A Phase 2b/3a, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Efficacy and Safety of AMAG-423, a Digoxin Immune Fab, in Antepartum Subjects with Severe Preeclampsia

Sponsor	AMAG Pharmaceuticals, Inc. [redacted]
Drug Product:	AMAG-423 (digoxin immune fab)
Protocol Number:	AMAG-423-201
IND Number	[redacted]
EudraCT Number	[redacted]
Protocol Version	Version 5.0

This study will be conducted in accordance with the Protocol and in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki, and any other applicable regulatory requirements. AMAG will also continue to support the principles of the Declaration of Helsini.

PROTOCOL APPROVAL SIGNATURE PAGE

Protocol Title: A Phase 2b/3a, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Efficacy and Safety of AMAG-423, a Digoxin Immune Fab, in Antepartum Subjects with Severe Preeclampsia

Protocol Number: AMAG-423-201

Authorized Sponsor Representative Signature

Signature: [redacted]

Date: 08 NOV 2018

Name: [redacted]
Title: [redacted]
Department: [redacted]

1 PROTOCOL SYNOPSIS

Title

A Phase 2b/3a, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Efficacy and Safety of AMAG-423, a Digoxin Immune Fab, in Antepartum Subjects with Severe Preeclampsia

Primary Objective

To determine the efficacy of AMAG-423 for the prevention of intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), or death in the offspring of women with severe preeclampsia.

Secondary Objectives

1. To determine the safety of AMAG-423 in women with severe preeclampsia.
2. To determine the safety of AMAG-423 in the offspring of women with severe preeclampsia.
3. To determine the pharmacokinetics (PK) of AMAG-423 in women with severe preeclampsia.

Design

This is a multi-center, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of 3.2 mg/kg of AMAG-423 in antepartum subjects with severe preeclampsia. AMAG-423, a digoxin immune fab (DIF), is being evaluated in severe preeclampsia under an Investigational New Drug (IND) Application specific to Digifab™ product.

Hospitalized subjects in tertiary or quaternary maternal care centers with severe preeclampsia in whom expectant management is their treatment plan will be invited to participate. (Note: Subjects will be excluded from enrollment if they require immediate delivery, i.e. the decision to deliver has already been made.) After obtaining informed consent, approximately 200 subjects will be randomized 1:1 to receive either 3.2 mg/kg AMAG-423, or placebo (normal saline) every 6 hours for 90 hours (16 total doses). Subject randomization will be stratified based on gestational age (≤ 27 6/7 weeks and > 27 6/7 weeks) of the fetus at the time of consent.

Standard of care treatment for preeclampsia will be provided by physicians blinded to treatment assignment. Activities associated with the entry of the subject into this study, including screening, consent, randomization or delivery of study drug, should not delay the institution of any aspect of standard of care treatment. To help standardize the treatment of subjects participating in this study, all subjects must receive, at a minimum, corticosteroids and magnesium sulfate as part of standard treatment.

Maternal and fetal monitoring will follow standard practice. The decision to deliver, either during the treatment period or after, will be made by physicians blinded to treatment based on standard of care practice at each institution. Delivery should be performed when clinically appropriate and not be delayed to complete administration of study drug.

The investigator or designee will manage maternal and fetal status until delivery following standard of care. After delivery, standard evaluation of the neonate/infant (henceforth referred to as infant) and mother will be performed. Mother and child will be followed for study purposes through the treatment period, and during the follow-up period (from 6 hours post dose through 6 weeks postpartum for mothers and from birth until 36 weeks corrected gestational age

for infants). Maternal outcome data will be collected 24 hours postpartum and up to 24 hours prior to discharge. At 6 weeks (± 1 week) postpartum, all attempts should be made for a clinic visit, but if a clinic visit is not possible, the visit may be conducted by phone. Infant outcome data will be collected at birth and 36 weeks (± 1 week) corrected gestational age. Unless there are any outstanding safety issues that require follow-up, mothers will be discharged from the study at the 6-week postpartum visit and infants will be discharged from the study at 36 weeks (± 1 week) corrected gestational age.

See Appendix 1 for the Schedule of Events.

Population & Sample Size

Approximately 200 women with severe preeclampsia as defined by modified American College of Obstetricians and Gynecologists (ACOG) guidelines (2013) at up to 90 centers will be enrolled globally. Guidelines have been modified for this study to reduce subjective components of the diagnosis.

Study drug

AMAG-423 will be shipped to the individual site pharmacies. Vials must be refrigerated at 2º to 8ºC (36º to 46ºF). Refrigerators must be in a secure location. Full information will be provided on the vial label regarding vial contents and storage.

Subjects will be randomized to one of two treatment groups and will receive AMAG-423 or placebo (normal saline) for up to 90 hours (16 total doses).

- Treatment Group #1: Days 1 – 4: 3.2 mg/kg of AMAG-423 will be administered via intravenous (IV) infusion (over a period of approximately 30 minutes) every 6 hours (Q6H)
- Treatment Group #2: Days 1 – 4: placebo will be administered via IV infusion (over a period of approximately 30 minutes) Q6H

The number of vials of AMAG-423 for each dose will be determined by the subject's weight at screen. If the number of vials calculated contains a fraction less than 0.25, the total amount of study drug should be rounded down to the whole vial, i.e., if the number of vials required to obtain a given dose is X.25 or less, the total number of vials used for that subject should be X.

Note: Individual subject mg/kg AMAG-423 dose may be slightly different as the number of vials is rounded down for fractions of vials that are 0.25 or less. See Appendix 2.

The contents of each vial (40 mg) should be dissolved with 4 mL of sterile water for injection, by gentle mixing, to give a clear, colorless, approximately isosmotic solution with a protein concentration of 10 mg/mL. Reconstituted product should be used promptly. If not used immediately, it may be stored at 2º to 8ºC (36º to 46ºF) for up to four hours.

The dose of AMAG-423 will be diluted in normal saline to a total volume of 50 mL and infused over a period of approximately 30 minutes. Placebo subjects will receive 50 mL of normal saline.

The pharmacy at each site will be informed of the treatment assignment for each subject via the interactive response technology (IRT) system. Study drug will be

delivered to the treatment unit premixed in an appropriately sized intravenous normal saline bag that has been labeled appropriately for investigational use. See Appendix 2 for Procedures for Handling and Preparation of Study Drug.

Entry Criteria

Inclusion

1. Has a fetal gestational age of 23 0/7 to 31 6/7 weeks. Gestational age should be confirmed by best obstetrical estimate using one of the following three options:
    - Confirmed last menstrual period (LMP) and confirmatory ultrasound
    - Ultrasound alone when LMP is not known or reliable
    - Known date of conception in instances of assisted reproductive technology
2. At least 18 years of age or older
3. Will be treated with expectant management
4. Singleton gestation
5. Meets modified ACOG (2013) criteria for either **preeclampsia** or **chronic hypertension with superimposed preeclampsia**, as specified below:

    Preeclampsia as defined by:

    a. Blood pressure greater than or equal to 140 mmHg systolic or greater than or equal to 90 mmHg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure; **OR**

    b. Blood pressure greater than or equal to 160 mmHg systolic or greater than or equal to 110 mmHg diastolic, hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy;

    AND

    i. Proteinuria:

    1. Greater than or equal to 300 mg per 24-hour urine collection (or this amount extrapolated from a timed collection); **OR**
    2. Protein/creatinine ratio greater than or equal to 0.3 (each measured as mg/dL)
    3. Dipstick reading of 3+ (used only if more quantitative methods not available)

    OR in the absence of proteinuria, hypertension with the new onset of any of the following:

    ii. Thrombocytopenia – platelet count less than 100,000/microliter

    iii. Renal insufficiency – serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease

    iv. Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (two times upper limit of normal for local lab)

    Chronic hypertension with superimposed preeclampsia as defined by:

    a. A sudden increase in previously well controlled hypertension or escalation of antihypertensive medications; **OR**

b. New onset proteinuria or a sudden increase in proteinuria in a woman with known proteinuria before or early in pregnancy.

6. Meets modified ACOG (2013) criteria for either **preeclampsia with severe features** or **chronic hypertension with superimposed preeclampsia with severe features**, as specified below:

   Preeclampsia with severe features as defined by at least one of the below:

   a. Systolic blood pressure of 160 mmHg or higher, or diastolic blood pressure of 110 mmHg or higher on two occasions at least 4 hours apart (unless antihypertensive therapy is initiated before this time)
   b. Thrombocytopenia – platelet count less than 100,000/microliter
   c. Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (two times upper limit of normal for local lab)
   d. Progressive renal insufficiency as defined by serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease

   Chronic hypertension with superimposed preeclampsia with severe features as defined by at least one of the below:

   a. Systolic blood pressure of 160 mmHg or higher, or diastolic blood pressure of 110 mmHg or higher despite escalation of antihypertensive therapy
   b. Thrombocytopenia – platelet count less than 100,000/microliter
   c. Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (two times upper limit of normal for local lab)
   d. Progressive renal insufficiency as defined by serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease

7. Willing and able to provide written informed consent

Exclusion

1. Prior to randomization, the decision to induce or deliver the subject within 24 hours has been made
2. Weight > 150 kg
3. Eclampsia
4. Significant antecedent obstetrical problems which may, in the opinion of the investigator, interfere with study assessments or safe participation in the study
5. Evidence of non-reassuring fetal well-being
6. Evidence of clinically significant fetal anomaly or known chromosomal abnormality
7. Chronic renal disease
8. Active hepatic disease, antiphospholipid antibody syndrome, or lupus
9. Medical or psychiatric disorder which, in the opinion of the investigator, is unstable or which might interfere with study assessments or safe participation in the study

10. Evidence on medical history/evaluation of use of or need for digitalis-like products currently or in the future (e.g., diagnosis of atrial fibrillation)
11. History of an anaphylactic allergic reaction to previous medication, atopy, or allergic reactions to pineapple enzyme bromelain, papain, chymopapain, or other papaya extracts. (Potential subjects with this history may be more susceptible to allergic reactions to digoxin immune fab [DIF])
12. Prior use of antibodies/Fab fragments from sheep (e.g. Digibind®, DigiFab®, CroFab®)
13. Serum creatinine ≥ 2.0 mg/dL
14. Platelet count < 50,000/μL
15. Pulmonary edema requiring treatment with a diuretic
16. Estimated fetal weight < 5th percentile
17. Any investigational drug use within 30 days of screen
18. Planned interventional clinical study participation for infants
19. Current history of methamphetamine or cocaine abuse

Primary Endpoint

Composite of the incidence of IVH (Grade ≥ 3) or NEC or death in infants from randomization to 36 weeks (± 1 week) corrected gestational age.

Key Maternal Secondary Endpoints:

- Change from baseline in serum creatinine.
- Incidence of pulmonary edema during the treatment period.

Safety Evaluations

The safety evaluations are as follows:

Maternal

- Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) – for purposes of this study, symptoms/sequelae of preeclampsia/eclampsia, conditions related to prematurity, and symptoms of pregnancy and childbirth are not considered adverse events unless they are unexpected or are significantly worse than would normally be expected in the opinion of the Investigator.
- Modified Early Obstetric Warning Score (MEOWS) – MEOWS based on systolic blood pressure, diastolic blood pressure, respiratory rate, heart rate, supplemental oxygen requirements, temperature, and level of consciousness.
- Vital signs (blood pressure, heart rate, respiratory rate, temperature, and pulse oximetry)
- Clinical laboratory tests (chemistry, hematology, and urinalysis)
- Preeclampsia symptom assessment
- Maternal outcome assessment will include: delivery data, use of assisted ventilation, anti-hypertensive use, treatment with non-red cell blood products, and length of hospital stay.
- Immunogenicity analysis, if available
- Body weight
- Physical examinations
- Mental status examinations

Fetal

- Fetal heart rate tracing
- Biophysical profile scores (fetal breathing movements, gross body movement, fetal tone, reactive fetal heart rate, qualitative amniotic fluid)

Infant

- Infant outcome at birth, including sex, and birth status
- Status at 36 weeks (± 1 week) corrected gestational age based on gestational age determined at study entry
- Duration of neonatal intensive care unit (NICU) stay
- Apgar scores at 1 and 5 minutes
- Apgar score at 10 minutes, if available
- Infant exam (weight, length, head circumference)
- Arterial cord gas pH and base excess/base deficit, if cord blood assessment available
- Infant outcomes including respiratory distress syndrome, retinopathy of prematurity (including stage), bronchopulmonary dysplasia, hypoxic ischemic encephalopathy, sepsis, cystic periventricular leukomalacia, ventilator use and duration, continuous positive airway pressure (CPAP) / high flow nasal cannula (HFNC) use and duration, hospitalization status, patent ductus arteriosus (PDA), and previously unrecognized anomalies (e.g. including but not limited to atrial septal defect [ASD] and ventricular septal defect [VSD])
- Blood transfusion receipt and any available related information
- Immunogenicity analysis, if available
- Adverse events and serious adverse events – for purposes of this study, symptoms/sequelae of preeclampsia/eclampsia, conditions related to prematurity, and symptoms of pregnancy and childbirth are not considered adverse events unless they are unexpected or are significantly worse than would normally be expected in the opinion of the Investigator.

