Phase IIb Clinical Trial to Evaluate Efficacy and Safety of Slow Release DHEA

Kirsten M. Kloepfer, MD, MS
Associate Professor of Pediatrics
Division of Pediatric Pulmonology, Allergy and Sleep Medicine
Riley Hospital for Children at IU Health
Indiana University School of Medicine

Sub-Investigators:

James F. Chmiel, MD, MPH
Division Chief of Pediatric Pulmonology, Allergy and Sleep Medicine
Professor of Pediatrics
Riley Hospital for Children at IU Health
Indiana University School of Medicine

Benjamin E. Gaston, MD
Professor of Pediatrics
Vice Chair for Pediatric Research
Riley Hospital for Children at IU Health
Indiana University School of Medicine

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1 BACKGROUND AND RATIONALE

Severe asthma results in significant mortality and morbidity, and in annual healthcare expenditures >$10 billion (1). Glucocorticoids (GCs) are the mainstay of treatment but are only incompletely effective in this condition. There is a critical need for novel, targeted and corticosteroid-sparing therapies for patients with severe asthma. Since asthma is sexually dimorphic with women being more affected than men (2,3), since GC treatment suppresses endogenous dehydroepiandrosterone (DHEA) production (4), and since our preliminary data demonstrate a variety of protective DHEA effects on automatic exposure control (AEC) function and inflammatory responses, there is a strong biological rationale to test whether DHEA-based treatment strategies are beneficial in this condition. Our data suggest that patients with low dehydroepiandrosterone-sulfate (DHEA-S) levels and HSD3B1 AA or AC genotypes represent a subgroup that will derive particular benefit from DHEA treatment, suggesting an exciting new potential for personalized medicine strategies in severe asthma. Our experience with studying DHEA treatment in asthma (Marozkina (5)), HSD3B1 genotype-phenotype correlations in asthma (Zein (4)) and sex hormone signaling in lung disease (Lahm (6)), make us uniquely equipped to perform the proposed study. Our overall goal is to perform a randomized, placebo-controlled pilot study to evaluate DHEA effects on FEV_1 and FeNO. This study will allow us to gather critical baseline data for designing larger trials in the future. Ultimately, this will allow for developing novel and personalized therapies for severe asthma.

Previous work has shown that the HSD3B1 genotype does not classically affect circulating DHEA-S levels, but rather affects tissue androgen levels (4, 8, 9). Based on our preliminary data and published reports (5), we anticipate that the maximal effect of DHEA will be observed in patients with the responsive genotype (4) and low DHEA-S levels (4) (**Table 1**). Because the homozygous HSD3B1(1245) AA genotype and heterozygous AC genotype in severe asthma populations are similar in lung function (4), and because the CC genotype is uncommon (12%; **Table 2**), we will focus on the "optimal response" cohort (AA/AC genotype & low DHEA-S levels). If we are successful, additional studies will be performed in subsequent, larger trials. Steady state levels in the pilot study were ~ 725 µg/dL (5). Therefore, we will study 100 mg of DHEA (10,11).

Table 1. Predicted biomarker response (based on previously published work from our group)(4,5).

	Serum DHEA-S levels (µg/dL)	
	<90 in males or <45 in females	≥90 in males or ≥45 in females
HSD3B1(1245) genotype		
CC	Intermediate Response	Poor Response
AA or *AC*	**Optimal Response**	Intermediate Response

2 CLINICAL SIGNIFICANCE

Severe asthma only accounts for ~10% of all asthma in the United States, but it accounts for nearly half of the annual mortality and cost of the disease (12-16). Estimates are that severe asthma takes over 1,000 lives per year, and that the annual financial burden of severe asthma may be several billion dollars in the United States alone. Important improvements in asthma outcomes have been realized with antibody-based

Table 2: HSD3B1(1245) genotype distribution in SARP I, II & III

Genotype	American Indian/ Alaskan Native	Asian	African American	White/ Caucasian	Hispanic	Other
AA - n(%)	4 (80)	30 (83)	375 (77)	411 (46)	22 (52)	27 (63)
AC - n(%)	1 (20)	5 (14)	105 (22)	386 (43)	18 (43)	13 (30)
CC - n(%)	0 (0)	1 (3)	6 (1)	100 (12)	2 (5)	3 (7)

therapies (for example, 17-19). However, these therapies are primarily effective for specific subpopulations of the Th-lymphocyte Type 2-high ("T2-high") asthma population, are normally not indicated in the "T2 low" population (17-21) and are expensive. Here, we propose to investigate potentially less expensive, less invasive, personalized approaches to managing certain severe patients, particularly including those who are not candidates for, or have failed, conventional severe asthma therapies and biological approaches.

