# INFORMED CONSENT FORM

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|---|---|
| STUDY TITLE: | A Phase 2 Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of SPR001 (Tildacerfont) in Children Aged 2 to 17 Years with Congenital Adrenal Hyperplasia |
| PROTOCOL NUMBER: | SPR001-205 |
| SPONSOR: | Spruce Biosciences, Inc. |
| STUDY DOCTOR: | [Investigator Name]<br>[Site Address]<br>[Office Hours Tel]<br>[Out of Hours Tel] |
| ETHICS COMMITTEE or INSTITUTIONAL REVIEW BOARD: | [EC/IRB Name]<br>[EC/IRB Address]<br>[Office Hours Tel] |

In this study, adults and children diagnosed with Classic Congenital Adrenal Hyperplasia (CAH) are invited to participate. To ensure that all study participants are being addressed, you will notice that the term “you/your child” is used throughout this informed consent form.

This form tells you about the details of this study. Please read this with care and ask the study doctor or study staff all your questions. When you understand what is in this form, you will be asked to sign it for you/your child to join this study. You will receive a signed and dated copy of this informed consent form.

Participation in this study is voluntary. This means that you/your child can choose whether or not to participate in the study. You/your child can leave the study at any time, without any reason. Doing so will not change your/your child’s health care or rights. If you/your child does not want to join the study, you can talk to the study doctor about your/your child’s health care.

If your child is at least 6 years old and can read, your child will be given an “assent” form. That form briefly describes the goal of the study, the procedures involved in the study, and any risks and benefits of taking part in the study. A signed assent by itself is not enough. If your child agrees to take part, you as a parent/guardian still need to give informed consent.

Spruce Biosciences, Inc. is a drug company focused on developing treatments for adrenal disorders like CAH. This drug company will run and pay for this study. The study doctor is paid by Spruce Biosciences, Inc. to conduct this study.

An ethics committee/Institutional Review Board has reviewed and approved this study to make sure that your/your child's rights and welfare are protected after joining this study. This committee will watch over this study while you/your child is taking part in it.

# INFORMATION ABOUT THIS STUDY

## Why is this study being done?

The study will test a drug called tildacerfont, which is being developed for treating people with CAH. Tildacerfont is not FDA-approved for treating CAH so it can only be used in a study like this one. Tildacerfont belongs to a group of drugs known as corticotropin-releasing factor type-1, also known as $CRF_1$, receptor antagonists. In previously completed studies, tildacerfont has been shown to reduce the over accumulation of hormones made by the adrenal glands by blocking the activity of the $CRF_1$ receptors on the pituitary gland. This may allow people with CAH to have normal levels of sex hormones without having to use excess amounts of glucocorticoids (GC), also known as steroids.

From this point forward, any references to the word "study drug" will mean tildacerfont.

The goal of this study is to test the safety and behavior of tildacerfont in your/your child's body. The main objective is to find a safe and accepted dose in people with CAH and to find how the body deals with the study drug at different dose levels.

## What will happen during the study?

This is an open-label study that will enroll approximately 55 children and 15 adults (70 participants total) in 10 cohorts to evaluate the safety, efficacy, and how different tildacerfont dosing regimens interacts with the body known as pharmacokinetics (PK), potentially up to 200 mg once daily (QD) for 12 weeks and up to 400 mg twice daily (BID) for 4 weeks in children and adults with classic CAH. The study will be conducted at approximately 15 investigative sites within North America.

Open-label means that you, your child, and the study doctor will know which dosage of tildacerfont is given. In this study, different doses of the study drug will be tested, and all enrolled participants will receive the study drug. While enrolled in the study, you/your child will continue to take your/their GC doses in addition to the study drug.

The cohorts will be grouped together as follows: Cohorts 1-3 and Cohorts 4-9.

In Cohorts 1-3, QD dosing for 12 weeks of treatment will be investigated; these cohorts are expected to enroll approximately 20 children (10 in the 11- to 17-year-old age group and 10 in the 2- to 10-year-old age group). There will be an additional optional Cohort 1a, depending on the results from Cohort 1; if this cohort is used, there will be up to 5 participants. Therefore, Cohorts 1 to 3 may enroll up to 25 children total: 15 in the 11- to 17-year-old age group and 10 in the 2- to 10-year-old age group.

In Cohorts 4-9, BID dosing for 4 weeks of treatment will be investigated; these cohorts are expected to enroll approximately 15 adults aged ≥18 years across Cohorts 4 and 5 and approximately 30 children across Cohorts 6, 7, 8, and 9. Cohorts 8 and 9 are optional and may be opened based on recommendations from the Data Monitoring Committee (DMC) and sponsor.

During the study "treatment period", there will be 7 scheduled visits over approximately 18 weeks for Cohorts 1 to 3 and 5 scheduled visits over approximately 10 weeks for Cohorts 4 to 9.