Pharmacokinetic Endpoints

Blood concentration-time data for AMAG-423 will be summarized by day with descriptive statistics at each scheduled time point. Individual and mean concentration-time profiles will be provided for each day. PK parameters for AMAG-423 will be determined (data permitting) for Dose 1 and the last dose administered. Compartmental modeling (potentially population PK) may also be conducted if data permit such an analysis.

Blood samples will be collected for PK and assay development at the following time points, as much as possible:

Dosing time (hour administered)	Sample Time			
	Pre-dose	End of infusion**	3 hours post dose	6 hours post dose
0	X*	X	X	X
24	X	X		
90***	X	X	X	X

*One sample collected as soon as possible after consent and a second sample just prior to dosing for assay development. Only one sample collected for PK analysis.
**End of infusion samples should be obtained at or just prior to stopping the infusion pump.
***If an earlier dose is known to be the last dose, collect PK according to the collection schedule for the 90-hour dose.
Note: An additional sample will be collected around the time of delivery for PK analysis.

Sample Size:

For purposes of sample size estimation, the expected placebo rate of IVH/NEC/death among infants is between 20-25%. A 15-percentage point difference would result in an expected incidence among treated infants between 5 and 10%. The statistical power to detect a 15% treatment difference from 100 per treatment group is expected to be between 76%-88%. The sample size and subsequent statistical power were obtained from nQuery Advisor (Statistical Solutions, LTD, V7.0) using Fishers Exact test of equal proportions.

Statistical Methodology:

Unless otherwise specified all statistical analyses will be performed using an alpha ≤ 0.05.

The primary outcome is the proportion of infants who have IVH (Grade ≥ 3) or NEC or death by 36 weeks ($\pm$ 1 week) corrected gestational age. An infant will achieve this composite outcome if it is either still born or dies or develops IVH (Grade ≥ 3) or develops NEC by 36 weeks ($\pm$ 1 week) corrected gestational age. Because infants are likely to remain hospitalized at 36 weeks, the risk of losing an infant who would meet the outcome criteria is very small. Therefore, the reason any infant released prior to 36 weeks and subsequently lost to follow up without data at 36 weeks is likely to be due to treatment success. Such subjects will be treated as a success in the primary efficacy analysis. The composite primary outcome measure will be analyzed for treatment differences using Fisher's Exact 2-sided test for equality proportions. To assess the sensitivity of assuming treatment success, another analysis will also be performed where all infants lost to follow-up will be assumed treatment failures.

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3 TABLE OF ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
AE	Adverse event
ALT	Alanine aminotransferase
ASD	Atrial septal defect
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{last}	Area under the concentration-time curve from time zero to time of last measurable concentration
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CL	Apparent total clearance after administration
cm	centimeter
C_{max}	Peak drug concentration
CO_2	Carbon dioxide
CPAP	Continuous positive airway pressure
CrCl	Creatinine clearance
CGA	Corrected gestational age
CRF	Case report form
DEEP	DIF Efficacy Evaluation in Preeclampsia
DIF	Digoxin immune fab
dL	deciliter
DMP	Data management plan
DSMB	Data safety monitoring board
ECG	Electrocardiogram
EDLF	Endogenous digitalis-like factor
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HDW	Hemoglobin distribution width
HELLP	Hemolysis, elevated liver enzymes, low platelet count
HFNC	High flow nasal cannula
ICH	International Conference on Harmonization
IND	Investigational new drug
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intent to treat
IV	Intravenous
IVH	Intraventricular hemorrhage
kg	kilogram
LDH	Lactate dehydrogenase
LMP	Last menstrual period
µL	Microliter
µM	Micromolar
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean cell volume

MedDRA	Medical dictionary for regulatory activities
MEOWS	Modified early obstetric warning score
mITT	Modified intent to treat
mg	milligram
mL	milliliter
mmHg	millimeters of mercury
MPV	Mean platelet volume
Na^+/K^+-ATPase	Sodium-potassium adenosine triphosphatase
NDA	New Drug Application
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
NPO	Nothing by mouth
PD	Pharmacodynamic
PDA	Patent ductus arteriosus
PE	Preeclampsia
PK	Pharmacokinetic(s)
PP	Per protocol
Q6H	Every six hours
RBC	Red blood cell
RDW	Red blood cell distribution width
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	Standard of care
SpO_2	Blood oxygen saturation level
TEAEs	Treatment-emergent adverse events
T_{max}	Time to maximum concentration
V	Volume of distribution
VSD	Ventricular septal defect
WBC	White blood cell

4 INTRODUCTION AND BACKGROUND

Preeclampsia (PE) is a life-threatening disease involving the development of hypertension with proteinuria and/or edema due to pregnancy or the influence of a recent pregnancy [American College of Obstetricians and Gynecologists (ACOG), 2002; Steegers, et al., 2010]. Preeclampsia is a leading cause of maternal and perinatal mortality and morbidity worldwide [Steegers, et al., 2010]. It is a leading cause of maternal death in the United States [Berg, et al., 2010]. It usually occurs after the 20th week of gestation but may develop before this time in the presence of trophoblastic disease. Preeclampsia can progress to eclampsia which involves convulsions not attributable to other cerebral conditions. In addition to the risks to the mother commonly including those described above as well as thrombocytopenia, disseminated intravascular coagulopathy and end organ damage (renal and hepatic), there are significant risks to the fetus. These include severe vasoconstriction resulting in decreased placental blood flow, stillbirth and developmental abnormalities. Preeclampsia is also associated with reduction in birth weight and in one Norwegian study, a 12% reduction in birth weight was associated with severe preeclampsia [Odegård, et al., 2000]. Very low birth weight (<1500 g) is in turn associated with an increased risk of death, intraventricular hemorrhage (IVH) and necrotizing enterocolitis (NEC) among other morbidities [Horbar, et al., 2012]. There are no treatments for preeclampsia, rather treatments are directed at the symptoms. Current practice is to extend gestational age as long as possible without significantly endangering the mother and/or fetus. The mainstay of therapy presently involves bed rest, administration of antenatal corticosteroids, and the use of antihypertensives. Magnesium sulfate is used to prevent seizures. The only effective treatment of preeclampsia is delivery of the fetus [ACOG, 2002; Steegers, et al., 2010; Lindheimer, et al., 2008].

The mechanisms involved in preeclampsia have remained elusive; however, there is growing evidence that elevated serum endogenous digitalis-like factors (EDLFs) play a central role by inhibiting sodium-potassium adenosine triphosphatase (Na^+/K^+-ATPase) resulting in increased intracellular calcium, vasoconstriction and hypertension [Bagrov, et al., 2009; Graves, 2007]. Circulating EDLFs have been identified in pregnant women, umbilical cord blood and neonates and are likely to be placentally derived. These factors are present in the placenta, follicular fluid and amniotic fluid. They are detectable in the first trimester of pregnancy and their concentration increases progressively with gestational age. Preeclampsia is associated with elevated EDLFs. EDLFs are cleared rapidly from the maternal circulation following delivery, coincident with the abrogation of the symptoms of preeclampsia. The precise identity of EDLFs has yet to be confirmed; ouabain and marinobufagenin have been proposed specifically as possible EDLFs in pregnancy and preeclampsia. Evidence suggests that, like digoxin, they bind and inhibit the Na^+/K^+-ATPase pump. EDLFs cross-react with some anti-digoxin antibodies and reversibly bind to a specific serum protein. There appears to be an increase in free (non-protein bound) EDLFs during gestation [Bagrov, et al., 2009; Graves, 2007].

Digoxin Immune Fab (DIF) is a polyclonal ovine Fab fragment marketed for the treatment of digoxin toxicity. Previously two DIF products were available, DigiFab® (BTG International) and Digibind® (GlaxoSmithKline). The first two clinical trials (Protocol 01 and Protocol 02) in the investigational program for preeclampsia were conducted using Digibind, which is no longer available. The current clinical trial is being conducted using DigiFab (referred to as AMAG-423 for the purpose of this trial) under an Investigational New Drug (IND) Application specific to the DigiFab product. As indicated above, Digibind and AMAG-423 (DigiFab) are both DIF and are basically equivalent with the same approved indication, dosing and administration, etc. Both appear to have relatively similar potency in preclinical testing for EDLFs potentially associated with preeclampsia [Ishkaraeva-Yakovleva, et al., 2012]. Dosing of DIF for the treatment of digoxin toxicity is based on the amount of circulating digoxin [DigiFab package insert, 2014]. Each vial of DIF containing 40 mg of purified digoxin-specific Fab, binds approximately 0.5 mg of digoxin.

In Protocol 01, a double-blind, placebo-controlled, randomized clinical trial in immediately postpartum subjects with severe preeclampsia, DIF (Digibind®) administration immediately postpartum resulted in a significantly lower mean arterial pressure than observed in placebo-treated subjects over the first 4 hours of treatment. There was no significant difference in blood pressure between the groups over the 24-hour postpartum period, presumably due to the fact that blood pressure decreases naturally in these subjects over this time period and that antihypertensive therapy was available for study subjects if necessary. Interestingly, 46% of the subjects in the placebo group but none of the subjects in the Digibind® treated group required conventional antihypertensive therapy. In this study, dosing was based on a hypothetical EDLF level equivalent to 2 ng/mL digoxin [Adair, Luper, et al., 2009].

Based on the results of the above study as well as a number of anecdotal reports [Goodlin, 1988; Adair, Buckalew, et al., 1996; Adair, Buckalew, et al., 2009], Protocol 02, a double-blind, placebo-controlled, randomized clinical trial in antepartum subjects with severe preeclampsia was conducted. The DIF Efficacy Evaluation in Preeclampsia (DEEP) study was a Phase IIb proof of concept study. The objective was to evaluate the efficacy, safety and biologic mechanisms of DIF (Digibind®) treatment of severe preeclampsia. Fifty-one subjects were randomized to receive DIF (n=24) or placebo (n=27) for 48 hours. In this study the dose was based on a hypothetical EDLF level of 4 ng/mL, compared to 2 ng/mL in the postpartum study, to allow for continued production of EDLF from the intact placenta. Efficacy was demonstrated on one of two primary efficacy variables - change in creatinine clearance [CrCl]) but not in the use of antihypertensives. DIF was well tolerated [Adair, Buckalew, et al., 2010]. The infant outcomes of IVH, NEC and death, all trended lower in the DIF group compared to the placebo group, but the differences did not reach statistical significance. The incidence of IVH (3 of 27), or NEC (3 of 27) or death (1 of 27) was 26% in the placebo group. The incidence of IVH (0 of 24), or NEC (1 of 24) or death (1 of 24) was 4% in the DIF treated group (Velo Bio, 2011).

Based on the results obtained to date, it is appropriate to further study AMAG-423 (DIF) for the treatment of severe preeclampsia. Because the affinity of DIF for compounds believed to be EDLFs, preclinical experiments were conducted to allow testing of higher doses of DIF in a Phase 2 clinical trial. Safety of higher plasma concentrations of DIF was demonstrated in "An Intravenous GLP Study of the Effects of DigiFab on Embryo/Fetal and Neonatal Development in Rats". Exposure to DIF as assessed by area under the plasma-concentration time curve (AUC) and peak plasma drug concentration (C_{max}) in the GLP rat study greatly exceeded plasma concentration exposure anticipated by pharmacokinetic (PK) modeling in this Phase 2b/3a study (Protocol AMAG-423-201). The no-observed-adverse-effect level for effects on pregnancy, parturition, and embryo/fetal and neonatal development was considered to be 400 mg/kg/day, the highest dose level tested.

In vitro and ex vivo experiments were also conducted to determine a target plasma concentration for AMAG-423 (DIF) in this Phase 2b/3a study. The effects of the postulated EDLF compounds ouabain, bufalin, and marinobufagenin on the Na^+/K^+-ATPase pump expressed in HEK-293 cells or human red blood cells and then the ability of DIF to reverse the inhibition was assessed. The assay was run using human plasma to mimic in vivo conditions. Concentration-response curves were generated for each EDLF in the absence and presence of increasing concentrations of DIF (0.01 to 1 μM). A concentration of 1 μM DIF reversed the Na^+/K^+-ATPase inhibition by EDLFs at concentrations well in excess of plasma concentrations observed in preeclampsia [Icagen, 2016].

Pharmacokinetic simulations using previously obtained population PK data from the DEEP study were conducted using Phoenix WinNonlin to determine a dose of AMAG-423 that would provide a target plasma concentration of 1 μM. Dose administration was simulated as 30-minute infusions every 6 hours over a 4-day period for a total of 16 doses to mimic the design of this study. . Based on this information, a dose of 3.2 mg/kg AMAG-423 administered every 6 hours for up to 90 hours (or until parturition) vs. placebo was selected. Based on PK modeling, a 3.2 mg/kg dose achieves a concentration of 0.8 μM by the time of the 4th dose and achieves a mean concentration of 1 μM at steady state, i.e., 3 days of dosing.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Primary Objective

The primary objective of this study is to determine the efficacy of AMAG-423 for the prevention of IVH, NEC, or death in the offspring of women with severe preeclampsia.