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVE:

- Determine if slow-release DHEA in patients with asthma improves quality of life based on ACQ/ACT scoring.

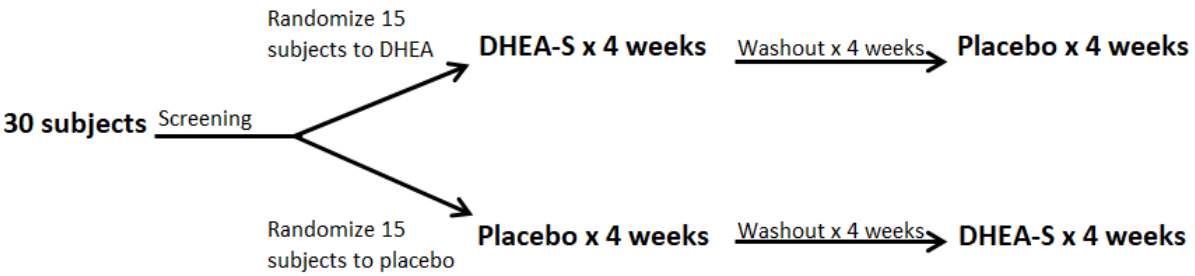
3.2 SECONDARY OBJECTIVE:

- Determine if slow-release DHEA increases FEV_1 in patients with asthma.
- Determine if SR DHEA in patients with asthma increases the change in pulmonary functions post maximum bronchodilator challenge.
- Determine if slow-release DHEA in patients with asthma decreases FeNO.
- Evaluate the safety and tolerability of DHEA in asthma.
    - Safety outcomes include changes in:
        - Adverse events (AEs)
        - Serious adverse events (SAEs)
        - Pulmonary function (FEV_1, FVC, FEV_1/FVC, FEF25-75)

    (An asthma exacerbation (physician decision to treat) will be considered an event of particular interest. Exacerbations not admitted to the hospital will be considered an AE. Exacerbations requiring admission will be considered a SAE.)

4 STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, cross-over study to determine if DHEA-S will increase FEV_1 and decrease FeNO.



4.1 MULTIPLE DOSE STUDY

The dose of DHEA will be 100 mg via slow release (SR) capsules. Subjects will take one capsule daily at the same time each day.

4.2 PROJECTED STUDY ENROLLMENT

The study cohort will consist of 30 subjects with asthma.

5 STUDY SUBJECT ELIGIBILITY

5.1 INCLUSION CRITERIA

1. Adult male or female age ≥ 18 and ≤ 50 years at the time of enrollment
2. Evidence of asthma demonstrated by reversibility at visit 0 or by historical methacholine or bronchodilator reversibility if testing was performed under either the 2017 ERS technical standard (22) or the 1999 ATS Guidelines (23) or outside studies, provided that full sets of flow volume loops have been reviewed and approved by the PI. These criteria are defined as one of the following:
    a. For bronchodilator reversibility: An increase in FEV_1 ≥ 10% (24) compared to the baseline (and 200 ml) after up to 8 puffs of albuterol
    b. For historical methacholine responsiveness: Positive methacholine defined as PC20 ≤ 16 mg/ml, or PD20 ≤ 400 mcg
3. Physician diagnosis of asthma according to NHLBI guidelines
4. Consistent use of an ICS inhaler for the prior 2 months
5. Non-smoker
6. Females must not be pregnant or breastfeeding
7. Absence of non-allergic comorbidities

5.2 EXCLUSION CRITERIA

1. Pregnant or actively trying to become pregnant; breastfeeding
2. Positive urine pregnancy test
3. Known lung disease other than asthma
4. Acute (non-asthma related) dyspnea, viral respiratory illness or asthma exacerbation within 4 weeks of screening
5. Systemic glucocorticoid dosing for maintenance >10 mg/day of prednisone or equivalent
6. Patients with significant non-allergic comorbidities (e.g. cerebral palsy, heart disease, kidney disease, liver disease, etc.)
7. Patients with any know central or peripheral endocrine abnormality such as precocious puberty or diabetes
8. Patients with any known previous adverse reaction to DHEA
9. Current smoker or pack year history > 5 years (includes vaping/nicotine inhalation devices)
10. Positive urine cotinine test (> 100 mg/mL)
11. Use of prednisone or antibiotics in the last 4 weeks
12. Use of any performance-enhancing drugs in the last 2 weeks
13. Use of DHEA in the last 2 weeks
14. Androgen use for any reason.