An independent group of experts called a Data Monitoring Committee (DMC) will review the data collected on an ongoing basis and will advise the sponsor based on their review if the study is safe to progress to the next cohort and the recommended dosing.

Participants will be assigned to a specific group (cohort) according to their age and when they join the study. The dosing details for each cohort are described in Table 1:

**Table 1. Study Cohorts**

| Cohort | Age | Corresponding Adult Dose | Number of Subjects | Treatment Duration |
|---|---|---|---|---|
| 1 | 11 to 17 years | 50 mg QD | 5 | 12 weeks |
| 1a[a] | 11 to 17 years | To be determined based on DMC recommendation (50 or 100 mg QD) | 5 | |
| 2 | 11 to 17 years | 200 mg QD | 7 | |
| 3 | 2 to 10 years | 50 mg QD, 100 mg QD, OR 200 mg QD | 18 | |
| 4 | ≥18 years | 200 mg BID | 5 | 4 weeks |
| 5 | ≥18 years | Up to 400 mg BID | 10 | |
| 6 | 11 to 17 years | 200 mg BID | 5 | |
| 8[b] | 11 to 17 years | Up to 400 mg BID | 10 | |
| 7 | 2 to 10 years | 200 mg BID | 5 | |
| 9[b] | 2 to 10 years | Up to 400 mg BID | 10 | |
| | | | Up to 70 subjects total | |

Abbreviations: BID=twice daily; DMC=Data Monitoring Committee; QD=once daily.
[a] Cohort 1a is an optional interim dose cohort that may be enrolled only if needed per DMC recommendation and Sponsor decision, in the event of a safety concern in participants in Cohort 1.
[b] Cohort 8 and 9 are adaptive cohorts that may be enrolled based on emerging safety data and per DMC and Sponsor recommendation/approval.

## Taking the Study Drug:

The study drug will be in the form of tablets –25 milligrams (mg), 50 mg, and 200 mg. Participants will take between 1 and 6 tablets daily, depending on the dose and Cohort assignment. Participants can either swallow the tablet[s] whole or crush the tablet[s] and sprinkle them on soft foods.

Cohorts 1-3 will take the doses once daily. The dose will be taken with the evening meal. However, the first 2 weeks in Cohorts 1, 1a, and 2 will require dosing with a morning meal.

Cohorts 4-9 will take the dose twice daily. Doses should be taken with the morning and evening meals.

Note: The morning doses of tildacerfont will be administered in the clinic on Day 1 and Day 14 for Cohorts 1, 2, 4, 5, 6, 7, 8 and 9 (and 1a, if this one is used) and on Day 1 only for Cohort 3.

**SCREENING PERIOD (Up to 2 weeks)**

**Visit 1 – Screening visit*:***

After you have signed the Informed Consent Form and if you/your child agrees to be in this study, you/he/she will be checked by the study doctor for eligibility to participate in the study during the screening period, which spans approximately 14 days before the first dose of study drug. Tests and procedures performed during the screening period are provided later in this document. You/your child will need to wait to take the morning GC dose until after all blood samples are drawn.

Questionnaires will also need to be completed by you and/or your child and by the study doctor for psychiatric assessments to confirm your child's eligibility. Depending on your child's age, different questionnaires will be used. The Columbia–Suicide Severity Rating Scale (C-SSRS) is used to assess suicidality for participants aged 6 years or older, the Patient Reported Outcomes Measurement Information System (PROMIS) is used to assess for symptoms of depression and anxiety in participants aged 5 years or older, and the Survey of Well-Being of Young Children (SWYC) is used to assess anxiety and depression in participants under 5 years of age (Cohorts 3, 7, and 9 only).

The study doctor will review the results of the screening tests to confirm if this research study is right for you/your child. If you/your child is not eligible to take part in this study, the study doctor will discuss the reasons for this decision and other treatment options.

**TREATMENT PERIOD (12 weeks for Cohorts 1-3; 4 weeks for Cohorts 4-9)**

**Visit 2 (Week 1, Day 1):**

On the first day of the dosing period (Day 1) you and your child will be at the study clinic in the morning. The first dose of study drug will be given to you/your child after a morning meal.

Prior to the administration of the first dose, some questionnaires will need to be completed by you and/or your child and by the study doctor for psychiatric assessments to confirm that there have been no significant change since the last visit. The

questionnaires to be administered include C-SSRS, PROMIS, and SWYC (depending on your child's age) to assess for symptoms of depression and anxiety.

Blood samples will be taken to assess the study drug's PK, how the body is breaking down the study drug, and pharmacodynamics (PD), how the drug is acting on the body. Samples will also be studied to measure the metabolites that are produced in your body while taking the study drug. This helps to understand the behavior of the study drug in your body. These will be taken before study drug is given to you/your child and at different time points (up to 5 hours) after the study drug is given.