5.2 Secondary Objectives

The secondary objectives of this study are to:

1. To determine the safety of AMAG-423 in women with severe preeclampsia.
2. To determine the safety of AMAG-423 in the offspring of women with severe preeclampsia.
3. To determine the PK of AMAG-423 in women with severe preeclampsia.

5.3 Primary Endpoint

The primary endpoint of this study is:

a. Composite of the incidence of IVH (Grade ≥ 3) or NEC or death in infants from randomization to 36 weeks (± 1 week) corrected gestational age.

5.4 Key Maternal Secondary Endpoints

1. Change from baseline in serum creatinine.
2. Incidence of pulmonary edema during the treatment period.
   Pulmonary edema defined as either of the following in which cardiovascular causes or magnesium toxicity have been clinically excluded:
   a. Chest X-ray consistent with pulmonary edema, or
   b. New onset hypoxemia (room air SpO_2 less than or equal to 94%) in association with tachypnea.

6 STUDY DESIGN

6.1 Overall Design

This is a Phase 2b/3a, multi-center, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of 3.2 mg/kg of AMAG-423 (DIF) in antepartum subjects with severe preeclampsia.

Hospitalized subjects in tertiary or quaternary maternal centers with severe preeclampsia in whom expectant management is their treatment plan will be invited to participate. (Note: Subjects will be excluded from enrollment if they require immediate delivery, i.e. the decision to deliver has already been made.) After obtaining informed consent, approximately 200 subjects will be randomized 1:1 to receive either 3.2 mg/kg AMAG-423, or placebo (normal saline) every 6 hours for 90 hours (16 total doses). Subject randomization will be stratified based on gestational age (≤ 27 6/7 weeks and > 27 6/7 weeks) of the fetus at the time of consent.

Standard of care treatment for preeclampsia will be provided by physicians blinded to treatment assignment. Activities associated with the entry of the subject into this study, including screening, consent, randomization or delivery of study drug, should not delay the institution of any aspect of standard of care treatment. To help standardize the treatment of subjects participating in this study, all subjects must receive, at a minimum, corticosteroids and magnesium sulfate as part of standard treatment.

Maternal and fetal monitoring will follow standard practice. The decision to deliver, either during the treatment period or after, will be made by physicians blinded to treatment based on standard of care practice at each institution. Delivery should be performed when clinically appropriate and not be delayed to complete administration of study drug.

The investigator or designee will manage maternal and fetal status until delivery following standard of care. After delivery, standard evaluation of the infant and mother will be performed. Mother and child will be followed for study purposes through the treatment period, and during the follow-up period (from 6 hours post dose through 6 weeks postpartum for mothers and from birth until 36 weeks corrected gestational age for infants). Maternal outcome data will be collected 24 hours postpartum and up to 24 hours prior to discharge. At 6 weeks (± 1 week) postpartum, all attempts should be made for a clinic visit, but if a clinic visit is not possible, the visit may be conducted by phone. Infant outcome data will be collected at birth and 36 weeks (± 1 week) corrected gestational age. Unless there are any outstanding safety issues that require follow-up, mothers will be discharged from the study at the 6-week postpartum visit and infants will be discharged from the study at 36 weeks (± 1 week) corrected gestational age.

See Appendix 1 for the Schedule of Events.

6.2 Study Personnel and Facility

The study will be conducted at approximately 90 tertiary or quaternary maternal care centers globally. The principal investigators will be obstetricians who specialize in maternal-fetal medicine.

6.3 Study Population

Approximately 200 women with severe preeclampsia as defined by modified American College of Obstetricians and Gynecologists (ACOG) guidelines (2013) [ACOG, 2013] will be enrolled globally. Guidelines have been modified for this study to reduce subjective components of the diagnosis.

6.3.1 Subject Recruitment

Subjects will be hospitalized women with severe preeclampsia. A sufficient number of subjects will be screened in order to achieve the planned number of subjects dosed in each treatment group. Subjects who prematurely discontinue following study drug administration will not be replaced.

6.3.2 Inclusion Criteria

Subjects must meet all of the following criteria to enter the study:

1. Has a fetal gestational age of 23 0/7 to 31 6/7 weeks. Gestational age should be confirmed by best obstetrical estimate using one of the following three options:
    - Confirmed last menstrual period (LMP) and confirmatory ultrasound
    - Ultrasound alone when LMP is not known or reliable
    - Known date of conception in instances of assisted reproductive technology
2. At least 18 years of age or older
3. Will be treated with expectant management
4. Singleton gestation
5. Meets modified ACOG (2013) criteria for either **preeclampsia** or **chronic hypertension with superimposed preeclampsia**, as specified below:

    Preeclampsia as defined by:

    a. Blood pressure greater than or equal to 140 mmHg systolic or greater than or equal to 90 mmHg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure; **OR**

    b. Blood pressure greater than or equal to 160 mmHg systolic or greater than or equal to 110 mmHg diastolic, hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy;
    AND

        i. Proteinuria:

            1. Greater than or equal to 300 mg per 24-hour urine collection (or this amount extrapolated from a timed collection); **OR**
            2. Protein/creatinine ratio greater than or equal to 0.3 (each measured as mg/dL)
            3. Dipstick reading of 3+ (used only if more quantitative methods not available)

    OR in the absence of proteinuria, hypertension with the new onset of any of the following:

        ii. Thrombocytopenia – platelet count less than 100,000/microliter
        iii. Renal insufficiency – serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease
        iv. Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (two times upper limit of normal for local lab)

Chronic hypertension with superimposed preeclampsia as defined by:

a. A sudden increase in previously well controlled hypertension or escalation of antihypertensive medications; **OR**
b. New onset proteinuria or a sudden increase in proteinuria in a woman with known proteinuria before or early in pregnancy.

6. Meets modified ACOG (2013) criteria for either **preeclampsia with severe features** or **chronic hypertension with superimposed preeclampsia with severe features**, as specified below:

Preeclampsia with severe features as defined by at least one of the below:

a. Systolic blood pressure of 160 mmHg or higher, or diastolic blood pressure of 110 mmHg or higher on two occasions at least 4 hours apart (unless antihypertensive therapy is initiated before this time)
b. Thrombocytopenia – platelet count less than 100,000/microliter
c. Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (two times upper limit of normal for local lab)
d. Progressive renal insufficiency as defined by serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease

Chronic hypertension with superimposed preeclampsia with severe features as defined by at least one of the below:

a. Systolic blood pressure of 160 mmHg or higher, or diastolic blood pressure of 110 mmHg or higher despite escalation of antihypertensive therapy
b. Thrombocytopenia – platelet count less than 100,000/microliter
c. Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (two times upper limit of normal for local lab)
d. Progressive renal insufficiency as defined by serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease

7. Willing and able to provide written informed consent

6.3.3 Exclusion Criteria

Any of the following will exclude subjects from the study:

1. Prior to randomization, the decision to induce or deliver the subject within 24 hours has been made
2. Weight > 150 kg
3. Eclampsia
4. Significant antecedent obstetrical problems which may, in the opinion of the investigator, interfere with study assessments or safe participation in the study
5. Evidence of non-reassuring fetal well-being
6. Evidence of clinically significant fetal anomaly or known chromosomal abnormality
7. Chronic renal disease
8. Active hepatic disease, antiphospholipid antibody syndrome, or lupus
9. Medical or psychiatric disorder which is unstable or which might, in the opinion of the investigator, interfere with study assessments or safe participation in the study
10. Evidence on medical history/evaluation of use of or need for digitalis-like products currently or in the future (e.g., diagnosis of atrial fibrillation)

11. History of an anaphylactic allergic reaction to previous medication, atopy, or allergic reactions to pineapple enzyme bromelain, papain, chymopapain, or other papaya extracts. (Potential subjects with this history may be more susceptible to allergic reactions to DIF).
12. Prior use of antibodies/Fab fragments from sheep (e.g. Digibind®, DigiFab®, CroFab®)
13. Serum creatinine ≥ 2.0 mg/dL
14. Platelet count < 50,000/µL
15. Pulmonary edema requiring treatment with a diuretic
16. Estimated fetal weight < 5th percentile
17. Any investigational drug use within 30 days of screen
18. Planned interventional clinical study participation for infants
19. Current history of methamphetamine or cocaine abuse

Subjects who do not meet all the inclusion and exclusion criteria defined in Sections 6.3.2 and 6.3.3 will not be eligible for study participation.

Should it be discovered after a subject has begun study treatment that the subject did not meet all inclusion and exclusion criteria or if during the study a subject ceases to meet all inclusion and exclusion criteria, the subject's continued participation in the study will be discussed with the Sponsor Medical Monitor.

6.3.4 Randomization and Subject Identification

Randomization will occur on Day 1 after study eligibility has been confirmed. Randomization will be stratified by gestational age: ≤ 27 weeks 6/7 days and > 27 weeks 6/7 days. Study drug will be prepared and dispensed by an unblinded Pharmacist at the study site, according to the study treatment assigned by the interactive response technology (IRT) system.

A unique subject screening number, e.g. M0101, should be assigned to each subject who signs an informed consent form. In order to more easily differentiate between mother and infant, infants will be assigned the same screening number with the letter 'I' replacing the 'M', e.g. I0101. Randomization numbers will be 3 digits starting with 101. The subject screening number and randomization number should be used on all Case Report Forms (CRFs) and in all correspondence between sites, sponsor, Institutional Review Boards (IRBs), and the United States Food and Drug Administration (FDA).

Subjects will be assigned a subject randomization number just prior to dosing. This number will correspond to the blinded treatment assignment. Only qualified subjects will be assigned a subject randomization number.

6.3.5 Discontinuation of Subjects

Reasons for subject discontinuation include:

1. Subject experiences an adverse event (AE) that renders her incapable of continuing with the remaining study visits and assessments.
2. Subject wishes to discontinue from the study at any time for any reason.
3. Subject refuses either study drug administration or refuses to comply with study procedures.
4. The Investigator determines it to be in the best interest of the subject.

In the event that study drug is terminated prematurely, all required assessments for the treatment period will be performed six hours following the last dose. With the subject's continued consent,

efforts will be made to obtain all follow-up data. Reasons for discontinuation from the study are to be documented on the CRF.

If a subject is lost to follow-up (i.e., fails to return for study visits) all reasonable efforts should be made to contact the subject and complete follow-up procedures.

6.4 Study Drug

6.4.1 Formulation and Packaging

AMAG-423 is provided invialscontaining 40 mg of purified lyophilized digoxin-specific Fab fragments. Sufficient product will be provided to each study site pharmacy, where study drug will be secured. Upon confirmation of subject eligibility, each site pharmacy will determine study drug treatment assignment through the IRT system. The unblinded pharmacist will be responsible for preparation and dispensing of study drug. The handling and preparation procedures are included in Appendix 2.

Each vial will have a two-part label that specifies the vial contents, concentration, manufacturer, manufacturing date, lot number, cautionary statement, and storage conditions. Each vial will be labeled “For Investigational Use Only”.

6.4.2 Stability and Storage of AMAG-423

AMAG-423 should be stored in the supplied packaging at 2° to 8°C (36° to 46°F). Do not freeze. The assigned shelf life for clinical supplies of AMAG-423 is 3 years. Once reconstituted, AMAG-423 must be used within 4 hours.

6.4.3 Planned Dosing

Subjects will be randomized to one of two treatment groups and will receive AMAG-423 or placebo (normal saline) for up to 90 hours (16 total doses).

- Treatment Group #1: Days 1 – 4: 3.2 mg/kg of AMAG-423 will be administered via intravenous (IV) infusion (approximately 30 minutes) every 6 hours (Q6H)
- Treatment Group #2: Days 1 – 4: placebo will be administered via IV infusion (approximately 30 minutes) Q6H

Table 1. Planned Dose to be Administered to Each Subject Cohort

Treatment Group	Planned Dose	Planned Number of Subjects
1	3.2 mg/kg – Q6H x 4 days	100
2	50 mL normal saline (placebo) Q6H x 4 days	100

6.4.4 Rationale for Planned Dose Level

A dose of 1.6 mg/kg was tested in a previous Phase 2 study; the DEEP study. In that study, efficacy was encouraging and DIF was found to be safe and well-tolerated in women with preeclampsia. Exploration of higher doses of DIF was warranted. To more accurately determine a target DIF serum concentration, the ability of increasing concentrations of DIF to prevent inhibition of Na^+/K^+-ATPase by compounds postulated to be EDLFs was conducted in vitro. A concentration of

1 µM DIF was found to prevent inhibition of Na^+/K^+-ATPase by concentrations of postulated EDLFs well in excess of what has been observed in the plasma of women with preeclampsia. Pharmacokinetic modeling of DIF plasma concentration data from previous studies predicted that a dose of 3.2 mg/kg would result in maximum plasma concentrations of approximately 1 µM DIF and therefore 3.2 mg/kg was selected as the dose for this study.

