COVER SHEET FOR

CONSENT/PARENTAL PERMISSION FORM FOR RESEARCH

Complement Regulation to Undo Systemic Harm in Preeclampsia: The CRUSH Study

Protocol Number: STUDY 00000039

National Clinical Trial (NCT) Identified Number: NCT04725812

Principal Investigator/IND Sponsor: Richard Burwick, MD MPH

Funded by: Alexion Pharmaceuticals

Document date: 31 January 2022

CEDARS-SINAI MEDICAL CENTER

CONSENT/PARENTAL PERMISSION FORM FOR RESEARCH

Title: COMPLEMENT REGULATION TO UNDO SYSTEMIC HARM IN PREECLAMPSIA: THE CRUSH STUDY

STUDY SUPPORT PROVIDED BY: ALEXION PHARMACEUTICALS

PRINCIPAL INVESTIGATOR: RICHARD M. BURWICK MD, MPH

STUDY CONTACT PHONE NUMBER AT CSMC: 310-423-3277

AFTER HOURS CONTACT (24 HOURS): 310-423-3277

This research study is supported by Alexion pharmaceuticals. Alexion pharmaceuticals only reimburses Cedars-Sinai Medical Center for the costs associated with running the study; Alexion pharmaceuticals is not providing additional compensation to Cedars Sinai Medical Center or the Principal Investigator for their participation in the study.

1. WHAT IS THE PURPOSE OF THIS RESEARCH STUDY?

You are being asked to take part in this research study because you are pregnant between 23 and 30 weeks and you have been diagnosed with preeclampsia. We are doing this study to determine if the study drug, eculizumab, is an effective treatment for preeclampsia. We want to know if treatment with eculizumab prolongs pregnancy in women with preterm preeclampsia, compared to a historical control group of women at our institution with preterm preeclampsia who did not receive eculizumab. The ratio of the historical control group to the treatment group will be 3:1. This study will enroll up to 48 women in total with 12 enrolled to receive treatment.

This research study is designed to test the investigational use of eculizumab (Soliris). This drug is approved by the U.S. Food and Drug Administration (FDA) for treatment of certain blood disorders and has been used in pregnant women. However, it is not approved by the FDA for treatment of preeclampsia.

2. WHAT WILL HAPPEN DURING THE STUDY?

This section provides a general overview of what will happen during your participation in this study. Information included below should be considered along with the flowchart of procedures attached as Appendix C.

The flowchart shows a timeline for research-related procedures that are involved in your participation in this study. **Research-related procedures** are those performed solely for the research. They would not be performed if you did not take part in the study.

A table describing common medical procedures done solely for the purposes of monitoring and assessing your condition during this study is attached as an Appendix D to the end of this consent form.

Overview of study:
This is a single-arm, open label research study. This means that all women enrolled in the study will receive the study drug. The study drug is eculizumab, which you will receive on day 1 of the study via intravenous infusion over 35 minutes in adults and 1 to 4 hours in pediatric patients via gravity feed, a syringe-type pump, or an infusion pump. You will continue to receive eculizumab weekly for the first 5 weeks of treatment and biweekly thereafter, until 48 hours after your delivery.

Eculizumab is intended to prolong pregnancy in women with preeclampsia diagnosed before 30 weeks gestation. As there is no currently effective treatment for preeclampsia other than delivery, women with preeclampsia before 30 weeks gestation are managed using a "watch and wait" approach. Due to the unpredictable nature of preeclampsia, this "watch and wait" approach places mother and child at significant risk until delivery occurs. Eculizumab may be an improvement over current standard of care as it provides a treatment option for patients who would otherwise be managed with expectant management alone.

Treatment with eculizumab is associated with an increased risk for meningococcal infection. Therefore, as part of this study, you will be given two meningococcal vaccines. The FDA warns that meningococcal vaccines should be given at least 2 weeks prior to starting eculizumab but as that would delay treatment with eculizumab, we will instead give you the first dose of both meningococcal vaccines before your first dose of eculizumab. To further decrease the risk of meningococcal infection, we will prescribe antibiotics which you will continue until 4 weeks after your last dose of eculizumab Finally, to complete meningococcal vaccination, you will receive the second dose of the meningococcal vaccines 1-2 months after the initial dose, as shown below in the study schema. The study team will closely monitor you throughout your treatment for any infection and will stop treatment with eculizumab if any infection develops, other than urine or yeast infection, which will be treated with standard medications by your doctor.

This study is designed to compare the medical results of women with preeclampsia, treated with eculizumab, to results from existing medical records of women with preeclampsia who did not use the drug. This comparison will allow the researchers to learn whether the study drug, eculizumab, is better, the same, or worse than the current standard of care for preeclampsia. Standard of care for preterm preeclampsia is expectant management of pregnancy, the "watch and wait" method of monitoring the expectant mother. For this study, you will receive eculizumab in addition to standard of care, which may include treatment of high blood pressure or magnesium sulfate to prevent seizure. There is no alternative treatment for preeclampsia other than delivery of the baby. Eculizumab has been tested for safety in pregnancy, but it is not part of current standard of care for the treatment of preeclampsia.