For Cohorts 1, 2, 4, 5, 6, 7, 8, and 9 (and 1a if indicated), blood samples will be collected at 3 timepoints.

For Cohort 3, only one pre-dose sample will be drawn.

Blood samples will also be collected for routine health monitoring, including analysis of chemistry, hematology, liver function, and thyroid function. These will be taken before you/your child's dose of glucocorticoids (GC) or the study drug, but you/your child will not need to fast.

At the end of Visit 2 Day 1, a 12-week or 4-week supply of study drug, depending on the cohort, will be given to you or your child to take home. This will be sufficient for the entire duration of the study; however, you or your child will need to bring in the study drug to the clinic for all study visits so the study doctor and team can make sure the correct amount is being administered. You and your child will also be provided instructions about how to take the study drug at home by the study doctor.

**Visit 3 (Week 2, Day 14 ±3 days):**

On Visit 3 of the dosing period, you and your child will return to the study clinic for an outpatient visit.

Cohorts 1, 2, 4, 5, 6, 7, 8, and 9 (and 1a if indicated) will receive study drug and morning GC dose after completion of a morning meal. Cohort 3 will have received study drug the evening prior and will not require supervised dosing or a meal.

At this visit, participants in Cohorts 1, 2, 4, 5, 6, 7, 8, and 9 (and 1a if indicated) must bring all unused study drug pouches and the study drug carton supplied to you.

During this visit, blood samples will be taken pre-dose for PK, PD, and routine health monitoring. Blood samples will also be taken post-dose for PK and PD. Samples will also be studied to measure the metabolites that are produced in your body while taking the study drug. This helps to understand the behavior of the study drug in your body. You and/or your child will also be asked to complete questionnaires including the C-SSRS, PROMIS, and SWYC (depending on your child's age).

A 12-lead electrocardiogram (ECG) will be performed on you/your child to assess heart function.

**Visit 4 (Week 4 ±3 days); Visit 5 (Week 8 ±3 days); Visit 6 (Week 12 ±3 days)**

Visits 4, 5, and 6 will follow a similar schedule as Visit 3. The exceptions are noted below.

For Cohorts 4-9, weight-based dose adjustments for the study drug will be performed, if indicated, at Visit 4. Additionally, Visit 4 is the end of Treatment Period. All participants will be given the opportunity to consent and enroll into the Extension period of the study. The details and procedures are described in the Extension Consent/Assent.

For Cohorts 1-3, a 12-lead ECG and urinalysis will only be performed on Visit 6. Additionally, Visit 6 is the end of Treatment Period. All participants will be given the opportunity to consent and enroll into the Extension period of the study. The details and procedures are described in the Extension Consent/Assent.

**Visit 7 (30 days after last dose ±7 days):**

Thirty (30) days after the last dose of study drug (after the treatment period or the extension period, if applicable), the study staff will contact you and your child by telephone for a safety follow-up assessment. If any health or safety concerns are noted during the phone call, you/your child may be asked to come into the clinic for additional assessments and an evaluation. Please see the table below for a complete list of these additional assessments.

**STUDY PROCEDURES**

The list below includes information that will be requested and the procedures that will be performed during the study. A table is also included to show what happens at each visit. If you do not know these tests or want to know more, please ask your/your child's study doctor to explain.

- **Medical History:** A complete review of health history will be done to make sure you/your child can join the study. You and your child will be asked about any history related to your/your child's CAH (like background and progress of disease), prior therapies (like other drugs used to treat CAH) response to those treatments, and details of other previous diseases, if any, to understand your/your child's health better. You and your child will be asked about birth date, sex, and race or background only for clinical research purposes.

- **Physical Examination:** A physical examination will be performed at defined visits. Height and weight will also be measured.

- **Vital Signs:** Body temperature, pulse rate, respiration rate, and blood pressure (in seated position) will be measured at Screening and before each study drug administration.

- **Concomitant Medications:** Review of drugs that you/your child is taking or has taken before joining the study. This will include all prescription drugs, over-the-

counter medication, herbal products, vitamins, minerals, supplements, and any other medications. Certain medications are prohibited and will be reviewed by the study doctor. It is important to contact the study doctor before starting any new drugs or supplements.

- **Electrocardiogram (ECG):** This is a painless test to check the health and rhythm of your heart.

- **Pregnancy Test:** If the participant can have a child (if menstrual periods have started), a blood sample will be collected to perform a pregnancy test at screening. Collection of a urine sample for a pregnancy test at every visit will also be requested.

- **Blood sampling for biomarkers:** A biomarker is a biological molecule found in blood that can be used to measure the presence or progress of a disease and the effects of treatment on the body. Blood samples will be taken to assess presence of these molecules in the body.