6.4.5 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be initiated by the Sponsor. The DSMB will be comprised of a chairperson with significant DSMB experience as a chairperson, and two physicians with expertise in Maternal and Fetal Medicine or Neonatology and clinical trial conduct. A DSMB charter approved by the DSMB members will outline the responsibility of the DSMB. The safety of AMAG-423 will be assessed based on AEs, vital signs (including blood pressure, heart rate, respiratory rate, temperature, and pulse oximetry), and clinical laboratory tests. The DSMB will convene prior to dosing of the first subject to determine if additional data will be needed at each review. At the initial meeting, the DSMB will determine frequency of meetings and whether meetings will be based on enrollment or be regularly scheduled calendar events.. The timing of the DSMB reviews and scope of the safety review will be detailed in the DSMB Charter. The DSMB will have authority to stop the study based on safety concerns or to require implementation of new safety assessments as appropriate.

6.4.6 Blinding

This is a double-blind study in that the Sponsor, the clinical staff and Investigator, and the study participants are blinded to the identity of the treatments during the study. The exceptions to this rule include the following:

- Individuals responsible for the generation of the randomization scheme and the IRT system;
- Site pharmacist or an appropriately trained individual, responsible for preparing and dispensing and labeling of study drug supplies at the clinical site;
- Bioanalytical laboratory personnel, responsible for the analysis of pharmacokinetic samples;
- DSMB members responsible for the review of interim subject safety data to ensure the safety and wellbeing of study subjects; and
- Sponsor study monitor responsible for monitoring unblinded study drug supplies and accountability records, but who is not involved in the monitoring of the safety and efficacy data or other aspects of the clinical trial.

The Investigators and Medical Monitor may be unblinded to the treatment of one or more subjects under exceptional circumstances as described in more detail below.

A study site pharmacist (or appropriate individual) who is not involved in the evaluation of the subjects will dispense each subject's assigned study drug dose according to the study treatment assigned by the IRT system. To maintain blinding, study drug will be delivered to the treatment unit pre-mixed and diluted in an appropriately sized intravenous normal saline bag that has been labeled for investigational use. No indication of treatment assignment other than the randomization number will be placed on the subject-specific dosing materials dispensed to the clinic staff. Please refer to the Pharmacy manual for additional blinding instructions.

The study site pharmacist may reveal the identity of the study drug if an emergency situation occurs that, in the Investigator's opinion, cannot be adequately treated without knowing the identity of the study drug. Every effort will be made to contact the Sponsor Medical Monitor prior to breaking the

blind. If this is not possible and the situation is an emergency, the Investigator may break the blind for only the subject(s) involved in the emergency situation and must contact the Medical Monitor as soon as possible. In any case of emergency unblinding, pertinent information including the date and reasons for breaking the blind must be documented in the subject's CRF and in the site and Sponsor study files.

6.4.7 Dose Preparation

All study drug doses will be prepared by the unblinded study site pharmacist and dispensed according to the study treatment assigned by the IRT system.

Upon enrollment of a study subject, the pharmacist will prepare, based on the treatment assigned by the IRT system, either a 50 mL preparation of AMAG-423 in normal saline or a 50 mL preparation of normal saline. No information will be provided on the label regarding the treatment assignment. The preparation will be dispensed to the clinical unit and labeled appropriately for investigational use. Please refer to the Pharmacy manual for additional blinding instructions.

Each vial of AMAG-423 contains 40 mg. The study drug dose will be determined by the subject's weight at screen.

Treatment Group #1 = 3.2 mg/kg every 6 hours (Q6H)
Treatment Group #2 = 50 mL normal saline (placebo) Q6H

Note: If the calculated number of vials required for dosing contains a fraction of 0.25 or less, then the total amount of study drug should be rounded down to the whole vial, i.e., if the number of vials required to obtain a given dose is X.25 or less, the total number of vials used for that subject should be X.

The contents of each vial (40 mg) should be dissolved with 4 mL of sterile water for injection, by gentle mixing, to give a clear, colorless, approximately isosmotic solution with a protein concentration of 10 mg/mL. Reconstituted product should be used promptly. If not used immediately, it may be stored at 2º to 8ºC (36º to 46ºF) for up to four hours. The reconstituted vials should be diluted in normal saline to a total of 50 mL.

6.4.8 Dose Administration

Subjects will be randomized to one of two treatment groups and will receive AMAG-423 or placebo (normal saline) for up to 90 hours (16 total doses).

- Treatment Group #1: Days 1 – 4: 3.2 mg/kg of AMAG-423 will be administered via IV infusion (over a period of approximately 30 minutes) Q6H
- Treatment Group #2: Days 1 – 4: placebo (50 mL normal saline) will be administered via IV infusion (over a period of approximately 30 minutes) Q6H

Note: Individual subject mg/kg AMAG-423 dose may be slightly different as the number of vials is rounded down for fractions of vials that are 0.25 or less.

The dose of AMAG-423 will be diluted in normal saline to a total volume of 50 mL and will be infused over a time period of at least 30 minutes. Placebo subjects will receive 50 mL of normal saline infused over a time period of at least 30 minutes. See Appendix 2.

Administration of study drug will be documented in the study drug record.

Following the approximate 30 minute infusion of study drug, an appropriate amount of saline will be infused at the same rate to ensure all study drug remaining in the line is infused.

6.4.9 Study Drug Accountability

The site pharmacist, as designated by the Investigator, will be responsible for dispensing study drug and for maintaining detailed records of receipt, use, storage, and return shipment. A review of drug accountability records during the study will be performed by an unblinded sponsor study monitor who is not involved in the monitoring of the safety and efficacy data or other aspects of the clinical trial. Unused study drug, except for quantities required for retention by the investigative site, will be returned to Sponsor or designee at the end of the study. No study drug usage outside of the protocol will be allowed.

7 STUDY PROCEDURES

7.1 Study Schedule

The schedule of events is summarized in Appendix 1. If a study visit or assessment occurs outside the specified time point, the reason for the deviation will be noted. Every attempt should be made to ensure that subsequent visits and assessments are performed on-time. In addition to the study visits and assessments described below, unscheduled visits/assessments may be performed if required to further evaluate laboratory parameters or the subject's clinical safety.

7.2 Screening / Baseline

Screening assessments may be completed up to 24 hours prior to the first planned dose of study drug.
Assessments collected at time of hospital admission, but prior to consent, e.g., labs and biophysical profile, may be used as baseline assessments, as long as these assessments were completed within the protocol required timeframe.

The following screening procedures will be performed:

- Signed informed consent
- Inclusion/exclusion criteria
- Complete medical history / pregnancy history / demography
- Physical examination, including mental status examination
- 12-lead electrocardiogram (ECG)
- Height and weight
- Clinical chemistry (including serum creatinine), hematology, and urinalysis. Abnormal clinical lab test results may be repeated once for confirmatory purposes. See Appendix 3.
    - Screening urinalysis should include electrolytes, as much as possible. See Appendix 3.
- Vital signs (blood pressure, heart rate, respiratory rate, body temperature, and pulse oximetry) measurements. For ambulatory subjects, vital signs should be measured after approximately 5 minutes of quiet rest with the subject comfortably seated, legs uncrossed, back and arm supported with the middle of the cuff on the upper arm. For non-ambulatory subjects, vital signs should be measured in a semi-reclined position.
- Preeclampsia symptom assessment – list of preeclampsia symptoms is included as Appendix 4
- Modified early obstetric warning score (MEOWS) – Appendix 5
- Biophysical profile
- Fetal heart monitoring
- Blood sample collection for anti-AMAG-423 antibody concentration (i.e., immunogenicity)
- Blood sample collection for assay development
- Prior / concomitant medication record
- Initiate adverse event monitoring

Screening assessments will be used as baseline assessments in the efficacy/safety analyses evaluating change except where indicated below:

- If screening clinical labs are collected greater than 6 hours prior to dosing, an additional blood sample should be collected for chemistry and hematology and an additional urine

sample should be collected for urinalysis prior to dosing. Results must be obtained prior to randomization and dosing.
- Vital signs should be collected just prior to dosing (within 1 hour of dosing).

All subjects who are screened but do not meet eligibility criteria or who decline to participate should have the reason for screen failure documented.

If corticosteroid administration (betamethasone or dexamethasone) and magnesium sulfate administration have not been initiated/completed by this time, it should be initiated as per standard of care at the individual site. If clinically appropriate, blood samples may be drawn from a central line, by venipuncture, or by a peripheral catheter.

7.3 Treatment Period – Days 1 – 4

The treatment period will begin with the first dose of study drug and end six hours following the last dose of study drug (i.e., a period of 96 hours for subjects completing the full course of treatment) or at the time of delivery if sooner. During the treatment period subjects will be administered study drug every six hours for a maximum total of sixteen doses. Efficacy and safety evaluations and blood samples for PK evaluations will be performed/obtained as noted in Sections 7.3, 7.4, 7.5, and 7.6 below. If a subject goes into labor during the treatment period, study drug will be continued, as much as possible, until delivery. Similarly, efficacy and safety evaluations will be completed up to delivery, as much as possible. If delivery occurs during the treatment period, as much as possible, study assessments should be conducted prior to delivery if ≥ 12 hours have elapsed since the previous collection.

For study purposes, standard of care assessments will not be captured unless there are clinical findings.

- Randomization
- Study drug administration – Every 6 hours x 4 days (16 doses)
- Mental status exam and brief physical exam – should be completed per standard of care, and/or minimally, once a day, starting approximately 24 hours after the first dose. As much as possible, mental status and brief physical exams should be completed 24 hours apart.
- Weight – collected per standard of care.
- ECG – completed per standard of care.
- Fetal heart rate monitoring – 24-hour continuous fetal heart rate monitoring (to be initiated at start of first dose) until 24 hours post first dose. For the remainder of the treatment period, continuous fetal heart rate monitoring should be conducted for one hour after initiation of each dose, unless additional fetal heart rate monitoring is clinically indicated. Clinically significant abnormal findings along with category designation (e.g., III) from fetal heart rate monitoring must be recorded. If continuous fetal heart rate monitoring is difficult or not possible due to subject's weight and/or fetal gestational age, attempts to obtain several one hour strips on Day 1 of treatment should be made documenting why continuous fetal heart rate monitoring is not possible.
- Biophysical profile – completed per standard of care.
- Laboratory assessments (clinical chemistry, hematology, and urinalysis), including serum creatinine – should be collected 24 hours after the first dose (± 2 hours) and then per standard of care, and/or minimally, once a day. As much as possible, labs should be collected 24 hours apart.
    - Urinalysis conducted 24 hours after the first dose should include electrolytes, as much as possible, and then SOC. See Appendix 3.

- A full set of vital signs (i.e., blood pressure and heart rate, respiratory rate, body temperature, and pulse oximetry) – should be collected every 4-6 hours after first dose, as much as possible.
- Preeclampsia symptom assessment – should be collected per standard of care, and/or minimally, once a day, starting approximately 24 hours after the first dose. See Appendix 4.
- MEOWS – should be conducted 24 hours after the first dose (± 2 hours) and then once a day. As much as possible, MEOWS should be completed 24 hours apart. See Appendix 5.
- Adverse event record
- Concomitant medication record
- AMAG-423 PK blood sample collection and blood sample collection for assay development per the following table, as much as possible:

Dosing time (hour administered)	**Sample Time**			
	Pre-dose	**End of infusion****	**3 hours post dose**	**6 hours post dose**
0	X*	X	X	X
24	X	X		
90***	X	X	X	X

*One sample collected as soon as possible after consent and a second sample just prior to dosing for assay development. One sample collected for AMAG-423 PK analysis.
**End of infusion samples should be obtained at or just prior to stopping the infusion pump
***If an earlier dose is known to be the last dose, collect AMAG-423 PK samples according to the collection schedule for the 90-hour dose.
Note: An additional sample will be collected around the time of delivery for PK analysis.

Blood samples will be collected, prepared, stored, and shipped to a bioanalytical laboratory for analysis according to pharmacokinetic sampling instructions that will be provided separately. Samples will be analyzed for AMAG-423 concentration.

7.4 Follow-up Period

The follow-up period begins 6 hours after the last dose of study drug (96 hours from initial dose for subjects completing the full course of treatment) or time of delivery if sooner and continues until 6 weeks (± 1 week) postpartum for the mother and until 36 weeks (± 1 week) corrected gestational age for the infant. If delivery occurs during the initial 24 hours of follow-up, every attempt should be made to complete applicable follow-up assessments at least once prior to delivery.

The following assessments will be conducted during the follow-up period.

Other than where specific timepoints are noted below, assessments will be conducted per standard of care during the follow-up period. For study purposes, standard of care assessments will not be captured unless there are clinical findings. If the time windows for assessments overlap (e.g., 24 hours postpartum occurs within an hour of 24 hours post final dose), then only the last set of assessments should be captured.

