantibody status, complement levels, platelet count, serum creatinine, and urine protein values (when reported) may include the most recent laboratory results prior to conception, at the time the pregnancy is initially reported, at end of 2nd trimester follow-up, and at the time of pregnancy outcome. For the continuous parameters, descriptive statistics will be displayed at each time point as well as for the change values at each time point compared to the most recent result prior to conception.

The PGA and/or SELENA SLEDAI scores when available will be summarized as other continuous variables: reporting the mean, standard deviation, median, minimum and maximum value, and the first and third quartile values.

All previously defined demographic and baseline characteristics will include the LTF subgroup and unblinded subjects and be stratified by study type (clinical, spontaneous, post marketing).

8.6. Subgroup Analyses

Table 1 below defines the subgroups of interest that will be used for additional summaries of the primary and secondary outcomes.

Table 1 Subgroups

Subgroup	Definition	Outcomes
Lost to Follow-up (Pregnancy)	Participants with no pregnancy outcome or birth data	Medical History, Maternal Age at LMP, SLE History, Geographic Region
Clinical[1] and Spontaneous cases	Participants grouped by clinical pregnancy and spontaneous event (including spontaneous report and post marketing surveillance).	Primary and Secondary Endpoints
Level of Belimumab Exposure	Defined using exposure dosage proximal to pregnancy start.	Primary and Secondary Endpoints in clinical subjects only
Maternal Age	<35 years and >=35 years based on age at estimated LMP	Primary and Secondary Endpoints
Geographical Region	North America, Europe, Rest of World (Asia, South America, Mexico)	Primary and Secondary Endpoints
Disease Severity 1	PGA >= 2 before pregnancy	Primary and Secondary Endpoints
Disease Severity 2	SDI > 1 before pregnancy	Primary and Secondary Endpoints
Immunosuppressants / Concomitant Medications	Concomitant medications and potential groupings of steroids, antimalarials and immunosuppressants (i.e., Steroids only, antimalarial only, steroids + antimalarials, Steroids + antimalarials +immunosuppressants, and all of their combinations). These will be reviewed by the medical monitor or healthcare professional for accuracy	Primary and Secondary Endpoints
Pregnancy Drug Category D or X	Any concomitant medication which is in categories D or X for pregnancy safety. Reviewed by medical monitor for accuracy	Primary and Secondary Endpoints

[1]Clinical and Spontaneous report will be compared to the BPR analysis, but BPR subjects will be excluded from these analyses.

All outcome data will be stratified by the trimester of exposure to belimumab at 5 half-lives (100 days) after last dose. Categories for timing of belimumab exposure are as follows:

- Prior to conception
- 1st trimester
- 2nd trimester
- 3rd trimester

All data summaries will include treatment comparisons of the cumulative timing of belimumab exposure.

8.7. Exposures and Outcomes

8.7.1. Belimumab

Each exposure to belimumab during the time period of interest is captured for all subjects. The time period of interest includes the four months prior to conception through the entire pregnancy duration. These data, including dose, route, and date of treatment will be reported in a listing.

Subjects with exposure in more than one time point will be counted for each of the appropriate time points. Additionally data will be stratified by dose prior to delivery and delivery method (IV, SC)

8.7.2. Primary Endpoint: Birth Defects

Each birth defect will be classified as known chromosomal or syndromic, or specific organ system defect (e.g. cardiovascular, musculoskeletal to include limb defects, urogenital, neural tube defects, gastrointestinal, and other structural defects (including cleft lip and cleft palate)). The prevalence of birth defects will be calculated as the percentage of total birth defects total and by organ system from the total number of live births n the study population and then also stratified by subgroup. Fetal losses with reported birth defects occurring at or after 20 weeks gestation will be included in the numerator of the estimate of risk for birth defects to increase sensitivity.

Birth defect and pregnancy outcome prevalence rates will be calculated. Confidence intervals for birth defect prevalence will be calculated under the exact binomial distribution assumption. A summary table will include birth defect prevalence rates and 95% confidence intervals. Results will also be stratified by timing of exposure and subgroup as previously defined.

8.7.3. Secondary Endpoints: Pregnancy Outcomes

Each pregnancy outcome is defined as one of the following: live birth, neonatal death, stillbirth, spontaneous miscarriage, elective termination, ectopic pregnancy, and molar pregnancy. Prevalence rates and 95% confidence intervals will be summarized for the primary and secondary pregnancy outcomes.