- **Side Effects:** You/your child will be monitored for side effects during the study.

- **Blood Tests:** Some amount of blood will be collected from you/your child for tests. The maximum volume of blood taken during the entire study will be around 135 mL (approx. 9 tablespoons). A needle will be used to collect blood from a vein in the arm. Sometimes a blood test may need to be repeated. This can be done during an unscheduled visit. If this happens, the total amount of blood collected will not exceed the blood limits as specified by local regulations. Blood samples will be collected to assess the following:

    - complete blood count (white and red blood cells, platelets)
    - blood clotting
    - kidney, liver, and thyroid function
    - cholesterol levels
    - how the body processes the study drug
    - levels of standard biomarkers for your/your child's CAH
    - levels of male and female hormones in your/your child's blood
    - confirm you/your child does not have Hepatitis B or C or HIV

- **Urine Tests:** Urine will be collected at Visits 1 (screening), 3, 6, Early Termination (if applicable), and Safety Follow-Up for Cohorts 1-3. It will be collected at Visits 1 (screening), 3, Early Termination (if applicable), and Safety Follow-Up for Cohorts 4-9. This will be a painless assessment where urine will be collected in a container and then analyzed.

- **Columbia–Suicide Severity Rating Scale (C-SSRS); Patient Reported Outcomes Measurement Information System (PROMIS); Survey of Well-Being of Young Children (SWYC) Questionnaires**: During every study visit, you and/or your child and the study doctor will need to answer these questionnaires for baseline psychiatric assessments and to confirm no significant change since the

last visit. These questionnaires are used to assess suicidality and symptoms of depression or anxiety.

- **X-ray:** During defined visits, an X-ray of left hand and wrist will be performed to assess bone age and calculate predicted adult height (if deemed appropriate by the principal investigator). An X-ray is a painless test that produces images of the structures inside the body, particularly the bones. This will not be performed in adults (Cohorts 4 and 5).

The below table shows what will happen during each study visit and what procedures are involved at each visit.

## SCHEDULE OF ACTIVITIES FOR COHORTS 1, 1A, 2, AND 3

| | | Treatment Period | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Screening** | **Day 1** | **Week 2** | **Week 4** | **Week 8** | **Week 12 (EOT)** | **Early Termination** | **Safety Follow-up** |
| **VISIT NUMBER** | **1** | **2** | **3** | **4** | **5** | **6** | | **7** |
| **STUDY DAY** | **≤14 days before V2** | **1** | **14** | **28** | **56** | **84** | | **Last dose +30 days** |
| Visit windows | | | ±3 days | ±3 days | ±3 days | ±3 days | | ± 7 days |
| Informed consent/assent | X | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | |
| Demography & medical history | X | | | | | | | |
| Review of prior medications from past year | X | | | | | | | |
| Review of concomitant medications | X | X | X | X | X | X | X | X |
| Hepatitis B & C and HIV Screening | X | | | | | | | |
| Pregnancy test for female of childbearing potential | X | X | X | X | X | X | X | X, as needed |
| Laboratory assessments | X | X | X | X | X | X | X | X, as needed |
| **Pharmacodynamics and Tildacerfont Concentration Samples (by Cohort)** | | | | | | | | |
| Cohorts 1, 2, and 1a (if indicated) PK & PD (Serial Samples) | | X | X | | | | | |
| Cohorts 1, 2, and 1a (if indicated) PK & PD (Single Sample) | | | | X | X | X | X | X, as needed |
| Cohort 3 PK & PD (Single Sample) | | X | X | X | X | X | X | X, as needed |

| | | Treatment Period | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Screening** | **Day 1** | **Week 2** | **Week 4** | **Week 8** | **Week 12 (EOT)** | **Early Termination** | **Safety Follow-up** |
| **VISIT NUMBER** | **1** | **2** | **3** | **4** | **5** | **6** | | **7** |
| **STUDY DAY** | **≤14 days before V2** | **1** | **14** | **28** | **56** | **84** | | **Last dose +30 days** |
| Visit windows | | | ±3 days | ±3 days | ±3 days | ±3 days | | ± 7 days |
| GC dose adjustment | | | | X | X | X | | |
| Weight-based tildacerfont dose adjustment | X | | | | | X | | |
| Urinalysis | X | | X | | | X | X | X, as needed |
| Vital signs, body weight | X | X | X | X | X | X | X | X, as needed |
| Physical exam | X | X | X | X | X | X | X | X, as needed |
| 12-lead ECG | X | | X | | | X | X | X, as needed |
| Bone age and predicted adult height | X | | | | | | | |
| C-SSRS assessment (participants aged 6-17) | X | | X | X | X | X | X | X, as needed |
| PROMIS assessment (participants aged 5-17) | X | | X | X | X | X | X | X, as needed |
| SWYC (Cohort 3 participants aged ≤5 years) | X | | X | X | X | X | X | X, as needed |
| Dispense study drug | | X | | | | | | |
| In-clinic drug administration | | X | X | | | | | |
| Review any side effects | | X | X | X | X | X | X | X |