15. Any other condition or finding that would compromise the safety of the subject or the quality of the study data, or otherwise interfere with achieving the study objectives, as determined by the PI
16. Menopausal amenorrhea by history
17. Positive PSA (>4 ng/ml) (Prostate Specific Antigen)
18. Prior diagnosis of vocal cord dysfunction, bronchopulmonary dysplasia, cystic fibrosis, chronic obstructive pulmonary disorder, or other lung disease
19. Systolic blood pressure > 150 mm Hg and/or diastolic blood pressure >90 mm Hg
20. Heart rates outside the range of 50 to 120 beats per minutes or with a pathologic irregularity
21. Patients afflicted with any additional acute or chronic pathology that in the opinion of the screening physician makes them unsuitable for study or increases the risks associated with the study.

6 SCHEDULED EVENTS

Assessments and Procedures	Visit 0	MCT	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Screening Day 0	**Anytime between days 1-7; at least 3 days prior to Visit 1**	**Day 7 ± 3 days**	**Day 21 ± 3 days (phone visit)**	**Day 35 ± 3 days**	**Day 63 ± 3 days**	**Day 77 ± 3 days (phone visit)**	**Day 91 ± 3 days**
Informed consent	X							
Medical history and demographics	X							
Concomitant medications	X		X	X	X	X	X	X
Review inclusion/ exclusion criteria	X							
Asthma Control Test (ACT) & Asthma Control Questionnaire (ACQ)	X		X	X	X	X	X	X
Height	X							
Weight, pulse oximetry, vital signs	X	X	X		X	X		X
Urine pregnancy test (when applicable)	X	X	X		X	X		X
Urine cotinine test	X							

Assessments and Procedures	Visit 0	MCT	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Screening Day 0	Anytime between days 1-7; at least 3 days prior to Visit 1	Day 7 ± 3 days	Day 21 ± 3 days (phone visit)	Day 35 ± 3 days	Day 63 ± 3 days	Day 77 ± 3 days (phone visit)	Day 91 ± 3 days
Prostate specific antigen test[1] (when applicable)	X							
Spirometry with bronchodilator response (maximum bronchodilator)	X							
Spirometry. If ≥ 10% decrease in FEV_1 from baseline, give bronchodilator and measure response			X		X	X		X
Methacholine Checklist[a]		X						
Methacholine Challenge Test (MCT) *(Asthma Participants Only)*[a]		X						
FeNO	X		X		X	X		X
Abbreviated physical exam	X		X		X	X		X
Blood draw	X		X		X	X		X
DHEA/placebo capsules dispensed in labeled bottle			X			X		
Collect any unused DHEA/placebo capsules					X			X
Adverse events	X	X	X	X	X	X	X	X
Give Dosing & Symptom Diary			X			X		

[1] This test is for male subjects only. The prostate specific antigen is a protein made by the prostate and found in blood. If the result of this test is >4 nanograms per milliliter, subjects will be informed they are unable to participate in the study. We will also call them prior to their next visit to let them know and recommend that they follow-up with their regular primary care physician.

Assessments and Procedures	Visit 0	MCT	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Screening Day 0	**Anytime between days 1-7; at least 3 days prior to Visit 1**	**Day 7 ± 3 days**	**Day 21 ± 3 days (phone visit)**	**Day 35 ± 3 days**	**Day 63 ± 3 days**	**Day 77 ± 3 days (phone visit)**	**Day 91 ± 3 days**
Collect Dosing & Symptom Diary					X			X

[a]The MCT and MCT with checklist done only if: 1) participants with asthma fail to demonstrate 10% reversibility in FEV1 (max BD testing) and there is no historical MCT available

7 DESCRIPTION OF EVENTS

Medical history and demographics, height, weight and vital signs

Relevant medical history, including history of current disease, spirometry results, other pertinent respiratory history, and information regarding underlying diseases will be recorded. Demographic and baseline clinical characteristics including age, gender, and race will be recorded. Pulse oximetry, height (at screening only) and weight will be measured, as well as vital signs (blood pressure, temperature, heart rate and respiration rate).

Concomitant medications

All concomitant medications and concurrent therapies will be documented at visit 0. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured for the 30 days prior to screening and during the study. The document will be reviewed and addended (if needed) at each visit.

Asthma questionnaires

Subjects will be asked to complete two questionnaires: the Asthma Control Test (ACT) and the Asthma Control Questionnaire (ACQ).