- Biophysical profile – should be completed 6 hours (± 2 hours) after final dose and then per standard of care until delivery.
- Weight – should be collected 6 hours (± 2 hours) after final dose, 24 hours postpartum (± 6 hours), up to 24 hours prior to discharge, and at 6 weeks postpartum (if visit conducted in the clinic).
- Mental status exam, brief physical examination, laboratory assessments (clinical chemistry, hematology, and urinalysis), preeclampsia symptom assessment, and MEOWS – should be

collected 24 hours (± 4 hours) after final dose, 24 hours postpartum (± 6 hours), up to 24 hours prior to discharge, and at 6 weeks postpartum (if visit conducted in the clinic).

- ECG – completed per standard of care.
- Fetal heart rate monitoring – completed per standard of care. Clinically significant abnormal findings along with category designation (e.g., III) from fetal heart rate monitoring must be recorded.
- A full set of vital signs (i.e., blood pressure and heart rate, respiratory rate, body temperature, and pulse oximetry) – should be collected 24 hours (± 4 hours) post final dose and then once a day until discharge, and at 6 weeks postpartum. If possible, vital signs should be collected in the morning.
- One blood sample should be collected around the time of delivery for PK analysis.
- Maternal outcome assessments will be completed 24 hours postpartum (± 6 hours) and up to 24 hours prior to discharge and will include:
    - Delivery data
    - Anti-hypertensive use
    - Use of assisted ventilation
    - Treatment with non-red cell blood products
    - Length of hospital stay
- Blood sample for immunogenicity analysis will be collected at the 6-week postpartum visit (if visit conducted in the clinic).
- Concomitant medication record will be collected until discharge. Additional information regarding anti-hypertensive medications and opioid medications should be collected through the 6-week postpartum visit.
- Adverse event record – will be collected until discharge and at 6 weeks postpartum (via clinic visit or phone). If no adverse events are identified that require follow-up for a given subject, then that subject's participation is considered completed and the subject will be discharged from the study. If AEs are identified that require follow-up, arrangements should be made with the subject to follow-up by phone or in person until the AEs are resolved or considered stable, at which time the study will be considered completed for that subject.

Subjects may be contacted in the future to obtain long term follow-up information about the mother and infant.

7.5 Infant Assessments

The following assessments will be conducted for the infant. For study purposes, standard of care assessments will not be captured unless there are clinical findings.

- If cord blood is available, a cord blood sample will be collected for the following assessments:
    - Arterial cord gas pH and base excess/base deficit
    - Analysis of AMAG-423 concentration
- Infant physical examination and laboratory assessments (clinical chemistry and hematology) – standard of care until 36 weeks (± 1 week) corrected gestational age.
- Blood sample for immunogenicity analysis will be collected at 36 weeks (± 1 week) corrected gestational age.
- Infant cranial ultrasound – Day 7 (± 1 day) and at 36 weeks (± 1 week) corrected gestational age.
    - Cranial ultrasounds should be performed per existing medical practice imaging process standards. Cranial ultrasounds will be recorded for review by a central

radiologist to confirm if IVH is present, and if so, grade of IVH. Cranial ultrasound collection and review procedures will be detailed in a separate document.

- Status at birth
  - Apgar scores at 1 and 5 minutes post birth
  - Apgar score at 10 minutes post birth, if available
- Infant exam (weight, length, head circumference)
- The infant outcome assessment will be completed at birth and at 36 weeks (± 1 week) corrected gestational age and will include:
  - Neonatal intensive care unit (NICU) stay
  - Ventilator use and duration
  - Continuous positive airway pressure (CPAP) / high flow nasal cannula (HFNC) use and duration
  - Status at 36 weeks (± 1 week) corrected gestational age (i.e., alive or expired, hospitalized or discharged).
- Blood transfusion receipt and any available related information (e.g., hemoglobin and hematocrit levels prior to transfusion and within 24 hours of transfusion, and nothing by mouth (NPO) status)
- Medical complications including:
  - Patent ductus arteriosus (PDA) – documentation regarding details of PDA condition and treatment should also be captured.
  - Respiratory distress syndrome
  - NEC (Appendix 6)
  - Retinopathy of prematurity, including stage
  - Bronchopulmonary dysplasia
  - Hypoxic ischemic encephalopathy
  - IVH, including grade (Appendix 7)
  - Cystic periventricular leukomalacia
  - Sepsis, early and late onset
  - Previously unrecognized anomalies (e.g., including, but not limited to, atrial septal defect [ASD] and ventricular septal defect [VSD]).
  - Other conditions of prematurity as outlined in Appendix 4
- Concomitant medication record will be collected until 36 weeks (± 1 week) corrected gestational age.
- Adverse event record – Will be collected until 36 weeks (± 1 week) corrected gestational age. If no adverse events are identified that require follow-up for a given subject, then that subject's participation is considered completed and the subject will be discharged from the study. If AEs are identified that require follow-up, arrangements should be made to follow-up by phone or in person until the AEs are resolved or considered stable, at which time the study will be considered completed for that subject.

7.6 Placental and Umbilical Cord Assessment

If a pathological examination of the placenta is considered part of standard of care, analysis will be conducted by the clinical site pathology department. If conducted, information obtained during the evaluation will be collected in the CRF.

Optional Assessments (US sites only)

A true cut biopsy of the placenta (measuring approximately 1 cm x 1 cm) will be collected for future analysis of Na^+/K^+-ATPase activity. The sample should be collected close to the insertion of the umbilical cord.

An approximately 3 cm length of umbilical cord will be collected for future analysis of Na^+/K^+-ATPase activity.

Placenta and umbilical cord samples will be collected, prepared, stored, and shipped according to sampling instructions that will be provided separately.

7.7 Assessment Windows

Every effort will be made to collect AMAG-423 PK samples at the time point specified; however, the actual collection times may deviate by:

- ± 5 minutes at the end of infusion;
- ± 15 minutes from the 3-hour and 6-hour time points;
- - 15 minutes for pre-dose time points

A full set of vital signs should be collected, as much as possible, every 4-6 hours (± 30 minutes) after the first dose during the treatment period, 24 hours (± 2 hours) post final dose, and then once a day until discharge.

Study drug infusions should occur every 6 hours (± 30 minutes).

All assessments that are scheduled for every 24 hours or ≥ 24 hours post dose should occur within 2 hours of the scheduled time point, as much as possible, except for the 24-hour postpartum assessments which have a window of ± 6 hours.

The 6-week follow-up visit/phone call should be conducted 6 weeks (± 1 week) postpartum.

For infants, corrected gestational age is based on gestational age determined at time of consent. Thirty-six week corrected gestational age assessments for infants should be conducted at 36 weeks (± 1 week) corrected gestational age.

In all cases, the actual time of sample collection or assessment completion will be recorded on the subject's CRF.

Missed samples or breakage of a sample must be recorded on a sample inventory list and as a comment on the subject's CRF.

If clinically appropriate, blood samples collected for analysis of AMAG-423 PK may be drawn from a central line, by venipuncture, or by placement of a peripheral catheter.

For instances where assessment times correlate with study drug dosing times, all assessments should be completed prior to start of dosing.

7.8 Concomitant Medications

Prior or current use of antibodies/Fab fragments from sheep (e.g. Digibind®, DigiFab®, CroFab®), digoxin, or other digitalis-like products is prohibited.

Routine medications such as those directly related to analgesia pre-delivery, epidural or other regional or local anesthesia, or general anesthesia, will be collected via checklist as noted in Appendix 8. Maternal concomitant medications not identified in Appendix 8 that have been taken within 28 days of screen and during the course of the study will be recorded in the CRF.

For infants, routine concomitant medications as noted in Appendix 8 will be captured via checklist. Infant concomitant medications not identified in Appendix 8 that are taken between birth and 36 weeks corrected gestational age will be recorded in the CRF.

7.9 Total Volume of Maternal Blood Collected

Up to eleven 6 mL blood samples will be collected for a total of 66 mL of blood collected per subject for AMAG-423 pharmacokinetic analysis.

Approximately 12 mL of blood will be collected at Screening, 12 mL per day for Days 2-5 and 12 mL each at 24 hours post final dose, 24 hours postpartum, up to 24 hours prior to discharge, and 6 weeks postpartum for a total of up to 108 mL of blood collected per subject for clinical laboratory assessments.

Approximately 6 mL of blood will be collected at Screening and 6 weeks postpartum for immunogenicity analysis.

In addition, two 6 mL blood samples will be collected for a total of 12 mL of blood collected per subject for assay development.

The total volume of blood collected from each subject over the entire study will be approximately 198 mL.

7.10 Total Volume of Infant Blood Collected

At the time of delivery, approximately 2 mL of cord blood, if available, will be collected for analysis of arterial cord gas pH and base excess/base deficit and AMAG-423 concentration.

At 36 weeks (± 1 week) corrected gestational age, approximately 0.5 mL of blood will be collected for immunogenicity analysis.

8 ASSESSMENT OF SAFETY

8.1 Overview of Safety Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the subject at his/her site and to report all AEs/SAEs that are observed or reported during the study, regardless of relationship to study drug or clinical significance.

The Medical Monitor has medical authority for the evaluation of the safety aspects of this clinical study. The Investigator may contact the Medical Monitor with specific medical questions on the study protocol, subject's eligibility, as well as AEs.

8.2 Safety Assessments

Safety assessments for the mother and fetus/infant will be collected.

Maternal assessments will include vital signs (blood pressure, heart rate, respiratory rate, body temperature, and pulse oximetry), body weight, mental status exams, physical examinations, clinical laboratory tests (chemistry, hematology, and urinalysis), immunogenicity analyses, MEOWS, preeclampsia symptom assessment, and adverse events. The schedule of these safety assessments has been discussed in the Study Procedures section above and is provided in Appendix 1.

Fetal/infant assessments will include fetal heart tracing, biophysical profile (fetal breathing movements, gross body movements, tone, reactive heart rate and qualitative amniotic fluid), infant outcome assessment, cord blood assessment if available (arterial cord gas pH and base excess/base deficit), cranial ultrasound, infant exam (weight, length, and head circumference), immunogenicity analysis, and adverse events.

For study purposes, standard of care assessments (e.g., ECG, infant labs) will not be captured unless there are clinical findings, at which point they will be captured as adverse events.

8.2.1 Vital Signs

Vital signs (i.e., blood pressure, heart rate, respiratory rate, body temperature, and pulse oximetry) will be obtained at Screen, during the treatment period, and during the follow-up period. During the treatment period a full set of vital signs will be obtained every 4-6 hours, as much as possible. During the follow-up period, vital signs will be collected 24 hours after the final dose and then once a day until discharge and at the 6-week postpartum visit (in the morning, when possible).

For ambulatory subjects, vital signs should be measured after approximately 5 minutes of quiet rest with the subject comfortably seated, legs uncrossed, back and arm supported with the middle of the cuff on the upper arm. For non-ambulatory subjects, vital signs should be measured in a semi-reclined position.

8.2.2 Physical Examinations and Mental Status Examination

A physical examination and a mental status examination will be performed at Screen. During the treatment period and during the follow-up period, a mental status examination and brief physical exam (heart and lung assessment, deep tendon reflex assessment, and clonus assessment) will be completed. During the treatment period, exams will be conducted per standard of care, and/or minimally, once a day, starting approximately 24 hours after the first dose. As much as possible,

mental status exams and brief physical exams should be completed 24 hours apart. During the follow-up period exams will be conducted per standard of care, and/or minimally, 24 hours after final dose (± 4 hours), 24 hours postpartum (± 6 hours), up to 24 hours prior to discharge, and at the 6-week postpartum visit (if available).

Any new clinically significant abnormalities occurring after Screening should be reported as adverse events.

8.2.3 Height and Weight Measurements

Height will be measured at Screen only; weight will be measured at Screen and during the follow-up period. During the treatment period weight will be collected per standard of care. During the follow-up period weight will be collected per standard of care, and/or minimally, 6 hours (± 2 hours) post final dose, 24 hours postpartum (± 6 hours), up to 24 hours prior to discharge, and at the 6-week postpartum visit (if available).

8.3 Clinical Laboratory Assessments

Clinical laboratory assessments (chemistry, hematology, urinalysis – see Appendix 3) will be performed at Screen and during the treatment and follow-up periods. During the treatment period, clinical labs will be collected 24 hours after the first dose (± 2 hours) and then per standard of care and/or minimally, once a day. As much as possible, labs should be collected 24 hours apart. During the follow-up period, clinical labs will be collected per standard of care and/or minimally, 24 hours post final dose (± 4 hours), 24 hours postpartum (± 6 hours), up to 24 hours prior to discharge, and at the 6-week postpartum visit (if available).

Any new clinically significant abnormal results occurring after Screening should be reported as adverse events.

8.4 Preeclampsia Symptom Assessment

Preeclampsia symptom assessment will be conducted at Screen and during the treatment and follow-up periods. During the treatment period preeclampsia symptom assessment will be conducted per standard of care, and/or minimally, once a day, starting approximately 24 hours after the first dose. During the follow-up period preeclampsia symptom assessment will be conducted per standard of care, and/or minimally, once a day until discharge and at the 6-week postpartum visit (or by phone if unable to come to clinic for visit).