## SCHEDULE OF ACTIVITIES FOR COHORTS 4, 5, 6, 8, 7, and 9

| | Screening | Treatment Period | | | Early Termination | Safety Follow-up |
|---|---|---|---|---|---|---|
| | | Day 1 | Week 2 | Week 4 (EOT) | | |
| **VISIT NUMBER** | **1** | **2** | **3** | **4** | | **5** |
| **STUDY DAY** | **≤14 days before V2** | **1** | **14** | **28** | | **Last dose +30 days** |
| Visit windows | | | ±3 days | ±3 days | | ±7 days |
| Informed consent/assent | X | | | | | |
| Inclusion/exclusion criteria | X | X | | | | |
| Demography & medical history | X | | | | | |
| Review of prior medications from past year | X | | | | | |
| Review of concomitant medications | X | X | X | X | X | X |
| Hepatitis B & C and HIV Screening | X | | | | | |
| Pregnancy test for female of childbearing potential | X | X | X | X | X | X, as needed |
| Laboratory assessments | X | X | X | X | X | X, as needed |
| **Pharmacodynamics and Tildacerfont Concentration Samples (by Cohort)** | | | | | | |
| Cohorts 4, 5, 6, 7 (and 8 and 9, if indicated) PK & PD (Serial Samples) | | X | X | | | |
| Cohorts 4, 5, 6, 7 (and 8 and 9, if indicated) PK & PD (Single Samples) | | | | X | X | X, as needed |
| GC dose adjustment | | | | X | | |
| Weight-based tildacerfont dose adjustment | X | | | | | |
| Urinalysis | X | | X | | X | X, as needed |
| Vital signs, body weight | X | X | X | X | X | X, as needed |
| Physical exam | X | X | X | X | X | X, as needed |
| 12-lead ECG | X | | X | | X | X, as needed |

| | Screening | Treatment Period | | | Early Termination | Safety Follow-up |
|---|---|---|---|---|---|---|
| | | Day 1 | Week 2 | Week 4 (EOT) | | |
| **VISIT NUMBER** | **1** | **2** | **3** | **4** | | **5** |
| **STUDY DAY** | **≤14 days before V2** | **1** | **14** | **28** | | **Last dose +30 days** |
| Visit windows | | | ±3 days | ±3 days | | ±7 days |
| Bone age and predicted adult height (not for adults) | X | | | | | |
| C-SSRS assessment (participants aged 6 and older) | X | | X | X | X | X, as needed |
| PROMIS assessment (participants aged 5 and older) | X | | X | X | X | X, as needed |
| SWYC (Cohort 3 participants aged ≤5 years) | X | | X | X | X | X, as needed |
| Dispense study drug | | X | | | | |
| Clinic drug administration | | X | X | | | |
| Review any side effects | | X | X | X | X | X, as needed |

## What happens to the samples collected from you/your child?

Your/your child's blood and urine samples will be sent to a central laboratory to be tested. To protect your/your child's privacy, samples will be labeled with a unique patient code. They will not be labeled with your/your child's name or any other personal details.

The samples may be securely stored for up to 5 years after the end of the study in the laboratory or long-term storage facility designated by the sponsor, in case any samples need to be re-tested. Back-up samples for re-testing will be stored at PPD Central Laboratory located at 2 Tesseneer Drive, Highland Heights, KY, USA, 41076 and XXX. After this period of time, samples will be destroyed. No information about your/your child will be mentioned on these samples.

During and after the study, you and your child have the right to contact the study doctor and request that the samples be destroyed (as long as the samples are still coded and can be found). All the samples and test data collected before you/your child left the study will still be used for study purposes. After leaving this study, no new samples or test data will be taken from you/your child for the study.

## What is expected from the study participant?

While participating in the study, you/your child should:

- Come to all study visits.
- Take the study drug and GC as directed by your/your child's study doctor.
- Not give your/your child's study drug to anyone else.
- Keep study drug at room temperature and out of reach of any unintended users.
- Not take any other drugs or remedies unless the study doctor has allowed them first. This includes prescription and over-the-counter drugs (including vitamins and herbal medicines).
- Tell the study doctor about any new treatment or drug you/your child takes during the study.
- Give correct and accurate information about your/your child's health history and current health.
- Tell the study doctor about any health problems during the study.
- If you/your child is female and becomes pregnant or if you/your child is a male and you/he gets your/his partner pregnant, tell the study doctor as soon as you or your child knows (for additional information, please see section on "Are there any reproductive risks?" below).
- Be in touch with the study doctor or staff and tell them if you or your child have a change in contact details or if you/your child no longer wishes to be in the study.
- Agree to not take part in any other study for 30 days before starting the study or during the study.
- Agree to not receive or donate blood for 90 days before starting the study or during the study.
- Avoid grapefruit, grapefruit juice, and other foods that can affect the study drug while on study. The study doctor will discuss these.
- Always carry your/your child's patient emergency card.
- Abstain from heavy exercise 8 hours prior to study visits.
- Agree to not post or discuss the study on social media.