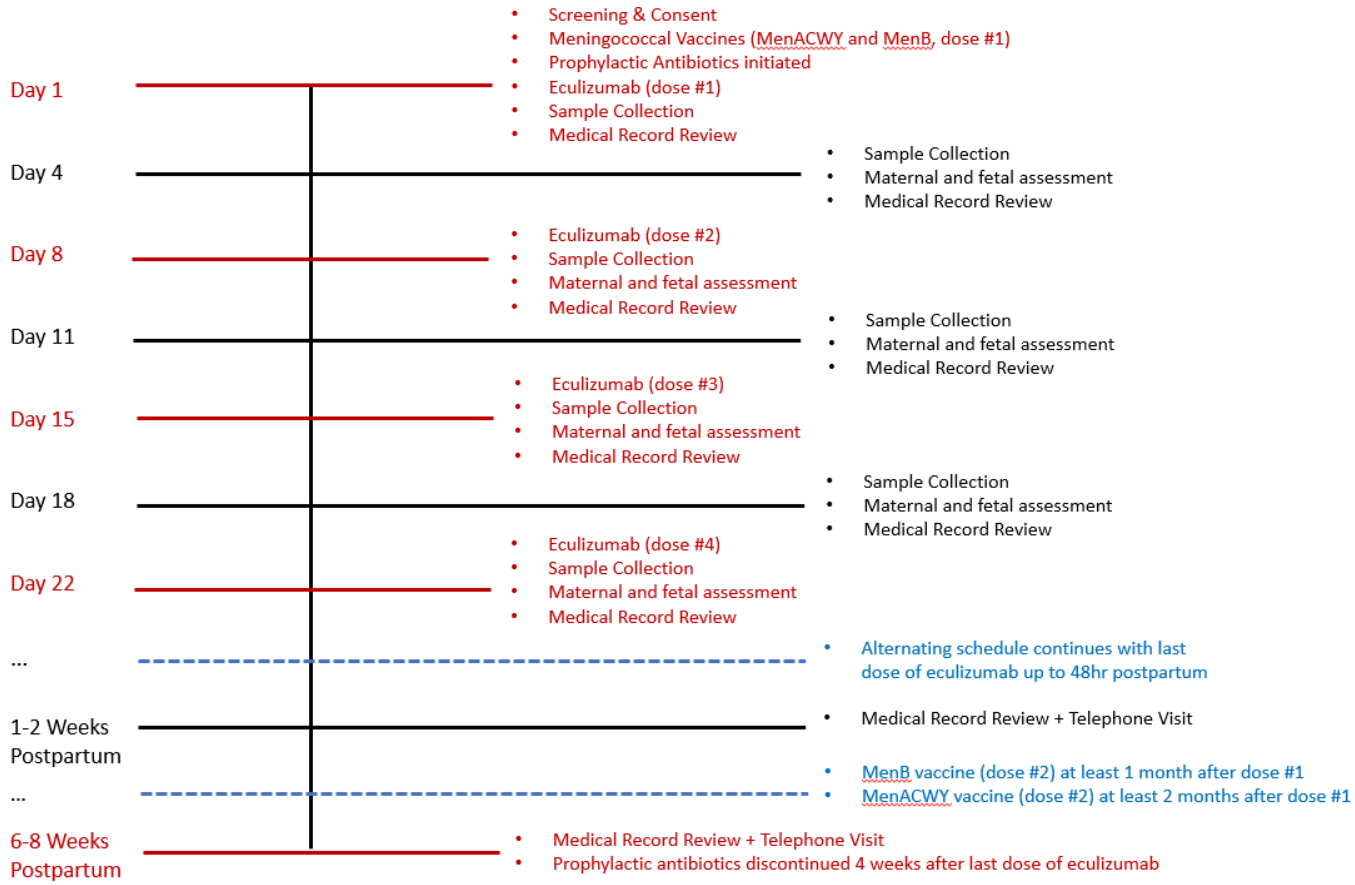
In order to properly follow the study's protocol (research plan), all the participants will receive treatments and procedures that have been pre-determined by the protocol. In effect, the protocol describes which medications you will receive, but would not interfere with those decisions being made by your personal doctor or based on your preference. There may be options available outside of this study that you will not be able to receive while participating in this study. We do not believe you should be at any increased risk due to this limitation.

Treatments for your disease can cause side effects such as nausea, headache, back pain, cough, or other flu-like symptoms, so you will receive medications to help deal with these side effects. The drugs you will receive are given as part of routine care for those symptoms.

Another purpose of this study is for researchers to learn if biomarker tests are helpful to monitor the effectiveness of the study drug. A biomarker is a biological molecule found in blood, other body fluids, or tissues that may be a sign of a condition or disease. For these biomarker tests, two extra tubes of blood (10cc each) and a urine sample (20cc) will be collected before and after you receive the study drug. Biomarker testing will not be used to make decisions about eligibility, treatment assignment, or other clinical management.

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.

Study Schema



Optional Sub-study

Details of an optional sub-study are described in Appendix B of this consent form. You are not required to participate in the sub-study in order to take part in this research study.

How long will you be in the study?

You will be in this study until approximately 6-8 weeks after your delivery. The total time includes study visits every 3-4 days, weekly or biweekly intravenous infusions of the study drug, and monitoring of antibiotic use and vaccine administration up to 8 weeks after your delivery After that,

we would like to keep track of your medical condition and your baby's health for 6-8 weeks postpartum. We would like to contact you by phone at 1-2 weeks and 6-8 weeks after your delivery, and review your medical records, to see how you and your baby are doing. Keeping in touch with you and checking on your condition every so often helps us look at long-term effects.

3. WHAT ARE THE POSSIBLE RISKS?

Risks of common medical procedures performed solely for research purposes are described in a table attached to the end of this consent form as Appendix D. Side effects and risks of standard of care procedures are not described in this consent form.