Because the prevalence of preterm birth is elevated in multiple gestations, these cases will be excluded or stratified in the analysis of preterm birth outcomes. In all other pregnancy outcome analysis multiples will be included independently in analysis.

All pregnancy outcomes will be summarized by the following subgroups:

- Maternal Age
- Region
- PGA Score (≥2)

- SDI (>1)(
- Concomitant Medications and Pregnancy Drug Category D or X

Result will also be presented by timing of belimumab exposure for the overall summaries and within each subgroup.

9. INTERIM ANALYSES

Interim analysis will be conducted annually to coincide with the Belimumab Pregnancy Registry (BPR) scientific advisory committee meetings. Each interim analysis will be based on cumulative data of the registry database as of a prospectively-defined cut-off date.

The first database lock will coincide with the Annual Safety Report on clinical trials of belimumab with AE events of pregnancy on or before March 8th, 2014. This report will include all of the discussed analysis but will only include clinical cases which are not LTF. Subsequent analysis will include LTF and spontaneous pregnancy events.

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11. APPENDIX

11.1. List of Trials

Studies included are: BEL110751, BEL110752, BEL112232, BEL112233, BEL112234, BEL112341, BEL113750, BEL114054, BEL114055, BEL114243, BEL114333, BEL114424, BEL114448, BEL115123, BEL115466, BEL115467, BEL115470, BEL115471, BEL116119, BEL116472, HGS1006-C1058, LBRA01, LBRA99, LBSL01_M, LBSL01_S, LBSL02, LBSL99.

Subjects in the study BEL112341, BEL113750, BEL114054, BEL115123, BEL115466, BEL115467 and BEL115471 are currently blinded. For BEL112341, BEL113750 and BEL115471, 66.6% of subjects are randomly assigned to the Belimumab group and 33.3% of subjects are randomly assigned to the Placebo group. For BEL114054, BEL114424, BEL115123, BEL115466 and BEL115467, subjects are randomly assigned in 1:1 ratio.

11.2. Table of Contents for Data Displays

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Table 16	Summary of Disease Severity Descriptive Statistics

11.3. Data Display Specifications

General

In general, summaries of clinical data will follow the appropriate IDSL standard. All tables, listings, and figures (TLF) will be produced in landscape format with font size 10.

11.4. Table Shells

Excel spreadsheets

TABLES FOR THE PRIMARY ENDPOINT BIRTH DEFECT

Table 1.A Primary endpoint birth defect overall prevalence and clinical study descriptions (total number of births = N)												
	Overall Birth Defect Prevalence		Advanced Maternal Age >=35 (at conception or delivery)		Advanced Maternal Age < 35 (at conception or delivery)		Geographic Region: North America		Geographic Region: Europe		Geographic Region:Other[1]	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
Any Exposure	`											
[1] Other geographic region includes Asia, South America and Mexico Groups are defined by cumulative exposure through pregnancy(SEE RAP)												

Table 1.B Primary Endpoint Birth defect by Beli dose (Total Number of births = N)												
	Total Births		1mg/kg		4 mg/kg		10 mg/kg		SC		Any Exposure	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
FOOTNOTE PLACEHOLDER												

Table 1.C Primary Endpoint Birth defect by disease severity (Total Number of births = N)										
	Total Births		PGA >=2 before pregnancy		PGA < 2 before pregnancy		SDI > 1 before pregnancy		SDI <= 1 before pregnancy	
	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure										
>0 - 12 (6/7) week Tri Beli Exposure										
13 - 26 (6/7) weeks Tri Beli Exposure										
>27weeks - delivery Trimester Beli exposure										
Any Exposure	`								`	

Table 1.D Primary endpoint birth defect by medication (total number of births = N)																	
	Steroid Use [1]		Antimalarial Use[1]		Immunosuppressant Use[1]		Steroid+ Anti Malarial Use		Steroid+ Immunosuppressant Use		Immunosuppressant+ Anti Malarial Use		Antimalarial + Steroid + Immonossupressant use		Cat D or X Drug[2]		
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
Preconception Beli Exposure																	
>0 - 12 (6/7) week Tri Beli Exposure																	
13 - 26 (6/7) weeks Tri Beli Exposure																	
>27weeks - delivery Trimester Beli																	
Any Exposure	`																
[1] Steroid, Antimalarial, and Immunosuppressant use independently																	
[2]Category D+X drug includes :																	