## What will happen at the end of the study or if you/your child stops participation early?

The study doctor will contact you when the study is close to the end to discuss how to stop the study drug and then return to the study clinic for the last treatment visit. At this visit, a final health exam and some lab tests will be done if needed or safety assessments for the study. The study doctor will also tell you/your child if additional follow-up is needed and if you/your child needs to visit the study clinic again. There will be the option to join the OLE portion of the study. The OLE description, assessments, and procedures are detailed in another ICF and Assent. The study doctor will also discuss future health care choices with you.

The study doctor and/or the study sponsor may also learn new facts during the study that might make you or your child want to stop taking the study drug or leave the study. You/your child will be told about the new facts and can then decide if you/your child still want to be in the study. There will be no penalty for leaving the study and no entitled benefits will be lost. Leaving the study will not affect the quality of the health care you/your child is given.

The study doctor may stop study drug or end your/your child's participation in this study for any of the following reasons:

- Staying on study drug or in the study would be harmful;
- If there are any suicidal thoughts during the study;
- If a treatment is needed that is not allowed in this study;
- An abnormal QT interval (an abnormal ECG reading) that meets the stopping criteria;
- Indication of abnormal liver chemistry results that meet the stopping criteria;
- Symptoms of depression or anxiety;
- Study instructions about what to do in the study were not followed;
- Experience any signs of acute adrenal insufficiency with symptoms such as low blood pressure, frequent headaches, nausea, and abdominal pain;
- Experience significant side effects;
- The study is cancelled, or your/your child's treatment group is stopped.

The study doctor will tell you the reason(s) why you/your child should stop being in the study.

If you/your child leaves the study early or if you/your child stops taking the study drug early and decides to leave the study, the study doctor will ask you/your child to complete the end of study tests (such as a final health exam and lab tests) for your/his/her own safety. If you/your child cannot see the study doctor in person, someone from the study staff will call you by phone. This is done to have complete data about your/your child's health and safety at the end of the study.

# BENEFITS AND RISKS

## Are there any possible benefits of being in the study?

Taking part in the study may or may not help treat your/your child's CAH. Your/your child's health could improve, stay the same, or get worse. However, the data we get from you/your child during this study may help doctors learn more about the study drug and your/your child's disease, which may help future patients.

## What are the potential risks and discomforts?

All drugs can cause effects that are not wanted. These are called side effects. So far, tildacerfont has been given to approximately 320 adults in research studies. People who received study drug in the past most often reported headache, followed by diarrhea, cough, and nausea. Most side effects were mild or moderate in intensity. The study doctor will discuss these and other side effects reported in tildacerfont studies with you/your child and answer any questions you/your child have.

Elevation of liver enzymes has been observed with tildacerfont use at doses higher than those given in this study, which may or may not be associated with a need to scratch (pruritus) or a rash. Your/your child's liver function will be monitored throughout the study as part of the laboratory tests, and the study doctor will tell you to stop taking/ giving your child tildacerfont if your/his/her liver function is of concern at any time during the study. Restart of tildacerfont dosing is possible if the study doctor and sponsor approve.

Tildacerfont is a drug that may act on the central nervous system (CNS). Drugs that act on the CNS may have an effect on your/your child's mood. Although the study drug has not been shown to be associated with an increased risk of suicidal thinking or behavior in previous clinical trials, it cannot yet be ruled out that there is an increased risk of suicidality in people who take tildacerfont. Suicidal behavior and thoughts will be monitored throughout the study.

If any of these happen to you/your child, tell your/your child's study doctor. There are some side effects that are not yet known. If you/your child notice any side effects even if they are not mentioned here, please tell your/your child's study doctor.

You/your child can also experience side effects of the tests performed during the study such as the following:

- Blood draw: Drawing blood may cause bruising where the needle goes into the skin. Fainting, and in rare cases infection, may occur.

- Blood pressure: The blood pressure cuff used to take your/your child's blood pressure may cause discomfort or bruising to the upper arm.

- ECG: The ECG involves placing patches on the skin on various parts of your/your child's body. The ECG is painless and takes about 5 minutes. The skin may become a little red, irritated, or itchy if you/your child have a reaction to the gel used on the electrode.