This section describes the possible risks and/or discomforts we anticipate you could experience that are related to the study procedures.

Unknown Risks
There may be other side effects or risks that we cannot predict. Many side effects may go away shortly after the study medication or procedure is stopped. However, in some cases they can be serious or long-lasting.

Risks of Eculizumab

In the list below, "**Serious**," refers to those side effects that may require hospitalization, may be irreversible, long-term, life-threatening or fatal.

Likely, Some May Be Serious (*Occurs in greater than 20% and up to 100 % of people***)**
- Nausea, vomiting, diarrhea
- Headache
- Nasopharyngitis (common cold)
- High or low blood pressure
- Anemia or leukopenia (low blood cell count)

Less Likely, Some May Be Serious (*Occurs in >3% - 20 % of people)*
- Back pain
- Fatigue
- Cough
- Herpes simplex infections
- Sinusitis
- Respiratory tract infection
- Constipation
- Pain in extremity(ies)
- Influenza-like illness
- Decreased kidney function
- Low levels of potassium in blood
- Insomnia
- Rash, itching

Rare AND Serious (*Occurs in 3% or less of people **and** may require hospitalization or may be irreversible, long-term, life-threatening or fatal***)**

- Infusion reaction, including anaphylaxis (serious allergic reaction) or other hypersensitivity reactions
- Viral infection
- Other infections
    - Streptococcus pneumoniae infection
    - Haemophilus influenza type b (Hib) infection
    - Aspergillus infection

In addition to the risks summarized above, the FDA has issued the following warning for eculizumab (Soliris):

> **FDA Blackbox Warning: SERIOUS MENINGOCOCCAL INFECTION**
>
> Soliris increases the risk of meningococcal infections
>
> • Vaccinate patients with a meningococcal vaccine at least 2 weeks prior to receiving the first dose of Soliris; revaccinate according to current medical guidelines for vaccine use
>
> • Monitor patients for early signs of meningococcal infections, evaluate immediately if infection is suspected, and treat with antibiotics if necessary

There is limited data on the use of eculizumab for treatment of preeclampsia. In one human case, a patient received eculizumab for treatment of preeclampsia at a dose of 1200 mg weekly and received three doses of the drug before delivery. There were no reported adverse effects to the mother or baby from use of eculizumab and the pregnancy was extended by 17 days. The authors reported trace levels of eculizumab in neonatal cord blood and no eculizumab in breast milk samples.

In a long-term follow up study of 64 children exposed to eculizumab due to maternal use of the drug in pregnancy for a rare blood disorder called paroxysmal nocturnal hemoglobinuria (a condition characterized by immune destruction of red blood cells), 64 of 64 (100%) met developmental milestones for vision, hearing, locomotion, fine-motor skills, behavior and physical health. In addition, 63 of 64 (98.4%) achieved milestones for speech and language (1 child was referred to a speech and language specialist for delayed speech). The authors concluded that eculizumab is safe for use in pregnant women. There are no expected safety concerns, but some may be unknown.

Eculizumab is approved in many countries for use in adults and pediatric patients (< 18 years of age) to treat other rare blood disorders. For pediatric and adolescent patients (aged 13 to <18 years with body weight ≥40kg) the dosing regimen for eculizumab is the same as for adults ≥18 years. The safety profile observed in adolescent patients (aged 13 to <18 years with body weight ≥40kg) is similar to that observed in the adult population.

Risks of Vaccines

Likely, Some May Be Serious (*Occurs in greater than 20% and up to 100 % of people***)**

- Pain or soreness at injection site

- Redness or swelling of the skin at injection site

Less Likely, Some May Be Serious (*Occurs in >3% - 20 % of people)*

- Fever
- Headache
- Nausea
- Vomiting
- Dizziness
- Vasovagal reaction (fainting)

Rare AND Serious (*Occurs in 3% or less of people* ***and*** *may require hospitalization or may be irreversible, long-term, life-threatening or fatal***)**

- Infusion reaction, including anaphylaxis (serious allergic reaction) or other hypersensitivity reactions

The meningococcal vaccine does not contain any live organisms and it is given to prevent bacterial meningitis from the organism Neisseria meningitidis. It is considered safe for use in women who are pregnant or breastfeeding, according to the American College of Obstetricians and Gynecologists. The meningococcal vaccine is not known to cause harm to the developing fetus and does not affect the neonate during breastfeeding. The Centers for Disease Control and Prevention recommends the meningococcal vaccine in adolescents and adults being treated with a complement inhibitor, such as the study drug eculizumab, because it blocks part of the immune system necessary to protect against bacterial meningitis.

Risks of Antibiotics

Penicillin

Likely, Some May Be Serious (*Occurs in greater than 20% and up to 100 % of people***)**

- Nausea or upset stomach

Less Likely, Some May Be Serious (*Occurs in >3% - 20 % of people)*

- Vomiting
- Diarrhea
- Oral candidiasis (fungal infection of the mouth)

Rare AND Serious (*Occurs in 3% or less of people* ***and*** *may require hospitalization or may be irreversible, long-term, life-threatening or fatal***)**

- Anaphylaxis (serious allergic reaction) or other hypersensitivity reactions
- Seizures
- Kidney damage
- Fever
- Exfoliative dermatitis (redness and peeling of the skin over large areas of the body)
- Severe anemia

Penicillin based antibiotics are not expected to increase the risk for adverse pregnancy outcomes. There is extensive data on use of penicillin during pregnancy, and there is no increased risk of birth defects or fetal harm. Penicillins are excreted into human milk in small amounts but this exposure is

unlikely to have detectable effects in the newborn, and penicillins are considered compatible with breastfeeding.