8.5 Modified Early Obstetric Warning Score (MEOWS)

Modified early obstetric warning score (MEOWS) (see Appendix 5) will be conducted at Screen and during the treatment and follow-up periods. During the treatment period MEOWS will be conducted 24 hours after the first dose (± 2 hours) and then, minimally, once a day. As much as possible, MEOWS should be collected 24 hours apart. During the follow-up period MEOWS will be conducted per standard of care, and/or minimally, 24 hours after final dose (± 4 hours), 24 hours postpartum (± 6 hours), up to 24 hours prior to discharge, and at the 6-week postpartum visit.

8.6 Immunogenicity Analysis

Blood samples will be collected for immunogenicity analysis of the mother at Screen and 6 weeks postpartum and for the infant at 36 weeks (± 1 week) corrected gestational age. Samples will be assayed for immune response against anti-AMAG-423 antibody concentration.

Immunogenicity blood samples will be prepared, stored and shipped to the bioanalytical laboratory for analysis according to immunogenicity sampling instructions that will be provided separately.

8.7 Fetal Heart Rate Monitoring and Biophysical Profile

Fetal heart rate monitoring will be conducted at Screen, and during the treatment period. During the treatment period, fetal heart rate monitoring will be performed continuously for 24 hours after the first dose (to be initiated at the start of the first dose), and for one hour after initiation of each dose during the remainder of the treatment period. During the follow-up period fetal heart rate monitoring will be conducted per standard of care. Clinically significant abnormal findings along with category designation (e.g., III) from fetal heart rate monitoring must be recorded.

If continuous fetal heart rate monitoring is difficult or not possible due to subject's weight and/or fetal gestational age, attempts to obtain several one hour strips on Day 1 of treatment should be made documenting why continuous fetal heart rate monitoring is not possible.

Biophysical profile (fetal breathing movements, gross body movements, tone, reactive heart rate and qualitative amniotic fluid) will be conducted at Screen, and per standard of care, and/or minimally, at 6 hours (± 2 hours) post final dose of study drug.

8.8 Infant Safety Assessments

The following assessments will be conducted for the infant (standard of care assessments will not be captured unless there are clinical findings):

- If cord blood is available, a cord blood sample will be collected for the following assessments:
  - Arterial cord gas pH and base excess/base deficit
  - Analysis of AMAG-423 concentration
- Infant physical examination and laboratory assessments (clinical chemistry and hematology) – standard of care until 36 weeks (± 1 week) corrected gestational age.
- Blood sample for immunogenicity analysis will be collected at 36 weeks (± 1 week) corrected gestational age.
- Infant cranial ultrasound – Day 7 (± 1 day) and at 36 weeks (± 1 week) corrected gestational age.
  - Cranial ultrasounds should be performed per existing medical practice imaging process standards. To ensure consistency of IVH grading, each site will digitally record the Day 7 and 36 weeks (± 1 week) corrected gestational age cranial ultrasounds for analysis by a central radiologist.
- Status at birth
  - Apgar scores at 1 and 5 minutes
  - Apgar score at 10 minutes, if available
- Infant exam (weight, length, head circumference)
- The infant outcome assessment will be completed at birth and at 36 weeks (± 1 week) corrected gestational age and will include:
  - NICU stay
  - Ventilator use and duration
  - CPAP / HFNC use and duration
  - Status at 36 weeks (± 1 week) corrected gestational age (i.e., alive or expired, hospitalized or discharged).

- Blood transfusion receipt and any available related information (e.g., hemoglobin and hematocrit levels prior to transfusion and within 24 hours of transfusion, and NPO status)
- Medical complications including:
    - PDA – documentation regarding details of PDA condition and treatment should also be captured.
    - Respiratory distress syndrome
    - NEC (Appendix 6)
    - Retinopathy of prematurity, including stage
    - Bronchopulmonary dysplasia
    - Hypoxic ischemic encephalopathy
    - IVH, including grade (Appendix 7)
    - Cystic periventricular leukomalacia
    - Sepsis, early and late onset
    - Previously unrecognized anomalies (e.g., including, but not limited to, ASD and VSD).
    - Other conditions of prematurity as outlined in Appendix 4

8.9 Adverse Events

An adverse event is defined as any untoward medical occurrence associated with use of a drug in humans, whether or not considered drug related. It can be any unfavorable and unintended sign (including laboratory values), symptom or disease temporally associated with use of the study treatment, whether or not it is associated with investigational treatment.

For purposes of this study, symptoms/sequelae of preeclampsia/eclampsia, symptoms of pregnancy and childbirth, and conditions related to prematurity are not considered adverse events unless they are unexpected or are significantly worse than would normally be expected (Appendix 4) in the opinion of the Investigator.

All AEs reported by the subject or observed will be recorded. Serious adverse events (SAEs) should be reported to the sponsor by telephone or fax within 24 hours of learning of their occurrence. Non-serious adverse event data will be recorded in each subject's CRF and submitted to the sponsor for review on an ongoing basis in conjunction with interim Sponsor monitoring visits.

Adverse event collection begins from the time of Informed Consent and continues throughout the study, until 6 weeks postpartum for the mother, and for the infant until 36 weeks (± 1 week) corrected gestational age. A separate AE record will be maintained for mothers and infants. Mothers will be questioned about their general health in conjunction with vital sign assessments. The question should be of a general nature and should not suggest symptoms to the subject (e.g., How are you feeling?" rather than "Do you have a headache?"). If an AE is reported or observed, the site staff should follow the initial question with clinical evaluations and additional questions aimed at obtaining additional details about the AE.

When adverse events are observed or reported, whether in response to indirect questioning or volunteered by subjects, all relevant evaluations will be completed and appropriate treatment provided, if necessary. Subjects with adverse events should be followed until the Investigator and Sponsor consider the event to have resolved, stabilized, or no longer require follow-up for study purposes.

In order to avoid vague, ambiguous, or colloquial expressions, the adverse event should be recorded in the CRF using standard medical terminology rather than the subject's own words.

Whenever the Investigator is confident of a unifying diagnosis, all related signs, symptoms and abnormal test results should be grouped together, as a single AE (e.g., cough, rhinitis, and sneezing should be reported as "upper respiratory infection" if that is the diagnosis).

All adverse events are to be evaluated for intensity and causal relationship to the use of study drug as well as evaluated for seriousness. Grading of intensity and causality will use the following scales.

Intensity

- **Mild:** Usually transient, requires no special treatment, and does not interfere with the subject's daily activities.
- **Moderate:** Usually causes a low degree of inconvenience or concern to the subject, and may interfere with daily activities, but usually is ameliorated by simple therapeutic measures.
- **Severe:** Significantly interferes with the performance of a subject's usual daily activities, and generally requires systemic drug therapy or other treatment.

Causality

- **Probably not related to study drug**:
  An event that is unlikely to have any relationship to the study drug even if such relationship cannot be definitely ruled out. This category should also be used for events that are known to be definitely unrelated to the study drug, e.g. events that occur after the subject has enrolled in a study but prior to study drug exposure.
- **Possibly related to study drug (i.e., suspected adverse reaction):**
  An event that follows a reasonable temporal sequence from administration of the drug and where a causal relationship between drug administration and event is a reasonable possibility, even if the event could readily have been produced by a number of other factors. The expression "reasonable possibility" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.
- **Probably related to study drug (i.e., adverse reaction):**
  An event that (1) follows a reasonable temporal sequence from administration of the drug, (2) follows a known or expected response pattern to the suspected drug, (3) is confirmed by stopping or reducing the dosage of the drug, or (4) could not be more reasonably explained by the known characteristics of the subject's clinical state.

8.10 Serious Adverse Events

An SAE is any adverse event that at any dose:

- results in death, or
- is life-threatening, or
- requires inpatient hospitalization or prolongs an existing hospitalization, or
- results in a persistent or significant incapacity or significant disruption of the ability to conduct normal life functions, or
- is a congenital anomaly or birth defect.

Medical and scientific judgment should be used in evaluating other AEs for seriousness, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the outcomes defining SAEs. These events may also be considered serious. Examples of such events are intensive treatment for bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization.

All SAEs, whether judged related or not to study drug, should be reported to the Sponsor or designee by telephone, e-mail or facsimile within 24 hours of the Investigator becoming aware of such SAEs. An SAE report form will be provided for use in reporting SAEs.

The Sponsor will assess the SAE with the Investigator and determine if the SAE is reportable to relevant regulatory agencies and all other Investigators as specified in the applicable regulations, especially United States Code of Federal Regulations (CFR) Title 21 Part 312 and Guideline International Conference on Harmonization (ICH)-E2A: Clinical Safety Data Management – Definitions and Standards for Expedited Reporting. The Investigator is responsible for reporting SAEs to the IRB as per the IRB's policy.

9 DATA MANAGEMENT AND STATISTICAL CONSIDERATIONS

A separate Data Management Plan (DMP) will be generated and finalized prior to initiating data management activities. A separate Statistical Analysis Plan (SAP) will also be generated that specifies the details of all statistical analyses to be performed.

9.1 Data Management

The sponsor or their designee, will generate the CRFs. A paper or electronic CRF will be used. Velo Bio clinical study monitors will review entered data and ensure that they correspond to data kept by the site in source documents. Data management activities such as query management and coding of AE terms will be performed by the sponsor or their designee. The final quality assured data will be electronically transferred to the statistician, unless otherwise specified in the DMP.

9.2 General Considerations for Statistical Analyses

All data will be provided in listing files. Study results and information will be displayed in descriptive summary tables. All summaries, statistical analyses, and individual subject data listings will be completed using Version 9.2 or later of the SAS Statistical Analysis System (SAS Institute, Inc. Cary, NC). Unless otherwise specified all statistical analyses will be performed using alpha ≤ 0.05. Inference testing for treatment difference will be made specifically for the primary and key secondary outcomes. Other secondary endpoints will be assessed for treatment differences on an exploratory basis to assist with development of any future studies. No adjustments for multiplicity will be made.

All continuous data (e.g., ages, height, weight, vital signs, lab result, etc.) will be summarized by treatment group with N representing the total number of mothers (or infants) in the group, and means, standard deviations (SD), medians, minimum and maximum values.

All categorical data (e.g., race, infant gender, scores, incidences, etc.) will be summarized by treatment group with N representing the total number of mothers (or infants) in the group, and the frequency within category and the percentage within category.

9.2.1 Analysis Populations

The intent-to-treat (ITT) population will be comprised of all mothers and their infants who are randomized. Mothers and infants will be grouped by treatment to which they are randomized whether or not treatment was actually dispensed or whether or not it was dispensed as per the randomization assignment. All demographic baseline characteristics, and primary and secondary efficacy outcomes will be summarized and analyzed using the ITT population.

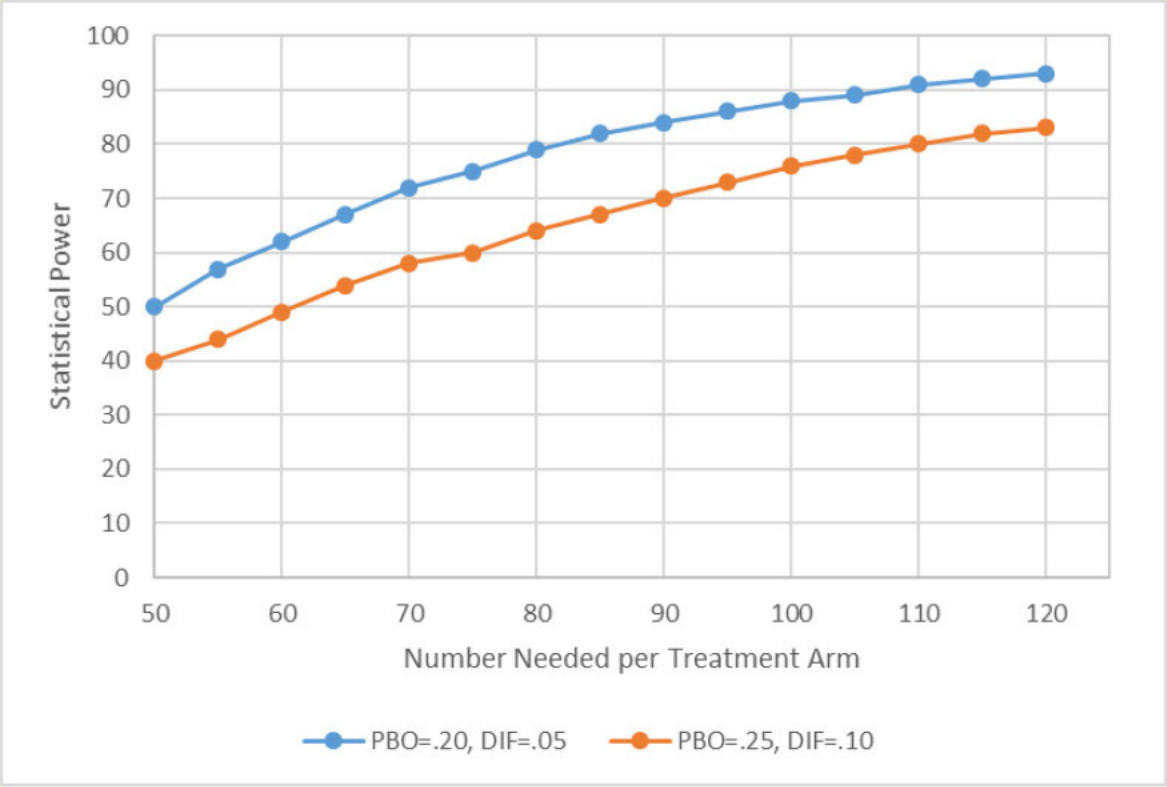
The safety population will include all ITT subjects that actually received treatment, and their treatment group will be based on drug actually received. All safety analyses will be summarized using the safety population.