Table 1.E Seconday Endpoint TYPE OF Birth Defect BY Organ System : (Total Number of births = N)														
	Chromosomal		Cardiovascular		Musculoskeletal		Urogenital		NeuralTube Defect		Gastrointenstinal		Other Structural Defect	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure														
>0 - 12 (6/7) week Tri Beli Exposure														
13 - 26 (6/7) weeks Tri Beli Exposure														
>27weeks - delivery Trimester Beli exposure														
Any Exposure	`													

TABLES FOR THE SECONDARY ENDPOINT CHROMOSOMAL BIRTH DEFECT

Table 2.A Secondary endpoint chromosomal birth defect overall prevalence and clinical study descriptions (total number of births = N)												
	Overall Birth Defect Prevalence		Advanced Maternal Age >=35 (at conception or delivery)		Advanced Maternal Age < 35 (at conception or delivery)		Geographic Region: North America		Geographic Region: Europe		Geographic Region:Other[1]	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
Any Exposure	`											
[1] Other geographic region includes Asia, South America and Mexico Groups are defined by cumulative exposure through pregnancy(SEE RAP)												

Table 2.B Secondary Endpoint chromosomal Birth defect by Beli dose (Total Number of births = N)												
	Total Births		1mg/kg		4 mg/kg		10 mg/kg		SC		Any Exposure	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
FOOTNOTE PLACEHOLDER												

Table 2.C Secondary Endpoint Chromosomal Birth defect by disease severity (Total Number of births = N)										
	Total Births		PGA >=2 before pregnancy		PGA < 2 before pregnancy		SDI > 1 before pregnancy		SDI <= 1 before pregnancy	
	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure										
>0 - 12 (6/7) week Tri Beli Exposure										
13 - 26 (6/7) weeks Tri Beli Exposure										
>27weeks - delivery Trimester Beli exposure										
Any Exposure	`								`	

Table 2.D Secondary endpoint chromosomal birth defect by medication (total number of births = N)																
	Steroid Use [1]		Antimalarial Use[1]		Immunosuppressant Use[1]		Steroid+ Anti Malarial Use		Steroid+ Immunosuppressant Use		Immunosuppressant + Anti Malarial Use		Antimalarial + Steroid + Immonossupressant use		Cat D or X Drug[2]	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure																
>0 - 12 (6/7) week Tri Beli Exposure																
13 - 26 (6/7) weeks Tri Beli Exposure																
>27weeks - delivery Trimester Beli																
Any Exposure	`															
[1] Steroid, Antimalarial, and Immunosuppressant use independently																
[2]Category D+X drug includes :																

TABLES FOR THE SECONDARY ENDPOINT CARDIO BIRTH DEFECT

Table 3.A Secondary endpoint cardio birth defect overall prevalence and clinical study descriptions (total number of births = N)												
	Overall Birth Defect Prevalence		Advanced Maternal Age >=35 (at conception or delivery)		Advanced Maternal Age < 35 (at conception or delivery)		Geographic Region: North America		Geographic Region: Europe		Geographic Region:Other[1]	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
Any Exposure	`											
[1] Other geographic region includes Asia, South America and Mexico Groups are defined by cumulative exposure through pregnancy(SEE RAP)												

Table 3.B Secondary endpoint cardio birth defect by Beli dose (Total Number of births = N)												
	Total Births		1mg/kg		4 mg/kg		10 mg/kg		SC		Any Exposure	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
FOOTNOTE PLACEHOLDER												

Table 3.C Secondary endpoint cardio birth defect by disease severity (Total Number of births = N)										
	Total Births		PGA >=2 before pregnancy		PGA < 2 before pregnancy		SDI > 1 before pregnancy		SDI <= 1 before pregnancy	
	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure										
>0 - 12 (6/7) week Tri Beli Exposure										
13 - 26 (6/7) weeks Tri Beli Exposure										
>27weeks - delivery Trimester Beli exposure										
Any Exposure	`								`	