## Are there any reproductive risks?

Females who are pregnant, breast-feeding, or planning to become pregnant during the study will not be allowed to take part in the study. Any female who could become pregnant must have a pregnancy test to rule out pregnancy before they start taking the

study drug. After joining the study, all females must tell the study doctor as soon as possible if they suspect they are pregnant while on the study.

If you/your child experiences a menstrual period, you/your child must use an approved method of birth control during the study. Birth control methods that can be used while in this study include the following:

- Be abstinent and agree to not have sexual intercourse from screening until 30 days after the last dose of the study drug.

- Agree to follow any one of the following contraceptive methods, which must be in place at least 1 month before screening until 30 days after the last dose of the drug.

    a. Combination hormonal contraception which contains estrogen and progestogen, which inhibits ovulation. These hormones can be taken orally, intra-vaginally, or by the transdermal route.

    b. Progestogen-only hormonal contraception, which inhibits ovulation. These hormones can be taken orally or by the injectable or implantable route.

    c. Intrauterine Device (IUD): An IUD is a small T-shaped plastic or copper device that is put into the female womb (uterus) by a doctor or nurse. It may release copper or various hormones, depending on the type, to protect against pregnancy.

    d. Intrauterine system (IUS): The IUS works by continuously releasing a low dose of progestin from the intrauterine system into the womb. It thickens the mucus of the cervix, which makes it harder for sperm to move freely and reach the egg and it also thins the lining of the uterus.

If you/your child becomes pregnant during the study, you must tell the study doctor immediately, and you/your child will have to stop taking the study drug. The study doctor will advise you/your child about health care and will ask about the pregnancy and its outcome.

If you/your child are/is male and taking part in the study, then you/he must also use an approved method of birth control for the entire study if you/he is having sex with any female. This is because it is not known if the study drug may affect your/your child's sperm or an unborn child. You/your child must agree to use a condom from screening until 90 days after the last dose of the study drug and your/his female partner must have one of the methods listed above for females participating in the study.

If you/your child becomes pregnant or if you/your child gets your/his/her partner pregnant; the study doctor may ask you/your child and your/his/her partner if it is okay to collect details about the health of the baby for scientific and safety reasons. If required by local law, you/your child and your/his/her partner may be asked to sign a new consent form to allow collection of data about the health of the baby.

## Are there any other treatments?

Instead of taking part in this study, you/your child may choose to receive standard treatment for your/your child's CAH.

The current standard of care for CAH is lifelong treatment with glucocorticoids (e.g., hydrocortisone, prednisone, prednisolone, dexamethasone) to replace cortisol and suppress adrenal androgen overproduction.

In patients with the salt-wasting form of CAH, which causes loss of salt from the body, mineralocorticoids (e.g., fludrocortisone) are also used to replace aldosterone. Sodium chloride (NaCl) supplements are also provided to prevent excess loss of salt from the body.

Your/your child's study doctor will explain the risks and benefits of these other treatments before you decide if you want to take part in the study.

# COSTS AND COMPENSATION FOR STUDY PARTICIPATION

## Are there any costs if you/your child decides to take part in the study?

The sponsor, Spruce Biosciences, Inc., who has initiated the study is providing financial support and material for this study. The hospital/clinic and the study doctor are being paid by Spruce Biosciences, Inc. to do this study.

Taking part in this study will not cost anything. You/your child will receive the study drug, tildacerfont, free of charge. You/your child will not be charged for any of the tests that are part of the study. Your/your child's insurance company will have to pay for any procedures unrelated to the study that are considered standard of care. The study doctor can review these with you.

Your/your child's travel expenses to and from the clinic may be reimbursed. Talk to the study doctor about your/your child's travel expenses.

## Will you/your child receive any payment if you take part in the study?

You/your child will receive payment for taking part in this study. You/your child will receive $XX per completed clinic visit.

## Will you/your child receive compensation for injury resulting from the study?

You should inform the study doctor as soon as you feel that you/your child had an illness or injury related to the study, so that you/he/she can get proper health care. If the injury is a result of taking part in this study, the study doctor will recommend or provide medical treatment, including emergency treatment, if necessary. Your/your child's

insurance may be billed for this treatment; however, you should check with the insurance company that taking part in this study will not affect your/your child's coverage under the medical insurance policy. The study doctor will explain more about this to you.

The study sponsor will pay for the reasonable medical charges that are not covered by your/your child's insurance policy or other insurance programs available to you/your child and that are necessary to treat the injury with the standard of care treatment, provided the injury was caused by the study drug or properly performed study procedures. The sponsor has no plans to reimburse for medical expenses related to the natural progression of, or failure of the study drug to improve your/your child's disease, illness, or condition, any other pre-existing condition, or any injury or event that would have been expected from the standard treatment for your/your child's condition. You and your child will not be reimbursed by the sponsor for any injury that was caused by you, your child, or a third party.