The per protocol (PP) population will include all subjects in the safety population who have no major protocol violations and who have either reached an endpoint or were followed until 36 weeks (± 1 week) corrected gestational age. To assess sensitivity to protocol deviations, the primary efficacy outcome will be summarized and analyzed by the PP population.

9.3 Sample Size Considerations

The incidence of infants with either severe IVH or NEC or death within 28 days of birth in the DEEP study was 26% in the placebo group which was consistent with published incidence of 22% among a population of low birth weight infants weighing between 1250 gm and 1500 gm at birth [Horbar, et al, 2012]. A reduction in incidence of IVH/NEC/death from 25% to 10% would be considered clinically meaningful.

For purposes of sample size estimation, the expected placebo rate of IVH/NEC/death among infants is between 20-25%. The expected incidence among treated infants is assumed to be between 5-10%. A sample size between 82 and 110 mothers per treatment group would provide 80% statistical power to detect this 15-percentage point difference (see figure below).



Enrollment of 100 subjects per treatment arm is planned. The statistical power to detect a 15% treatment difference from 100 per treatment group is expected to be between 76% and 88%. The sample size and subsequent statistical power were obtained from nQuery Advisor (Statistical Solutions, LTD, V7.0) using Fishers Exact test of equal proportions.

9.4 Demographic and Baseline Characteristics

Listings and summaries of demographic and baseline characteristics will be provided for all subjects (mothers and infants).

9.5 Pharmacokinetic Analysis

The pharmacokinetics of AMAG-423 will be determined using blood samples collected at the predetermined time points. Concentration-time data for AMAG-423 will be summarized by day

with descriptive statistics at each scheduled time point. Individual and mean concentration-time profiles will be provided for each day.

Individual concentration data at actual elapsed times will be analyzed using noncompartmental methods (WinNonlin Phoenix Version 6.3 or later, Pharsight Corporation). For Dose 1 and the last administered dose, the following PK parameters will be determined (data permitting) for AMAG-423 in blood: C_{max}, time to maximum concentration (T_{max}), and area under the concentration-time curve from time zero to time of last measurable concentration (AUC_{last}). These PK parameters will be summarized using descriptive statistics for each dose.

Compartmental modeling (potentially population pharmacokinetics using NONMEM 7.3, ICON Solutions) may also be conducted if data permit such an analysis. Pharmacokinetic parameters to be estimated in such an analysis include apparent total clearance after administration (CL) and volume of distribution (V).

9.6 Analysis of Efficacy Outcomes

The primary outcome is the proportion of infants who have IVH grade ≥ 3 (as identified by central radiology reading) or NEC or death by 36 weeks (± 1 week) corrected gestational age. Stillbirth and fetal demise will be counted as death. An infant will achieve this composite outcome if it either is stillborn or dies or develops IVH grade ≥ 3 or develops NEC by 36 weeks (± 1 week) corrected gestational age. Because infants are likely to remain hospitalized at 36 weeks, the risk of losing an infant who would meet the outcome criteria is very small. Therefore, the reason any infant released prior to 36 weeks and subsequently lost to follow up without data at 36 weeks is likely to be due to treatment success. Such subjects will be treated as a success in the primary efficacy analysis. The composite primary outcome will be analyzed for treatment differences among the ITT analysis group, using Fisher's Exact 2-sided test for equality of proportions. To assess the sensitivity of assuming treatment success, another analysis will also be performed where all infants lost to follow-up will be assumed treatment failures.

Each of the components of the primary outcome will also be summarized and analyzed individually as secondary infant outcomes using the same statistical method as the composite.

The key secondary outcomes of this study are the change from baseline of the mother's serum creatinine levels at 24 hours post initiation of treatment and the incidence of pulmonary edema reported for the mother during the treatment period. Change from baseline serum creatinine will be assessed for treatment differences using analysis of covariance with baseline serum creatinine as covariate and treatment group as the factor.

Incidence of pulmonary edema will be analyzed for treatment differences using Fisher's Exact 2-sided test for equality of proportions.

Other secondary maternal outcomes include:

- Proportion of mothers with MEOWS ≥ 3 at 24 hours post initiation of treatment. Treatment differences will be assessed using Fisher's Exact 2-sided test for equality of proportions.
- Delivery Latency (time from initiation of treatment to delivery). This outcome will be summarized in hours and analyzed for treatment differences using a Kaplan-Meier estimation of median time to event.
- Antihypertensive use during treatment. This outcome will be summarized as the incidence of concomitant antihypertensive medication use once treatment has been initiated. The

incidence will be analyzed for treatment group differences using Fisher's Exact 2-sided test for equality of proportions.

9.7 Analysis of Safety Data

Safety data as outlined in Section 8 will be summarized by treatment group for both mothers and infants. Summary statistics will be prepared for measured values and changes from baseline values for each dose group. No statistical inference testing will be performed on the safety data.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary and summarized by relatedness, intensity, and seriousness. AEs may also be summarized by other factors such as gestational age or intensity of baseline preeclampsia symptoms. Summaries of the adverse event data will be completed for all subjects. Summaries of the number and percentage of subjects with at least one treatment emergent AE, classified according to preferred term and/or body system using the MedDRA dictionary, will be provided overall and by treatment group for:

- Overall summary
- All treatment-emergent AEs
- Treatment-emergent AEs by relationship (probably not related, possibly related, probably related)
- Treatment-emergent AEs by intensity (mild, moderate, severe)
- SAEs
- Treatment-emergent AEs leading to withdrawal from the study

Heart rate, systolic and diastolic blood pressure, temperature, respiratory rate, and pulse oximetry versus time data will be summarized by treatment group with descriptive statistics at each scheduled time point. Individual and mean values versus time profiles will be provided for each treatment group. Summaries of treatment-emergent clinically important abnormalities in vital sign and laboratory data will be provided. No inferential statistical analysis is planned.

Clinically significant new abnormal findings of vital signs or clinical laboratories will be reported as adverse events.

Laboratory parameters, vital sign data, and weight will be summarized by treatment group and presented in tabular and graphic formats where appropriate. Appropriate cross-tabulations will be provided to detect any significant changes in laboratory parameters, vital sign values, or weight but no formal statistical tests are planned.

9.7.1 Other Maternal Outcomes of Special Interest

The following maternal outcomes will be analyzed:

- Renal function – Change from baseline to all assessment time points in measurements of blood urea nitrogen (BUN), serum creatinine, and urine electrolytes.
- Hepatic function – Change from baseline to all assessment time points in measurements of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin.
- Platelet count – Change from baseline to all assessment time points.
- Pulmonary edema – Defined as either of the following in which cardiovascular causes or magnesium toxicity have been clinically excluded:
    a. Chest X-ray consistent with pulmonary edema, or
    b. New onset hypoxemia (room air SpO_2 less than or equal to 94%) in association with tachypnea.

- HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome
- Placental abruption
- Delivery latency
- Percent progression to HELLP
- Percent progression to eclampsia

9.7.2 Other Fetal/Infant Outcomes of Special Interest

Newborn outcome data, including sex, will be collected at birth and 36 weeks (± 1 week) corrected gestational age including:

- Status at birth (i.e., stillborn or alive)
- NICU stay (number of days)
- Infant exam (weight, length, head circumference)
- Retinopathy of prematurity (Stage ≥ 3)
- Bronchopulmonary dysplasia
- Hypoxic ischemic encephalopathy
- Cystic periventricular leukomalacia
- Sepsis, late onset
- PDA – details of PDA condition and treatment should also be captured.
- Previously unrecognized anomalies (e.g., including, but not limited to, ASD and VSD).
- Respiratory distress syndrome
- Other conditions of prematurity as outlined in Appendix 4
- Status at 36 weeks (± 1 week) corrected gestational age (i.e. alive or expired, hospitalized or discharged)
- Intrauterine growth restriction
- Blood transfusion receipt and any available related information (e.g., hemoglobin and hematocrit levels prior to transfusion and within 24 hours of transfusion, and NPO status)

9.8 Concomitant Medications

Concomitant medications will be listed by major therapeutic class, but no formal analyses will be performed. Further categorization into more specific categories may be done for select therapeutic classes of medications.

9.9 Study Reports

The following reports will be generated:

- Bioanalytical method validation report for the measurement of AMAG-423 in human blood
- Bioanalytical study report for the measurement of AMAG-423 in human blood
- Immunogenicity method validation report
- Immunogenicity study report

An integrated clinically study report will be generated in ICH format.

10 ETHICAL AND REGULATORY CONSIDERATIONS

10.1 Regulatory Compliance

This study will be conducted in accordance with Good Clinical Practice (GCP) requirements described in the current revision of ICH Guidelines and all applicable regulations, including current United States CFR, Title 21, Parts 50, 54, 56, and 312 and Title 45, Part 164. Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. This study will also be carried out in accordance with local legal requirements.

10.2 Institutional Review Board (Ethics Committee)

The protocol and informed consent form will be reviewed and approved by an IRB (ethical committee) before subjects are screened for entry. The IRB will comply with applicable regulations defined in the United States CFR, Title 21, Part 56 and Good Clinical Practices: Consolidated Guideline (E6), ICH.

Amendments to the protocol will be subject to the same requirements as the original protocol. The Investigator will submit all periodic reports and updates as required by the IRB. The Investigator will inform the IRB of any reportable adverse events or reportable protocol violations.

10.3 Informed Consent

Each subject will be provided with oral and written information describing the nature and duration of the study, in language they can understand, and must consent in writing to participate before receiving any investigational procedures or treatments. The signed consent form will be retained with the study center's records. Each subject will also be given a copy of his or her signed consent form.

10.4 Medical Supervision

Medical supervision is the responsibility of the Principal Investigator named on Form FDA 1572. The Investigator may delegate day-to-day activities to a Sub-Investigator listed on Form FDA 1572, but retains overall responsibility for ensuring that the study is conducted properly and in accordance with the study protocol. The Investigator is responsible for ensuring that drugs and devices are available for treating possible medical emergencies. The Investigator is responsible for ensuring that the study is conducted according to GCP, other applicable regulatory guidelines, and sound medical practices.

10.5 Quality Control and Quality Assurance

10.5.1 Trial Monitoring

Before an investigational site can enter a subject into the study, a Sponsor representative or their designee will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or their designee. This will be documented in a Clinical Study Agreement between the Sponsor and the investigator.

During the study, a monitor from the Sponsor or their designee will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g. clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

Drug accountability records will be reviewed during the study by an unblinded study monitor who is not involved in the monitoring of the safety and efficacy data or other aspects of the clinical trial.

10.5.2 Audits and Inspections

Authorized representatives of the Sponsor or their designee, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

10.6 Records Retention

The Investigator will maintain adequate records for the study including subjects' CRFs, medical records, laboratory reports, signed consent forms, drug accountability records, safety reports, information regarding discontinued subjects, and any other pertinent data.

All records are to be retained by the Investigator for a period of two years after the FDA approves the New Drug Application (NDA). If no NDA is filed, the records must be retained for two years following notification by the Sponsor that investigations have been discontinued and that the FDA has been notified. These records will be available for copying and inspection if requested by a properly authorized employee of the FDA or other government regulatory agency, in accordance with federal regulations. The Investigator must notify the Sponsor prior to transfer or in cases of accidental loss or destruction of any study records. Subject identification codes must be retained for at least 15 years after completion or discontinuation of the trials as required by European Community Commission Directive 91/507/EEC.

10.7 Publication Policy

This study is a multi-center study and the Sponsor retains the first right to disclose the study results in a publication. Following the earlier of the Sponsor publication or 12 months after completion or termination of the study at all study sites, the site shall have the right to prepare a publication based on the data generated at the site.

The site shall submit to the Sponsor for its review, a copy of any proposed publication resulting from the research at least 30 days prior to the estimated date of submission for publication and the Sponsor shall return comments to the site within 30 days of receipt of the draft and the site agrees to give due consideration to the Sponsor's comments. The site shall, upon reasonable request, remove from such proposed publication any Sponsor confidential information other than the results of the study generated at the site. If the Sponsor reasonably determines that the proposed publication contains patentable subject matters which require protection, the Sponsor may require the delay of publication for a period of time not to exceed 60 days for the purpose of filing patent applications. If no written response is received from the Sponsor within the applicable review period, it may be conclusively presumed that publication may proceed.