Table 3.D Secondary endpoint cardio birth defect by medication (total number of births = N)																	
	Steroid Use [1]		Antimalarial Use[1]		Immunosuppressant Use[1]		Steroid+ Anti Malarial Use		Steroid+ Immunosuppressant Use		Immunosuppressant + Anti Malarial Use		Antimalarial + Steroid + Immonossupressant use		Cat D or X Drug[2]		
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
Preconception Beli Exposure																	
>0 - 12 (6/7) week Tri Beli Exposure																	
13 - 26 (6/7) weeks Tri Beli Exposure																	
>27weeks - delivery Trimester Beli																	
Any Exposure	`																
[1] Steroid, Antimalarial, and Immunosuppressant use independently																	
[2]Category D+X drug includes :																	

TABLES FOR THE SECONDARY ENDPOINT MUSCULAR-SKELETAL BIRTH DEFECT

Table 4.A Secondary endpoint muscular birth defect overall prevalence and clinical study descriptions (total number of births = N)												
	Overall Birth Defect Prevalence		Advanced Maternal Age >=35 (at conception or delivery)		Advanced Maternal Age < 35 (at conception or delivery)		Geographic Region: North America		Geographic Region: Europe		Geographic Region:Other[1]	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
Any Exposure	`											
[1] Other geographic region includes Asia, South America and Mexico Groups are defined by cumulative exposure through pregnancy(SEE RAP)												

Table 4.B Secondary endpoint muscular by Beli dose (Total Number of births = N)												
	Total Births		1mg/kg		4 mg/kg		10 mg/kg		SC		Any Exposure	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
FOOTNOTE PLACEHOLDER												

Table 4.C Secondary endpoint muscular by disease severity (Total Number of births = N)										
	Total Births		PGA >=2 before pregnancy		PGA < 2 before pregnancy		SDI > 1 before pregnancy		SDI <= 1 before pregnancy	
	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure										
>0 - 12 (6/7) week Tri Beli Exposure										
13 - 26 (6/7) weeks Tri Beli Exposure										
>27weeks - delivery Trimester Beli exposure										
Any Exposure	`								`	

Table 4.D Secondary endpoint muscular by medication (total number of births = N)																	
	Steroid Use [1]		Antimalarial Use[1]		Immunosuppressant Use[1]		Steroid+ Anti Malarial Use		Steroid+ Immunosuppressant Use		Immunosuppressant+ Anti Malarial Use		Antimalarial + Steroid + Immonossupressant use		Cat D or X Drug[2]		
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
Preconception Beli Exposure																	
>0 - 12 (6/7) week Tri Beli Exposure																	
13 - 26 (6/7) weeks Tri Beli Exposure																	
>27weeks - delivery Trimester Beli																	
Any Exposure	`																
[1] Steroid, Antimalarial, and Immunosuppressant use independently																	
[2]Category D+X drug includes :																	

TABLES FOR THE SECONDARY ENDPOINT UROGENITAL BIRTH DEFECT

Table 5.A Secondary endpoint urogenital birth defect overall prevalence and clinical study descriptions (total number of births = N)												
	Overall Birth Defect Prevalence		Advanced Maternal Age >=35 (at conception or delivery)		Advanced Maternal Age < 35 (at conception or delivery)		Geographic Region: North America		Geographic Region: Europe		Geographic Region:Other[1]	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
Any Exposure	`											
[1] Other geographic region includes Asia, South America and Mexico Groups are defined by cumulative exposure through pregnancy(SEE RAP)												

Table 5.B Secondary endpoint urogenital birth defect by Beli dose (Total Number of births = N)												
	Total Births		1mg/kg		4 mg/kg		10 mg/kg		SC		Any Exposure	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
FOOTNOTE PLACEHOLDER												

Table 5.C Secondary endpoint urogenital birth defect by disease severity (Total Number of births = N)										
	Total Births		PGA >=2 before pregnancy		PGA < 2 before pregnancy		SDI > 1 before pregnancy		SDI <= 1 before pregnancy	
	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure										
>0 - 12 (6/7) week Tri Beli Exposure										
13 - 26 (6/7) weeks Tri Beli Exposure										
>27weeks - delivery Trimester Beli exposure										
Any Exposure	`								`	

Table 5.D Secondary endpoint urogenital birth defect by medication (total number of births = N)																	
	Steroid Use [1]		Antimalarial Use[1]		Immunosuppressant Use[1]		Steroid+ Anti Malarial Use		Steroid+ Immunosuppressant Use		Immunosuppressant + Anti Malarial Use		Antimalarial + Steroid + Immonossupressant use		Cat D or X Drug[2]		
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
Preconception Beli Exposure																	
>0 - 12 (6/7) week Tri Beli Exposure																	
13 - 26 (6/7) weeks Tri Beli Exposure																	
>27weeks - delivery Trimester Beli																	
Any Exposure	`																
[1] Steroid, Antimalarial, and Immunosuppressant use independently																	
[2]Category D+X drug includes :																	