Risks of Azithromycin

Likely, Some May Be Serious (*Occurs in greater than 20% and up to 100 % of people***)**

- Nausea or upset stomach

Less Likely, Some May Be Serious (*Occurs in >3% - 20 % of people)*

- Vomiting
- Diarrhea
- Liver inflammation

Rare AND Serious (*Occurs in 3% or less of people* ***and*** *may require hospitalization or may be irreversible, long-term, life-threatening or fatal***)**

- Anaphylaxis (serious allergic reaction) or other hypersensitivity reactions
- Liver failure
- QT interval prolongation (heart rhythm disorder)

Based on experimental animal studies and human reports, azithromycin use during pregnancy is not expected to increase the risk of birth defects. Azithromycin has been used widely in pregnancy without an increase in adverse fetal or neonatal effects, and its use is considered compatible with breastfeeding. Azithromycin may present in breast milk, so any breastfed newborns and infants should be monitored for diarrhea, vomiting or rash.

Reproductive and Lactation Risks

Taking part in this research study can affect an unborn baby. There is insufficient data to adequately characterize the safety of eculizumab in pregnant women with preeclampsia. However, data on reproductive and lactation risks from eculizumab have been largely gathered from pregnant women receiving the drug for treatment of the rare blood disorder paroxysmal nocturnal hemoglobinuria. That data, which includes data from clinical studies and registry data, indicates that eculizumab is unlikely to increase the risk of birth defects, or fetal and neonatal toxicity. Specifically, pregnancy data show no difference in the risk of overall major birth defects for eculizumab (0.94 per 100 live-birth) compared with the background rate for major birth defects of 2.7% in the US reference population. The rate of fetal death (miscarriage and still birth) observed with use of eculizumab is 16.2%, while the estimated background rate of miscarriage in the US general population is between 15% - 20%.

Limited available data suggest that eculizumab is not excreted in human milk. In one case, a patient received eculizumab for treatment of preeclampsia and had no detectable drug in breast milk samples. In a study of women with paroxysmal nocturnal hemoglobinuria, authors evaluated breastmilk samples from 10 women who breastfed their infants while taking eculizumab and the drug was not detected in any of the samples. The authors concluded that eculizumab is safe for use in breastfeeding women.

Unknown Risks to the Developing Embryo or Fetus (an unborn baby)

The study drug, vaccine and antibiotics might involve risks to an embryo or fetus, which are currently unknown.

Collection of Pregnancy Outcomes
We will collect information on the outcome of your pregnancy including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, abnormalities, or complications, and the health status of your child. By signing this consent, you are agreeing to have this information about you and your child collected from your medical records and by telephone calls at 1-2 weeks and 6-8 weeks after delivery. However, you are always free to withdraw your consent to participate in any research procedure.

Follow-up Visit for Discontinuing Participants
While you are free to discontinue your participation at any time, we encourage you to complete a final clinical and laboratory assessment by the study team if you discontinue the study prior to hospital discharge. During this visit, we will conduct tests to collect safety data, and discuss any information that may be important to share with your treating physician.

4. ARE THERE BENEFITS IN TAKING PART IN THE STUDY?

If you agree to take part in this research study, there may or may not be direct medical benefit to you. The possible benefits of taking part in the research study are prolongation of pregnancy compared to standard of care alone. Prolongation of pregnancy may allow additional time for your baby to develop in the womb and reduce prematurity-related complications after delivery. It is also possible that treatment with the study drug, compared to standard of care alone, will reduce your risk of developing serious complications such as seizure, stroke, or damage to other organ systems in your body. However, no benefit is guaranteed. It is possible that your condition may remain unchanged or even get worse.

We hope the information learned from this research study will benefit other individuals with preeclampsia in the future by helping us to learn if eculizumab is an effective treatment option.

5. WILL I BE INFORMED OF RESEARCH RESULTS?

Some of the research tests done in this study follow standard clinical procedures and are performed in certified clinical labs. These test results may be shared with you and may be placed in your Cedars-Sinai medical record. Other research tests done in this study are for research purposes only and are performed in a research only lab where the results are not intended for clinical use. These research-only results will not be shared with you or included in your Cedars-Sinai medical record.

Unanticipated Incidental Findings
If, unexpectedly, we find that results of your research procedures could suggest important medical information and we determine there is something you or your doctors can do in response to this finding, we will contact you using the last contact information provided by you. If necessary, we may recommend additional clinical testing to confirm the research finding. The cost of any additional testing and any related treatment will be your responsibility.

6. WHY WOULD MY PARTICIPATION BE STOPPED?

Your participation in this study may be stopped at any time by the researcher or the sponsor without your consent for any reason, including:

- The study is stopped or suspended;
- Funding for the study is reduced, stopped or withdrawn;

- If it is in your best interest;
- You do not consent to continue in the study after being told of changes in the research that may affect you;
- You do not follow the study procedures;
- Febrile illness (Temperature > 100.4˚ F);
- Signs or symptoms of hypersensitivity or anaphylaxis to study drug;
- If you are discharged prior to being given the study drug;
- Significant study intervention non-compliance;
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in your best interest;
- Disease progression which requires discontinuation of the study intervention;
- If you meet an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation;
- You are unable to receive study drug for more than 8 days from previous dose.