It is important that you/your child be careful to follow all the instructions given by the study doctor and study staff about this study.

By signing this form, you are not giving up your/your child's legal rights and are not releasing the study doctor or drug company from their legal and professional responsibilities.

## CONFIDENTIALITY AND AUTHORIZATION TO COLLECT, USE, SHARE AND DISCLOSE PERSONAL HEALTH DATA

### What happens to the data collected about you/your child?

The information below explains how your/your child's health records and the research data we get from the samples collected during the study may be used and shared with others.

The hospital/clinic will record basic personal details about you/your child, including name, contact details, sex, height, weight, and racial origin (to be used only for study purposes), as well as data on health history and any study data collected during the study.

The following people may review your/your child's health records, to make sure that the study is being run as planned, and that the data collected are correct:

- government health agencies and their staff
- drug company staff observing the study (monitors and auditors)
- members of the ethics committee/Institutional Review Board
- contractors and consultants working for the drug company and for health authorities
- other representatives of the drug company

- employees of the drug company or its authorized agents, who may be with the study monitors and auditors for quality and training purposes.

All staff with access to your/your child's records are required to keep the data private.

To ensure privacy, you/your child will only be identified by a code. Your/your child's name and other data that can identify you/your child will not be attached to records or samples released to the drug company and its service providers. Only the study doctor and allowed staff will be able to connect this code to your/your child's name with a list that will be kept safe by the hospital/clinic for at least 2 years after the end of the study or longer according to local regulations. If allowed by local laws, your/your child's birth date and initials may also be recorded to help identify your/his/her study records.

After your coded data are sent to the drug company, the results of the study will be analyzed and reported. The drug company may use your coded information to get the study drug approved for use in different countries.

The results may also be analyzed again at a later date or may be combined with the data of other studies. The drug company and people who work with the drug company may use the results of this study to understand the disease better or to review the safety or effectiveness of the study drug, or for other research purposes.

Your/your child's personal data will be shared with the drug company if you agree to take part in the study.

You have the right to access, correct, and limit the access to your/your child's personal data at any time during the study. You can exercise those rights by telling the study doctor.

## What if you/your child changes your mind and do not want your/your child's data to be used or disclosed?

If you/your child leaves the study early, data obtained while you/he/she was in the study may still be kept with other data obtained as part of the study. Normally, no new data will be obtained for the study unless you clearly agree to that. However, the law requires that you report side effects that you/your child experiences even after you/he/she leaves the study.

## Will information about this study be publicly available?

A description of this clinical trial will be available at https://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.

A brief report of this study will also be available at https://www.clinicaltrialsregister.eu. This website will not include data that can identify you. It will include a scientific report of the results of the study. You can search this website at any time.

After this study is over, a brief report of the overall results will be prepared for the general public. The study results may also be shared with scientific journals and the scientific community. Whenever the results of the study are shared or published, your/your child's identity will remain confidential.

# CONTACTS

## Who can you/your child contact with further questions?

If you/your child have any questions about the study or feel that this study has caused you/your child harm or injury, please contact the study doctor whose details are given on the first page of this form.

If you have any questions about your rights or your child's rights as a person taking part in this study, please contact the Institutional Review Board that has reviewed and approved this study, also given on the first page of this form.

# STATEMENT OF CONSENT

- I have read and understand the statements in this Informed Consent Form.
- I have had the chance to ask questions, and I am satisfied with the answers given to me.
- I understand that this study may only be performed by collecting and using my data/my child's health data. Therefore, by signing this form, I specifically give permission for my data/my child's data to be checked, transferred, and processed as follows:
    - The authorized representatives of Spruce Biosciences, Inc., the Institutional Review Board, and inspectors for regulatory authorities may review my data/my child's health data by directly accessing my health records/my child's health records.
    - Study data, including my coded health data/my child's coded health data, may be used and shared for legitimate study and scientific purposes.
- I agree for myself/my child to participate in this study by my own free will.
- I understand that I and/or my child's legal representative will receive a copy of this signed and dated written Informed Consent Form.

_____

**Printed Name of Subject/Subject's Parent (or Legally Authorized Representative or Legal Guardian), in full**

_____

**Signature of Subject/Subject's Parent (or Legally Authorized Representative or Legal Guardian)**

_____

**Date (dd-mmm-yyyy)**

- I have presented the study and answered the subject's/subject's parents and subject's/subject's questions.
- I will give the subject/legal representative a copy of this signed and dated Informed Consent Form.

_____

**Printed Name of Person Obtaining Consent (Investigator/Delegate), in full**

_____

**Signature of Person Obtaining Consent** **Date (dd-mmm-yyyy)**

If required,

_____

**Printed Name of Impartial Witness, in full**

_____

**Signature of Witness** **Date (dd-mmm-yyyy)**