TABLES FOR THE SECONDARY ENDPOINT NEURAL TUBE BIRTH DEFECT

Table 6.A Secondary endpoint neural tube birth defect overall prevalence and clinical study descriptions (total number of births = N)												
	Overall Birth Defect Prevalence		Advanced Maternal Age >=35 (at conception or delivery)		Advanced Maternal Age < 35 (at conception or delivery)		Geographic Region: North America		Geographic Region: Europe		Geographic Region:Other[1]	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
Any Exposure	`											
[1] Other geographic region includes Asia, South America and Mexico Groups are defined by cumulative exposure through pregnancy(SEE RAP)												

Table 6.B Secondary endpoint neural tube birth defect by Beli dose (Total Number of births = N)												
	Total Births		1mg/kg		4 mg/kg		10 mg/kg		SC		Any Exposure	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
FOOTNOTE PLACEHOLDER												

Table 6.C Secondary endpoint neural tube birth defect by disease severity (Total Number of births = N)										
	Total Births		PGA >=2 before pregnancy		PGA < 2 before pregnancy		SDI > 1 before pregnancy		SDI <= 1 before pregnancy	
	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure										
>0 - 12 (6/7) week Tri Beli Exposure										
13 - 26 (6/7) weeks Tri Beli Exposure										
>27weeks - delivery Trimester Beli exposure										
Any Exposure	`								`	

Table 6.D Secondary endpoint neural tube birth defect by medication (total number of births = N)																
	Steroid Use [1]		Antimalarial Use[1]		Immunosuppressant Use[1]		Steroid+ Anti Malarial Use		Steroid+ Immunosuppressant Use		Immunosuppressant+ Anti Malarial Use		Antimalarial + Steroid + Immonossupressant use		Cat D or X Drug[2]	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure																
>0 - 12 (6/7) week Tri Beli Exposure																
13 - 26 (6/7) weeks Tri Beli Exposure																
>27weeks - delivery Trimester Beli																
Any Exposure	`															
[1] Steroid, Antimalarial, and Immunosuppressant use independently																
[2]Category D+X drug includes :																

TABLES FOR THE SECONDARY ENDPOINT GASTROINTESTINAL BIRTH DEFECT

Table 7.A Secondary endpoint gastro birth defect overall prevalence and clinical study descriptions (total number of births = N)												
	Overall Birth Defect Prevalence		Advanced Maternal Age >=35 (at conception or delivery)		Advanced Maternal Age < 35 (at conception or delivery)		Geographic Region: North America		Geographic Region: Europe		Geographic Region:Other[1]	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
Any Exposure	`											
[1] Other geographic region includes Asia, South America and Mexico Groups are defined by cumulative exposure through pregnancy(SEE RAP)												

Table 7.B Secondary endpoint gastro birth defect by Beli dose (Total Number of births = N)												
	Total Births		1mg/kg		4 mg/kg		10 mg/kg		SC		Any Exposure	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
FOOTNOTE PLACEHOLDER												

Table 7.C Secondary endpoint gastro birth defectt by disease severity (Total Number of births = N)										
	Total Births		PGA >=2 before pregnancy		PGA < 2 before pregnancy		SDI > 1 before pregnancy		SDI <= 1 before pregnancy	
	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure										
>0 - 12 (6/7) week Tri Beli Exposure										
13 - 26 (6/7) weeks Tri Beli Exposure										
>27weeks - delivery Trimester Beli exposure										
Any Exposure	`								`	

Table 7.D Secondary endpoint gastro birth defect by medication (total number of births = N)																
	Steroid Use [1]		Antimalarial Use[1]		Immunosuppressant Use[1]		Steroid+ Anti Malarial Use		Steroid+ Immunosuppressant Use		Immunosuppressant + Anti Malarial Use		Antimalarial + Steroid + Immonossupressant use		Cat D or X Drug[2]	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure																
>0 - 12 (6/7) week Tri Beli Exposure																
13 - 26 (6/7) weeks Tri Beli Exposure																
>27weeks - delivery Trimester Beli																
Any Exposure	`															
[1] Steroid, Antimalarial, and Immunosuppressant use independently																
[2]Category D+X drug includes :																