You may choose (or you may be required) to withdraw from certain parts of the study but invited to continue with other parts. For example, you might stop taking a study drug, but continue with follow-up visits or allow us to continue to collect data from your medical records. Separate written consent will be requested if your continued participation will involve procedures not described in this consent form.

7. ARE THERE ANY OTHER OPTIONS?

Your participation is voluntary, so you have the right to decline to participate or to withdraw from this research study at any time without any penalty or loss of benefits to which you would be entitled outside of the study. Choosing not to participate will not affect the care you receive at Cedars-Sinai Health System.

If you decide not to take part in this study, you have other choices. For example:

- you may choose to be treated following the usual clinical approach: expectant management, treatment of high blood pressures, magnesium sulfate to prevent seizure;
- you may choose to take part in a different study at CSMC or elsewhere, if one is available;
- you could decide not to be treated.

The researcher will discuss these options and their risks and benefits with you.

8. WILL MY INFORMATION BE KEPT CONFIDENTIAL?

We will do our best to make sure that the personal information collected as part of this study is kept private. However, we cannot guarantee total privacy. A copy of your research consent and authorization forms may be filed in your electronic medical record at CSMC. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other identifiable personal information will not be used. Organizations that may look at and/or copy your medical records for research oversight, quality assurance, and data analysis include: accrediting agencies, government and regulatory groups (such as Food and Drug Administration (FDA), Office for Human Research Protections (OHRP), etc.), safety monitors, companies that sponsor the study, and authorized representatives of the sponsor.

Attached to this consent form is an "Authorization Form" that outlines with whom your information may be shared for the purposes of this research and under what circumstances.

We might share your information and/or research samples collected in this study with other researchers at Cedars-Sinai, other academic institutions, or third party commercial entities for future research without additional informed consent from you. Information that identifies you will be removed and will not be shared with other researchers or anyone outside of Cedars-Sinai.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.

9. WHAT IF I BECOME ILL OR INJURED BECAUSE OF TAKING PART IN THIS STUDY?

Contact your study doctor at once if you feel that you are ill or have been injured because of taking part in this study. If it is a medical emergency, call 911 or go to an emergency room. Promptly notify your study doctor of your situation at the phone number listed on page 1 of this consent form.

Who pays for my research related illness or injury?
Cedars-Sinai has no plans to pay for costs associated with the treatment of research-related injury or illness. We will make every effort to seek reimbursement from your health plan. However, you will be responsible for any deductibles and co-payments required under your health plan and for any claims ultimately denied by your health plan. Financial assistance may be available under Cedars-Sinai's Charity Care Policy and Procedure. If you feel that you have had a research-related injury and need financial assistance, please contact the IRB Office at 310-423-3783. You do not waive any of your legal rights by signing this form.

10. FINANCIAL CONSIDERATIONS

Costs of Participation
You and your insurance company will not be charged for your participation in this research study. The Sponsor will cover the cost of all items, drugs and services required by this study, including any procedures required by the study that may be standard of care.

Compensation for Participating
You will not be paid for participating in the research study.

Financial Interest in the Research
A significant financial interest is a situation in which financial considerations have the potential to influence a person's professional judgment. This study has been designed to minimize the impact of the investigator's financial interest. You are encouraged to ask the investigator to explain how the financial interest disclosed below will be managed.

Richard Burwick, MD, MPH receives payment from the company supporting this study. Dr. Burwick is on the Speaker's Bureau for Alexion Pharmaceuticals and he receives payments for educational lectures on atypical hemolytic uremic syndrome, which is treated with eculizumab. The PI and institution have no other potential financial conflict of interest with respect to this study.

11. WHAT IF I HAVE QUESTIONS OR PROBLEMS?

Please contact one of the investigators listed on the first page of this form for questions or concerns about the research.

If you have questions, problems, or concerns that you want to discuss with someone who is not associated with this study, or want to offer suggestions or feedback, please contact:

Cedars-Sinai Human Research Protection Program (HRPP)
Phone: (310) 423-3783
Email: ResearchConcerns@cshs.org

The Cedars-Sinai HRPP has been established to protect the rights and welfare of research participants. You may also contact the Cedars-Sinai HRPP if you want to offer input or obtain information regarding the study.

12. CONSENT PROVISIONS

If you sign this form below, it means that:

(1) You have taken the time to carefully read and understand the information presented in this informed consent form; you should discuss it with others, and if appropriate seek a second opinion to make an informed decision;
(2) The information concerning the research study and its involved procedures has been fully explained to you and your questions have been answered to your satisfaction;
(3) You have received and understand all of the information you desire regarding your participation in the research study;
(4) You have considered the potential risks, any anticipated benefits and alternatives (and their relative risks and benefits) of participation;
(5) You are voluntarily agreeing to participate in this research study;
(6) You understand that by consenting to participate in the research, you are not giving up any of your legal rights;
(7) You understand that you have the right to be informed of significant new findings related to this research study which may affect your willingness to continue participating in this study; and
(8) You have been provided with a copy of the "Experimental Subject's Bill of Rights", if applicable to this research study, and have been provided with an opportunity to ask questions regarding the Bill of Rights.

We will give you a copy of this signed and dated consent form and the Experimental Subject's Bill of Rights.