Additional details regarding the publication policy are included in the clinical trial agreement between the Sponsor and the site.

11 PROTOCOL AGREEMENT

I have received and read the protocol AMAG-423--201 "A Phase 2a/3b, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Efficacy and Safety of AMAG-423, aDigoxin Immune Fab, in Antepartum Subjects with Severe Preeclampsia" and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Principal Investigator's Name

Principal Investigator's Signature

Date

12 REFERENCES

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Appendix 1: Schedule of Events

	Screen / Baseline	Treatment Period	Follow-up Period			
Assessment		**Days 1 – 4**	**Post final dose through delivery**	**24 hours postpartum**	**Discharge and 6 weeks postpartum (if available)**	**Infant**
Informed consent	X					
Inclusion/Exclusion	X					
Medical history/Demography	X					
Mother physical exam, including mental status*	X	SOC and/or, minimally, once a day, starting 24 hours after first dose	24 hours post final dose, then SOC	X	X	
Mother ECG**	X	SOC	SOC			
Mother height and weight***	X	SOC	6 hours after final dose, then SOC	X	X	
Mother clinical labs (chemistry, hematology, urinalysis)	X	24 hours after first dose, then SOC and/or, minimally, once a day	24 hours post final dose, then SOC	X	X	
Vital signs (blood pressure, heart rate, respiratory rate, temperature, pulse oximetry)	X	Every 4-6 hours	Every 24 hours	X	Every 24 hours until discharge and 6 weeks postpartum	
Preeclampsia symptom assessment	X	SOC and/or, minimally, once a day, starting 24 hours after first dose	24 hours post final dose, then SOC	X	X – After discharge information can be collected via phone	
MEOWS	X	24 hours after first dose, then once a day	24 hours post final dose, then SOC	X	X	
Fetal heart rate monitoring	X	Continuous monitoring for 24 hours after initiation of first dose, for one hour after initiation of each dose during the remainder of the treatment period	SOC			
Biophysical profile	X	SOC	6 hours after final dose, then SOC			
PK sample collection		X****	At delivery			
Immunogenicity sample collection – mother	X				Only at 6 weeks postpartum, if available	
Immunogenicity sample collection – infant						36 weeks CGA
Placenta, cord, and cord blood sample collection			At delivery			
Infant cranial ultrasound						Day 7 and 36 weeks CGA
Infant physical examination						SOC
Infant hematology and clinical chemistry						SOC
Maternal outcome assessment				X	Within 24 hours of discharge only	
Infant outcome assessment						At birth and 36 weeks CGA
Study drug administration		Every 6 hours Days 1 – 4 or until delivery if sooner than Day 4				
Prior / Con Medications – mother	X	X	X	X	Until discharge	
Con Medications – infant						Until 36 weeks CGA
Adverse event monitoring – mother	X	X	X	X	Until discharge and additional check 6 weeks postpartum	
Adverse event monitoring – fetus / infant	X	X	X	X		Until 36 weeks CGA

* Brief physical exam after Screen; *
** 12-lead ECG at screen
*** Weight only after screen
****See protocol Section 7.3 for sampling schedule
SOC – Standard of care, CGA – corrected gestational age

Appendix 2: Procedures for Handling and Preparation of Study Drug

Handling

AMAG-423 (digoxin immune Fab) will be shipped to the individual site pharmacies. Vials must be refrigerated at 2º to 8ºC (36º to 46ºF). Refrigerators must be located in a secure location.

Preparation

All study drug doses will be prepared by the unblinded study site pharmacist and dispensed according to the study treatment assigned by the IRT system.

Upon enrollment of a study subject, the pharmacist will prepare, based on the treatment assigned by the IRT system, either a 50 mL preparation of AMAG-423 in normal saline or a 50 mL preparation of normal saline. No information will be provided on the label regarding the treatment assignment. The preparation will be dispensed to the clinical unit and labeled appropriately for investigational use.

Each vial of AMAG-423 contains 40 mg. The study drug dose will be determined by the subject's weight at screen.

Treatment Group #1 = 3.2 mg/kg Q6H
Treatment Group #2 = placebo Q6H

Note: If the calculated number of vials required for dosing contains a fraction of 0.25 or less, then the total amount of study drug should be rounded down to the whole vial, i.e., if the number of vials required to obtain a given dose is X.25 or less, the total number of vials used for that subject should be X.

The contents of each vial (40 mg) should be dissolved with 4 mL of sterile water for injection, by gentle mixing, to give a clear, colorless, approximately isosmotic solution with a protein concentration of 10 mg/mL. Reconstituted product should be used promptly. If not used immediately, it may be stored at 2º to 8ºC (36º to 46ºF) for up to four hours. The reconstituted vials should be diluted in normal saline to a total of 50 mL.

Dose

The pharmacy at each site will be informed of the treatment assignment for each subject via the IRT system. Study drug will be delivered to the treatment unit premixed in an appropriate sized intravenous normal saline bag.

Appendix 3: Clinical Laboratory Testing – Maternal

Chemistry	**Hematology**	**Urinalysis**
Albumin	Hematocrit	Bilirubin
Alkaline phosphatase	Hemoglobin	Blood/RBCs
ALT	Mean cell volume (MCV)	Color
AST	Mean corpuscular hemoglobin (MCH)	Glucose
Bicarbonate or CO_2	Mean corpuscular hemoglobin concentration (MCHC)	Ketones
BUN	Mean platelet volume (MPV)	Leukocytes or WBCs
Calcium	Platelet count	Microscopic exam
Chloride	Red blood cell count	Nitrite
Creatinine	White blood cell count	pH
Glucose	White blood cell (WBC) differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils) – both absolute count and percentages	Protein
Lactate dehydrogenase (LDH)		Specific gravity
Magnesium		Urobilinogen
Potassium		Electrolytes (sodium, potassium, chloride, calcium, and creatinine)*
Sodium		
Total Bilirubin; if elevated obtain direct bilirubin		

*Urine electrolytes to be collected at Screen and 24 hours after first dose, as much as possible, and then standard of care.

Appendix 4: Symptoms / Sequelae of Preeclampsia and Conditions of Prematurity

The following list of symptoms / sequelae of preeclampsia and conditions of prematurity will not be considered an adverse event or a serious adverse event unless they are unexpected or are significantly worse than would normally be expected in the opinion of the investigator. All of these events will be collected in the case report form and included in the Final Study Report.

Maternal

- Hypertension and hypertensive sequelae (e.g. hypertensive crisis, cerebral hemorrhage)
- Proteinuria
- Edema
- Abruptio placentae
- Disseminated intravascular coagulation
- Right upper quadrant pain
- Epigastric pain
- HELLP syndrome
- Alteration in hepatic function (e.g. enzyme elevation, jaundice)
- Hepatic failure
- Alteration in renal function (e.g. oliguria, serum creatinine elevation, decreased creatinine clearance)
- Renal failure
- Headache
- Visual changes (e.g. blurred vision, diplopia, photophobia, scotomata, amaurosis)
- Hyperreflexia
- Clonus
- Eclampsia
- Pulmonary edema
- Encephalopathy
- Hemolysis
- Thrombocytopenia
- Hypoxemia

Fetus / Infant

Symptoms/Conditions of Preeclampsia

- Fetal demise
- Neonatal demise (within 30 days)
- Abnormal biophysical profile
- Diminished fetal blood flow
- Heart tracing abnormalities (e.g. late decelerations, variable decelerations, bradycardia)
- Intrauterine growth restriction

Conditions of Prematurity

- Necrotizing enterocolitis
- Retinopathy of prematurity
- Bronchopulmonary dysplasia
- Hypoxic ischemic encephalopathy
- Intraventricular hemorrhage

- Cystic periventricular leukomalacia
- Sepsis
- Respiratory distress syndrome
- Hyperbilirubinemia
- Electrolyte imbalance (e.g., hyponatremia, hypermagnesemia, hypocalcemia, hypokalemia)
- Anemia of prematurity
- Apnea of prematurity
- Sinus bradycardia
- Sinus tachycardia
- Previously unrecognized anomalies (e.g. including but not limited to patent ductus arteriosus, atrial septal defect, and ventricular septal defect)

Appendix 5: Modified Early Obstetric Warning Score (MEOWS)

	3	2	1	0	1	2	3
Systolic blood pressure (mmHg)	< 80	80-89		90-139	140-149	150-159	≥ 160
Diastolic blood pressure (mmHg)				< 90	90-99	100-109	≥ 110
Respiratory rate (breaths/min)	< 10			10-17	18-24	25-29	≥ 30
Heart rate (beats/min)	< 60			60-110		111-149	≥ 150
$\%O_2$ required to maintain $SpO_2 \geq$ 96%				Room air	24-39%		≥ 40%
Temperature (°C)	< 34.0		34.0-35.0	35.1-37.9	38.0-38.9		≥ 39
Consciousness level				Alert[1]			Not alert[2]

1. Alert and oriented, equivalent to Glasgow Coma Score (GCS) 15 and A on Alert/Voice/Pain/Unresponsive (AVPU) scale
2. GCS 3-14 or V, P, or U on AVPU scale

Source Reference: Carle, et al., 2013

Appendix 6: Necrotizing Enterocolitis Definition

Necrotizing Enterocolitis (NEC)

Answer "**Yes**" if the infant had NEC diagnosed at surgery, at postmortem examination, or clinically and radiographically using the following criteria:

At least one of the following clinical signs present:

- Bilious gastric aspirate or emesis
- Abdominal distension
- Occult or gross blood in stool (no fissure)

AND

At least one of the following radiographic findings is present:

- Pneumatosis intestinalis
- Hepato-biliary gas
- Pneumoperitoneum

Answer "**No**" if the infant did not satisfy the above definition of NEC.

Note: Infants who satisfy the definition of NEC above but are found at surgery or post-mortem examination for that episode to have a "Focal Intestinal Perforation" should be coded as having "Focal Intestinal Perforation", not as having NEC.

Source reference: https://nightingale.vtoxford.org/help/!SSL!/WebHelp/NEC.htm

Appendix 7: Intraventricular Hemorrhage

Intraventricular hemorrhage (IVH) is a condition in which blood vessels within the brain burst and bleed into the ventricles.

The following grading system should be used for IVH:

Grade 0: No subependymal or intraventricular hemorrhage
Grade 1: Subependymal germinal matrix hemorrhage only
Grade 2: Intraventricular blood, no ventricular dilation
Grade 3: Intraventricular blood, ventricular dilation
Grade 4: Intraparenchymal hemorrhage

Appendix 8: Routine Maternal and Infant Concomitant Medications

Maternal Pre-Delivery:

- Analgesia pre-delivery (e.g., Fentanyl, Tylenol, Nubain/phenergan). Opioids should not be collected as a routine medication.
- Antacids/ Indigestion preparations (e.g., Tums, Pepcid, Zantac)
- Antiemetic (e.g., Compazine, Phenergan, Reglan, Zofran)
- Asthma inhaler or preventative treatment (e.g., Albuterol, Advair, Flovent)
- Epidural or other regional anesthesia
- General anesthesia
- Local anesthesia (pudendal block) for episiotomy
- Iron (Ferrous sulfate) for anemia prevention or treatment
- IV fluids, including use of lidocaine to start IV (e.g. D5W, NSS, Ringers lactate)
- Laxative/ stool softener/ other constipation treatment (e.g., Colace, Metamucil)
- Oxygen (via mask or nasal)

Maternal Post-Delivery:

- Analgesia post delivery (e.g., Fentanyl, Tylenol, Nubain/phenergan). Opioids should not be collected as a routine medication.
- Antacids/ Indigestion preparations (e.g., Tums, Pepcid, Zantac)
- Antiemetic (e.g., Compazine, Phenergan, Reglan, Zofran)
- Asthma inhaler or preventative treatment (e.g., Albuterol, Advair, Flovent)
- Birth control
- Hemorrhoid medication (e.g., Preparation H, Proctofoam, Tucks)
- Iron (Ferrous sulfate) for anemia prevention or treatment
- IV fluids (e.g. D5W, NSS, Ringers lactate)
- Injection for prevention of rhesus antibody formation, (e.g., Rhogam)
- Laxative/ stool softener/ other constipation treatment (e.g., Colace, Metamucil)
- Sitz bath

Infant:

- Antibiotic eye drops
- Vitamin D
- IV fluids
- Diuretics
- Vitamin A supplements
- Corticosteroids
- Prophylactic Vitamin K
- Systemic antibiotics
- Surfactant
- Iron supplements
- Bronchodilators
- Caffeine
- Retinopathy of prematurity exam medications (e.g., cyclopentolate, proparacaine)
- Total parenteral nutrition
- Calcium
- Multivitamin (with or without iron)