TABLES FOR THE SECONDARY ENDPOINT OTHER BIRTH DEFECT

Table 8.A Secondary endpoint other birth defect overall prevalence and clinical study descriptions (total number of births = N)												
	Overall Birth Defect Prevalence		Advanced Maternal Age >=35 (at conception or delivery)		Advanced Maternal Age < 35 (at conception or delivery)		Geographic Region: North America		Geographic Region: Europe		Geographic Region:Other[1]	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
Any Exposure	`											
[1] Other geographic region includes Asia, South America and Mexico Groups are defined by cumulative exposure through pregnancy(SEE RAP)												

Table 8.B Secondary endpoint other birth defect by Beli dose (Total Number of births = N)												
	Total Births		1mg/kg		4 mg/kg		10 mg/kg		SC		Any Exposure	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
FOOTNOTE PLACEHOLDER												

Table 8.C Secondary endpoint other birth defectt by disease severity (Total Number of births = N)										
	Total Births		PGA >=2 before pregnancy		PGA < 2 before pregnancy		SDI > 1 before pregnancy		SDI <= 1 before pregnancy	
	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure										
>0 - 12 (6/7) week Tri Beli Exposure										
13 - 26 (6/7) weeks Tri Beli Exposure										
>27weeks - delivery Trimester Beli exposure										
Any Exposure	`								`	

Table 8.D Secondary endpoint other birth defect by medication (total number of births = N)																
	Steroid Use [1]		Antimalarial Use[1]		Immunosuppressant Use[1]		Steroid+ Anti Malarial Use		Steroid+ Immunosuppressant Use		Immunosuppressant + Anti Malarial Use		Antimalarial + Steroid + Immonossupressant use		Cat D or X Drug[2]	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure																
>0 - 12 (6/7) week Tri Beli Exposure																
13 - 26 (6/7) weeks Tri Beli Exposure																
>27weeks - delivery Trimester Beli																
Any Exposure	`															
[1] Steroid, Antimalarial, and Immunosuppressant use independently																
[2]Category D+X drug includes :																

TABLES FOR THE SECONDARY ENDPOINT BIRTH OUTCOMES

Table 9. Seconday Endpoint Birth Outcome (Total Number of births = N)												
	Live Births		Preterm Births		Term Births		Spontaneous Miscarriage		Stillbirth		Elective Termination	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
1st Tri Beli Exposure												
2nd Tri Beli Exposure												
3rd Trimester beli exposure												
Any Exposure												

TABLES FOR THE SECONDARY ENDPOINT BIRTH OUTCOMES:LIVE BIRTH

Table 10.A Primary endpoint live birth overall prevalence and clinical study descriptions (total number of births = N)												
	Overall Prevalence		Advanced Maternal Age >=35 (at conception or delivery)		Advanced Maternal Age < 35 (at conception or delivery)		Geographic Region: North America		Geographic Region: Europe		Geographic Region:Other[1]	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
Any Exposure	`											
[1] Other geographic region includes Asia, South America and Mexico Groups are defined by cumulative exposure through pregnancy(SEE RAP)												

Table 10.B Primary endpoint live birth by Beli dose (Total Number of births = N)												
	Total Births		1mg/kg		4 mg/kg		10 mg/kg		SC		Any Exposure	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
FOOTNOTE PLACEHOLDER												

Table 10.C Primary endpoint live birth by disease severity (Total Number of births = N)										
	Total Births		PGA >=2 before pregnancy		PGA < 2 before pregnancy		SDI > 1 before pregnancy		SDI <= 1 before pregnancy	
	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure										
>0 - 12 (6/7) week Tri Beli Exposure										
13 - 26 (6/7) weeks Tri Beli Exposure										
>27weeks - delivery Trimester Beli exposure										
Any Exposure	`								`	

Table 10.D Primary endpoint live birth by medication (total number of births = N)																	
	Steroid Use [1]		Antimalarial Use[1]		Immunosuppressant Use[1]		Steroid+ Anti Malarial Use		Steroid+ Immunosuppressant Use		Immunosuppressant + Anti Malarial Use		Antimalarial + Steroid + Immonossupressant use		Cat D or X Drug[2]		
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
Preconception Beli Exposure																	
>0 - 12 (6/7) week Tri Beli Exposure																	
13 - 26 (6/7) weeks Tri Beli Exposure																	
>27weeks - delivery Trimester Beli																	
Any Exposure	`																
[1] Steroid, Antimalarial, and Immunosuppressant use independently																	
[2]Category D+X drug includes :																	