SIGNATURE PAGE

Consent Form for Research and
Authorization for Use and Disclosure of Identifiable Health Information (Research)

SIGNATURE BY THE PARTICIPANT
(Adult or Pregnant Minor between 13 to <18 years old)

Main Research Study: *I hereby agree to participate in the research study described to me during the informed consent process and in this informed consent form. I also give my permission for the researchers to collect my child's health information, as described in this informed consent form.* ***You will be given a signed and dated copy of this form.***

_____

Name of Participant (Print) Signature Date Signed

Optional Sub-study: *I hereby agree that I and my child may participate in the optional sub-study described to me during the informed consent process and described in the attached Appendix B to this form.*

_____

Name of Participant (Print) Signature Date Signed

Authorization for Use and Disclosure of Identifiable Health Information (Research): *I hereby agree that my and my child's identifiable health information may be used and/or disclosed in accordance with this "Authorization for Use and Disclosure of Identifiable Health Information (Research)" form attached as Appendix to this form.*

_____

Name of Participant (Print) Signature Date Signed

Optional Sub-Study: Authorization for Use and Disclosure of Identifiable Health Information (Research): *I hereby agree that my and my child's identifiable health information may be used and/or disclosed in accordance with this "Authorization for Use and Disclosure of Identifiable Health Information (Research)" form attached as Appendix to this form.*

_____

Name of Participant (Print) Signature Date Signed

SIGNATURE BY THE INVESTIGATOR

I attest that all the elements of informed consent described in this form have been discussed fully in non-technical terms with the participant. I further attest that all questions asked by the participant were answered to the best of my knowledge.

Name of Investigator (Print)	Signature	Date Signed

SIGNATURE BY THE INTERPRETER/WITNESS

(Signature of an interpreter is only required when a non-English speaking subject is consented with the assistance of an interpreter and an IRB-approved 'short form.' The witness may be any person who is conversant in both English and the language of the Non-English speaking subject, such as the interpreter (the certified hospital interpreter), study staff, a family member, or other person. The witness signs the consent forms to confirm that the oral interpretation occurred.)

Name of Witness (Print)	Signature	Date Signed

CEDARS-SINAI MEDICAL CENTER

APPENDIX A: EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

In accordance with California Health and Safety Code 24172, any person who is required to consent to participate as a subject in a research study involving a medical experiment or who is requested to consent on behalf of another has the right to:

1. Be informed of the nature and purpose of the experiment.

2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized.

3. Be given a description of any attendant discomforts and risks to the subject reasonably to be expected from the experiment.

4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.

5. Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be advantageous to the subject, and their relative risks and benefits.

6. Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.

7. Be given an opportunity to ask any questions concerning the experiment or the procedure involved.

8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation in the medical experiment without prejudice.

9. Be given a copy of any signed and dated written consent form used in relation to the experiment.

10. Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.

CEDARS-SINAI MEDICAL CENTER

AUTHORIZATION FOR USE AND DISCLOSURE OF IDENTIFIABLE HEALTH INFORMATION FOR RESEARCH

- **USE AND DISCLOSURE OF HEALTH INFORMATION**

If you agree to this Authorization, you give permission to the research team at Cedars-Sinai Medical Center ("CSMC") to use or disclose your identifiable health information ("private information") for the research study titled "Complement Regulation to Undo Systemic Harm in Preeclampsia: the CRUSH study " which is described in the Consent Form for Research ("Consent Form") to which this Authorization is attached. In particular, you authorize the research team acting under the direction of the Principal Investigator to review your medical records and collect your private information from the following sources:

☒ Laboratory tests
☒ Pathology reports
☒ Imaging reports (e.g., x-rays or scans)
☐ Photographs or videos of your image
☒ Doctor/clinic records
☒ Hospital/medical records
☐ Mental health records
☐ Billing records
☒ Other tests or other types of medical information: Neonatal records

- **WHO WILL HAVE ACCESS TO YOUR PRIVATE INFORMATION?**

Your private information will be used by and/or shared with the CSMC investigators listed in Section A of the Consent Form and their research staff.

In addition to the research team, if applicable, the following parties may receive your private information and inspect your records:

- The reviewing Institutional Review Boards and CSMC offices with authority to oversee research compliance.
- U.S. government agencies, such as the Food and Drug Administration and the Department of Health and Human Services.
- Researchers at other organizations who are participating in this research study.
- The Study Sponsor and its business partners, for matters related to research study oversight, data analysis and use of research results in product development.
- Representatives from regulatory agencies in other countries may join in the review of your research records, including research-related medical reports and information, with the Sponsor and/or the FDA.

CSMC is required by law to protect your private information. However, the recipients described above may re-disclose (or share) your information with other parties unless such sharing is prohibited by law.

- **WHEN WILL MY AUTHORIZATION EXPIRE?**

By signing this document, you authorize the use and sharing of your private information until the end of the research study.

- **REVOKING AUTHORIZATION**

You may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, the research team may still use or disclose private information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. To revoke this Authorization, you must write to the Principal Investigator of the research study. The mailing address is: Richard Burwick, MD, MPH. 8635 W. 3rd St. Medical Office Tower, Suite 160W, Los Angeles, CA 90048.

- **NOTICE OF RIGHTS AND OTHER INFORMATION**

You do not have to agree to this Authorization, but if you do not agree, you may not participate in the research study. CSMC may not condition (withhold or refuse) treating you on whether you agree to this Authorization.

If you agree to this Authorization, please sign on the appropriate signature line below. You will receive a copy of this Authorization.

- **OPTIONAL SUB-STUDY**

In addition to the main research study, you have the option to agree to participate in one or more optional sub-studies as explained to you during the informed consent process. Your decision to take part in the optional sub-study(ies) does not impact your ability to participate in the main research study.

If you agree that your identifiable health information may be used and/or disclosed for the optional sub-study described in the informed consent process and above, you will be required to sign a second time in the signature section.

CEDARS-SINAI MEDICAL CENTER

APPENDIX B: OPTIONAL SUB-STUDY

INTRODUCTION

This Appendix is provided to you as a supplement to the main study consent form. In addition to the main study, you are also invited to take part in this optional sub-study. **You do not have to agree to this optional sub-study to be in the main study. Your medical care at Cedars-Sinai Medical Center (CSMC) will not be changed in any way as a result of your decision.**

Before you make a decision, please read the rest of this Appendix and ask the researchers any questions to help you understand the sub-study.

This Appendix will be given with the study consent form. If you agree to participate in the optional sub-study, then you will be asked to sign separate sub-study signature lines in the main consent form.

A. PURPOSE OF THIS OPTIONAL SUB-STUDY

We are interested in storing specimens and data collected from you during this study for future research. Your samples and data could be used to research the causes of hypertensive disorders of pregnancy such as preeclampsia, its complications, and other conditions for which individuals with hypertensive disorders of pregnancy are at increased risk, and to improve treatment.

B. STUDY PROCEDURES INVOLVED IN THIS OPTIONAL SUB-STUDY

No additional procedures will be conducted for this optional sub-study. Your samples and data will have been collected only for research purposes during a research-specific procedure.

Your specimens and data will be de-identified. Any information that could identify you will be removed and kept separately from your specimens and medical information. The only link between your specimens/medical data and your identity will be a list with a unique study number that will link your identity so that only the research team, or other trusted researchers, can recognize you.

C. LENGTH OF THIS OPTIONAL SUB-STUDY

In this optional sub-study, testing of your specimens may go on for a long period of time. Therefore, while your direct participation in this optional sub-study will be done once you have completed the procedures/visits described above, your specimen(s) may be studied for many years.

D. POSSIBLE RISKS OR DISCOMFORTS OF THIS OPTIONAL SUB-STUDY

There are no additional risks to you for participating in this optional sub-study.

E. BENEFITS OF THIS OPTIONAL SUB-STUDY

You should not expect to benefit from taking part in this optional sub-study.

While no benefit is ever guaranteed, we hope the information learned from this optional sub-study will benefit other individuals with the condition being studied in the future.

F. PAYMENT

You will not be paid for providing data and samples for this study. Once you provide the samples for the research, you no longer have access to them. The donated samples become the property of CSMC or the study sponsor. Researchers might use your samples (even if identifiers are removed) to develop new products, tests or discoveries. Sometimes, these inventions may result in commercial profit for the researchers, CSMC, and/or other organizations. If this happens, you will not receive any financial benefits.

APPENDIX C: FLOWCHART OF PROCEDURES

Schedule of Activities

	Screening Day -7 to Day -1	Visit 1 Day 1	Visit 2 Day 4	Visit 3 Day 8	Visit 4 Day 11	Visit 5 Day 15	Visit 6 Day 18	Visit 7 Day 22	Visit 8 Day 25	Visit 9 Day 29	… ***
Eligibility checklist	X										
Informed consent	X										
Medical history and demographics	X										
Physical exam (pre-infusion on treatment days)	X	X		X		X		X		X	X
Screening labs Platelet count, ALT, AST, LDH, Cr, PT/PTT, INR	X										
Quadrivalent meningococcal conjugate vaccine (MenACWY) *	X	X									X
Meningococcus serogroup B vaccine (MenB)*	X	X									X
Prophylactic Antibiotics**		X	X	X	X	X	X	X	X	X	X
Eculizumab 900 mg IV		X		X		X		X			
Eculizumab 1200 mg IV										X	X
Safety Labs:† CBC, CMP, LDH (pre-infusion on treatment days)		X	X	X	X	X	X	X	X	X	X
Lab Tests for Research† C3, C4, CH50, Haptoglobin (pre-infusion on treatment days)		X	X	X	X	X	X	X	X	X	X
Blood collection for Research Labs †		X	X	X	X	X	X	X	X	X	X
Urine collection†† (pre-infusion on treatment days)		X	X	X	X	X	X	X	X	X	X
Medical record review		X	X	X	X	X	X	X	X	X	X
Assessment for adverse maternal/fetal outcomes‡		X	X	X	X	X	X	X	X	X	X
Total time		60 min	20 min	60 min	20 min	60 min	20 min	60 min	20 min	60 min	20-60 min

Postpartum follow up	1-2 weeks postpartum	6-8 weeks postpartum	0-8 weeks Postpartum
Quadrivalent meningococcal conjugate vaccine (MenACWY), 2nd dose (at least 2 months from 1st dose)*			X
Meningococcus serogroup B vaccine (MenB) (at least 1 month from 1st dose)*			X
Prophylactic Antibiotics**	X	X	
Medical record review	X	X	
Assessment for adverse maternal outcomes (chart review / telephone visit)‡‡	X	X	
Assessment for adverse neonatal outcomes (chart review / telephone visit)‡‡	X	X	
Total time	20 min	20 min	20 min

Sample and Procedure Table:

Visit days above refer to the number of days from initiation of study drug (Day 1 = first day of eculizumab), they do not refer to antepartum or postpartum state.