TABLES FOR THE SECONDARY ENDPOINT BIRTH OUTCOMES:PRETERM BIRTH

Table 11.A Primary endpoint preterm birth overall prevalence and clinical study descriptions (total number of births = N)												
	Overall Prevalence		Advanced Maternal Age >=35 (at conception or delivery)		Advanced Maternal Age < 35 (at conception or delivery)		Geographic Region: North America		Geographic Region: Europe		Geographic Region:Other[1]	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
Any Exposure	`											
[1] Other geographic region includes Asia, South America and Mexico Groups are defined by cumulative exposure through pregnancy(SEE RAP)												

Table 11.B Primary endpoint preterm birth by Beli dose (Total Number of births = N)												
	Total Births		1mg/kg		4 mg/kg		10 mg/kg		SC		Any Exposure	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
FOOTNOTE PLACEHOLDER												

Table 11.C Primary endpoint preterm birth by disease severity (Total Number of births = N)										
	Total Births		PGA >=2 before pregnancy		PGA < 2 before pregnancy		SDI > 1 before pregnancy		SDI <= 1 before pregnancy	
	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure										
>0 - 12 (6/7) week Tri Beli Exposure										
13 - 26 (6/7) weeks Tri Beli Exposure										
>27weeks - delivery Trimester Beli exposure										
Any Exposure	`								`	

Table 11.D Primary endpoint preterm birth by medication (total number of births = N)																
	Steroid Use [1]		Antimalarial Use[1]		Immunosuppressant Use[1]		Steroid+ Anti Malarial Use		Steroid+ Immunosuppressant Use		Immunosuppressant + Anti Malarial Use		Antimalarial + Steroid + Immonossupressant use		Cat D or X Drug[2]	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure																
>0 - 12 (6/7) week Tri Beli Exposure																
13 - 26 (6/7) weeks Tri Beli Exposure																
>27weeks - delivery Trimester Beli																
Any Exposure	`															
[1] Steroid, Antimalarial, and Immunosuppressant use independently																
[2]Category D+X drug includes :																

TABLES FOR THE SECONDARY ENDPOINT BIRTH OUTCOMES:SPONTANEOUS MISCARRIAGE

Table 12.A Primary endpoint spontaneous miscarriage overall prevalence and clinical study descriptions (total number of births = N)												
	Overall Prevalence		Advanced Maternal Age >=35 (at conception or delivery)		Advanced Maternal Age < 35 (at conception or delivery)		Geographic Region: North America		Geographic Region: Europe		Geographic Region:Other[1]	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
Any Exposure	`											
[1] Other geographic region includes Asia, South America and Mexico Groups are defined by cumulative exposure through pregnancy(SEE RAP)												

Table 12.B Primary endpoint spontaneous miscarriage by Beli dose (Total Number of births = N)												
	Total Births		1mg/kg		4 mg/kg		10 mg/kg		SC		Any Exposure	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
FOOTNOTE PLACEHOLDER												

Table 12.C Primary endpoint spontaneous miscarriage by disease severity (Total Number of births = N)										
	Total Births		PGA >=2 before pregnancy		PGA < 2 before pregnancy		SDI > 1 before pregnancy		SDI <= 1 before pregnancy	
	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure										
>0 - 12 (6/7) week Tri Beli Exposure										
13 - 26 (6/7) weeks Tri Beli Exposure										
>27weeks - delivery Trimester Beli exposure										
Any Exposure	`								`	

Table 12.D Primary endpoint spontaneous miscarriage by medication (total number of births = N)																	
	Steroid Use [1]		Antimalarial Use[1]		Immunosuppressant Use[1]		Steroid+ Anti Malarial Use		Steroid+ Immunosuppressant Use		Immunosuppressant + Anti Malarial Use		Antimalarial + Steroid + Immonossupressant use		Cat D or X Drug[2]		
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
Preconception Beli Exposure																	
>0 - 12 (6/7) week Tri Beli Exposure																	
13 - 26 (6/7) weeks Tri Beli Exposure																	
>27weeks - delivery Trimester Beli																	
Any Exposure	`																
[1] Steroid, Antimalarial, and Immunosuppressant use independently																	
[2]Category D+X drug includes :																	