* For subjects without meningococcal vaccination in the prior 5 years, administer Quadrivalent meningococcal conjugate vaccine (MenACWY): 2 doses of Menactra or Menveo with the first dose of the vaccine on Day 1 (prior to the first dose of eculizumab) or up to 7 days prior to Day 1 (after informed Consent), and the second dose of the vaccine at least 2 months later. Also, administer Meningococcus serogroup B vaccine (MenB): 2 doses of Bexsero with the first dose of the vaccine on Day 1 (prior to the first dose of eculizumab) or up to 7 days prior to Day 1 (after informed Consent), and the second dose of the vaccine at least 1 month later. For subjects with prior vaccination, revaccinate in accordance with the recommendation of the Advisory Committee on Immunization Practices, considering the duration of eculizumab therapy. The second dose of the two meningococcal vaccines may be administered up to 8 weeks postpartum, however in some subjects, the second dose may become due prior to delivery.

** Penicillin 500 mg PO bid, or Azithromcyin 250 mg PO daily (if allergy to penicillin), until 4 weeks after the last dose of eculizumab

*** Following induction dose of eculizumab (900 mg IV every 7 days x 4 weeks), eculizumab will be given at maintenance dose of 1200 mg IV on week 5, followed by 1200 mg every 2 weeks. Eculizumab should be given until 48 hours postpartum. Alternating study visits for specimen collection & medical record review will continue until hospital discharge. Blood draws and urine samples are to be drawn the day of and prior to every eculizumab infusion and 3 days after every eculizumab infusion, even if patient is in the postpartum period. If the patient discontinues participation in the study before hospital discharge, a final discontinuation visit will be performed on that day, including collection of blood and urine samples and assessment of maternal and fetal status. Blood and urine collections will be discontinued upon hospital discharge

† Safety labs (CBC, CMP, and LDH), as well as other labs specific to the research study (C3, C4, CH50, and haptoglobin), will be sent to the Cedars-Sinai Laboratory. Additional research samples to be collected will include one 10ml purple-top tube for plasma and one 10ml red-top tube for serum. To assess peak and trough effects of the study drug, subjects will have blood collected three days after each study drug administration (peak) and just prior to the study drug infusion on each subsequent treatment day (trough). These additional research samples will be processed and stored in Karumanchi laboratory. Future research assays, including measurements of C5a, C5b-9, CD59, sFLT1, PlGF and PK/PD assays, will be performed in the Karumanchi laboratory or Alexion Pharmaceuticals laboratory, and such results will not be available to the treatment team or study participant.

† † Urine sample to be sent clinically for protein assessment (one of the following: urine protein/creatinine ratio, 24hr urine protein or urinalysis), and an additional research sample will be collected up to 20ml. Future research assays, including measurements of urinary C5a, C5b-9, CD59, sFLT1 and PlGF, will be performed in the Karumanchi laboratory, and such results will not be available to the treatment team or study participant.

‡ In addition to the study visits designated in the table, a member of the study team will write a brief progress note daily assessing maternal and fetal status.

‡‡ For postpartum visits, maternal and neonatal outcomes will be assessed by chart review and telephone call to the patient. Up to three telephone calls will be made to reach the study participant, after which they will be deemed lost to follow up.

APPENDIX D: Detailed Description of Common Medical Procedures Performed for Research Purposes and Associated Risks

The procedures listed below are often performed as part of routine care for a person with your condition. They are being repeated or performed more frequently as part of this research. However, the risks associated with each procedure should be comparable to what you would experience even if you were undergoing the procedure outside this research study.

Study Procedure	Related Risks
Blood draw: A needle is placed in the vein in your arm to draw blood.	Blood drawing may cause some pain and has a small risk of bleeding, bruising, or infection at the puncture site. There is also a small risk of fainting.
Infusion Procedure: Infusion is the administration of drugs directly into your bloodstream using intravenous (IV) lines. The risks associated with IV lines are described separately below.	Occasionally, people have allergic reactions (including life-threatening reactions) when taking any medication. Symptoms of any allergic reaction can include a rash, hives, itching, and/or difficulty breathing, closing of the throat, swelling of the lips, tongue or face, and rarely death. If you experience any difficulty breathing, closing of the throat, swelling of the lips, tongue or face, or hives, you should stop taking your study drug and immediately seek emergency medical attention. In general, allergic reactions to medicines are more likely to occur in people who have allergies to other drugs, foods, or things in the environment, such as dust or grass. If you have allergies to other medicines, foods, or other things in the environment, or if you have asthma, you should let your researcher know.
Injection: A method for putting fluids into the body using a syringe and a hollow needle that is pierced through the skin	These reactions could include bruising, pain, bleeding, and rarely infection at the injection site, feeling lightheaded and fainting. As with any injection, there may be some irritation at the injection site where the study drug is administered.
Intravenous (IV) lines: You will receive the study drug or other medications or contrast agent through an intravenous (IV) line. An IV line is a small tube that is attached to a catheter and inserted by needle into a vein usually in your hand or arm. Qualified medical professionals will place IV lines for use in this study.	IV lines are usually safe and well tolerated and complications are rare, but can include phlebitis (swelling of the vein) and infection. The IV may come out accidentally or blood may leak around the line. If the IV is not in the vein, medication or fluid can enter the surrounding soft tissues, and can be associated with swelling, discomfort, bruising and irritation. Rarely, a clot can develop in the IV line itself. If this happens, the staff may remove the old IV line and start a new IV line.

	There is also a small risk of feeling lightheaded and fainting.
Medical History Review: You will be asked about your medical and surgical history with attention to other medical conditions, medication use, smoking and drug habits, and prior infections.	There are no physical risks associated with this procedure.
Urine Collection: You will be asked to provide a urine sample in a specimen cup.	There are no risks associated with this procedure.
Demographic Information: You will be asked about your age, gender, race, and ethnicity.	There are no physical risks associated with these procedures.