TABLES FOR THE SECONDARY ENDPOINT BIRTH OUTCOMES:STILLBIRTH

Table 13.A Primary endpoint stilbirth overall prevalence and clinical study descriptions (total number of births = N)												
	Overall Prevalence		Advanced Maternal Age >=35 (at conception or delivery)		Advanced Maternal Age < 35 (at conception or delivery)		Geographic Region: North America		Geographic Region: Europe		Geographic Region:Other[1]	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
Any Exposure	`											
[1] Other geographic region includes Asia, South America and Mexico Groups are defined by cumulative exposure through pregnancy(SEE RAP)												

Table 13.B Primary endpoint stilbirth birth defect by Beli dose (Total Number of births = N)												
	Total Births		1mg/kg		4 mg/kg		10 mg/kg		SC		Any Exposure	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
FOOTNOTE PLACEHOLDER												

Table 13.C Primary endpoint stilbirth by disease severity (Total Number of births = N)										
	Total Births		PGA >=2 before pregnancy		PGA < 2 before pregnancy		SDI > 1 before pregnancy		SDI <= 1 before pregnancy	
	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure										
>0 - 12 (6/7) week Tri Beli Exposure										
13 - 26 (6/7) weeks Tri Beli Exposure										
>27weeks - delivery Trimester Beli exposure										
Any Exposure	`								`	

Table 13.D Primary endpoint stilbirth by medication (total number of births = N)																	
	Steroid Use [1]		Antimalarial Use[1]		Immunosuppressant Use[1]		Steroid+ Anti Malarial Use		Steroid+ Immunosuppressant Use		Immunosuppressant + Anti Malarial Use		Antimalarial + Steroid + Immonossupressant use		Cat D or X Drug[2]		
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
Preconception Beli Exposure																	
>0 - 12 (6/7) week Tri Beli Exposure																	
13 - 26 (6/7) weeks Tri Beli Exposure																	
>27weeks - delivery Trimester Beli																	
Any Exposure	`																
[1] Steroid, Antimalarial, and Immunosuppressant use independently																	
[2]Category D+X drug includes :																	

TABLES FOR THE SECONDARY ENDPOINT BIRTH OUTCOMES:ELECTIVE ABORTION

Table 14.A Primary endpoint elective abortion overall prevalence and clinical study descriptions (total number of births = N)												
	Overall Prevalence		Advanced Maternal Age >=35 (at conception or delivery)		Advanced Maternal Age < 35 (at conception or delivery)		Geographic Region: North America		Geographic Region: Europe		Geographic Region:Other[1]	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
Any Exposure	`											
[1] Other geographic region includes Asia, South America and Mexico Groups are defined by cumulative exposure through pregnancy(SEE RAP)												

Table 14.B Primary endpoint elective abortion by Beli dose (Total Number of births = N)												
	Total Births		1mg/kg		4 mg/kg		10 mg/kg		SC		Any Exposure	
	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure												
>0 - 12 (6/7) week Tri Beli Exposure												
13 - 26 (6/7) weeks Tri Beli Exposure												
>27weeks - delivery Trimester Beli exposure												
FOOTNOTE PLACEHOLDER												

Table 14.C Primary endpoint elective abortion by disease severity (Total Number of births = N)										
	Total Births		PGA >=2 before pregnancy		PGA < 2 before pregnancy		SDI > 1 before pregnancy		SDI <= 1 before pregnancy	
	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure										
>0 - 12 (6/7) week Tri Beli Exposure										
13 - 26 (6/7) weeks Tri Beli Exposure										
>27weeks - delivery Trimester Beli exposure										
Any Exposure	`								`	

Table 14.D Primary endpoint elective abortion by medication (total number of births = N)																
	Steroid Use [1]		Antimalarial Use[1]		Immunosuppressant Use[1]		Steroid+ Anti Malarial Use		Steroid+ Immunosuppressant Use		Immunosuppressant + Anti Malarial Use		Antimalarial + Steroid + Immonossupressant use		Cat D or X Drug[2]	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Preconception Beli Exposure																
>0 - 12 (6/7) week Tri Beli Exposure																
13 - 26 (6/7) weeks Tri Beli Exposure																
>27weeks - delivery Trimester Beli																
Any Exposure	`															
[1] Steroid, Antimalarial, and Immunosuppressant use independently																
[2]Category D+X drug includes :																