- The ACT is a validated asthma assessment tool used to assess asthma symptoms over a 4-week period. Each item on the ACT has a possible score ranging from 0 to 5, and the total score is used to determine asthma control.
- The ACQ includes six questions on symptoms, activity limitation and beta2-agonist use, with an optional assessment on airway caliber over a 7-day period. Each question is scored from 0 (well controlled) to 6 (extremely poorly controlled) with the total score being the average of the questions.

Urine pregnancy test

A urine pregnancy test will be performed at Visits 0 and Visit 1 (if not the same day as screening visit) if the subject is a female of child bearing potential.

Urine cotinine test

A urine cotinine test will be performed at Visit 0 for all subjects to measure cotinine levels.

Prostate specific antigen test

Blood will be obtained from male subjects for PSA because administration of supplemental DHEA in people with prostate cancer could theoretically result in a flare-up of their prostate cancer.

Spirometry with maximum bronchodilator response

Pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 will be measured using spirometry. The FEV_1 is the volume of air which can be forcibly exhaled from the lungs in the first second, measured in liters. Spirometry will be done according to American Thoracic Society/European Respiratory Society procedural guidelines (25). Current reference equations (26) will be used.

Airway Reversibility

Airway reversibility will be demonstrated by measuring the change in FEV_1 before and after inhalation of albuterol; reversibility testing should be attempted after withholding long-acting beta-agonist (LABA) therapy for at least 12 hours and short-active beta agonist (SABA) therapy for at least 6 hours. Up to 8 puffs of albuterol should be used for reversibility testing, as tolerated. If a subject's FEV_1 improves at least 10% between the 2 tests, then he/she will be deemed as having airway reversibility.

Methacholine Challenge Test (MCT)

MCT will be performed only in participants with asthma who do not demonstrate reversibility and with a pre-diluent FEV1 of >50% predicted and at least 1.0 liter. A physician will be available during the challenge and testing will be performed according to standard of care. Participants will not be discharged until their FEV1 is within 10% of their baseline FEV1.

FeNO

FeNO stands for Fractional Exhaled Nitric Oxide and it is a non-invasive procedure that is considered to be an indirect measurement of airway inflammation. It involves taking a deep breath and blowing air out into a mouth piece at a constant pressure as directed by the study team. Measurements will be recorded.

Medication withhold:

To prepare for lung function testing, subjects will be asked to withhold certain medications so that screening procedures produce the most accurate results. Subjects will receive a list of medications that must be withheld prior to certain study visits, and length of withholding time.

Abbreviated physical exam

An abbreviated physical exam will consist of HEENT, cardiovascular system, chest/lung, abdomen, extremities, skin, and any other areas as appropriate. This exam will be performed by a physician.

Blood collection

Blood will be drawn at visits 0, 1, 3, 4, and 6. A CBC with differential and comprehensive metabolic panel will be performed as safety labs throughout the study. A prostate specific antigen (PSA) level will be measured in male subjects at the screening visit. DHEA-S levels will be measured at the screening visit and at the conclusion of the study. Blood will also be used for measurements including but not limited to: cytokine responses, hormone levels, PBMCs, genomics, and DHEA. The maximum amount of blood to be obtained at each visit is up to 40 ml.

Genotyping

Single nucleotide polymorphism testing for HSD3B1 genotype will be performed from blood drawn at the screening visit and results must be available before the first dose of study drug. If a genotype test has been performed previously and is documented in the subject's medical or research records, the subject's eligibility must be approved by the PI. If a historic genotype result is not available at screening or if the historic genotype result is not approved by the medical monitor, subjects will be tested for genotype at screening and the results must be reviewed before the first dose of study drug. Subjects will not receive the study drug if genotype is not confirmed by both an approved historic genotype and approval of medical monitor result OR by genotype testing at screening. Study subjects with HSD3B1 AA or AC specific variants will be enrolled in the study. No further genetic studies will be performed on the subject's DNA. The subject will be fully informed of the genotype results relevant to this study.

DHEA

DHEA is available as an over-the-counter supplement that is available on the market without prescription. The DHEA used in this study will be formulated for slow release and will be dispensed at a compounding pharmacy by prescription only. They produce 100mg capsules that will be used for this study. The prescribed DHEA capsules will be received, stored and distributed by the Gaston Pediatric Translational Research Lab Group in the Herman B Wells Center for Pediatric Research. Accountability records will be maintained by the study team.

Randomization

Randomization will occur at the compounding pharmacy that manufactures DHEA and placebo. The study drug will be distributed with a code and study team will be blinded from code. Only the compounding pharmacy and the DSMB will have access to the unblinded data.

Dosing and Symptom diary

Subjects will complete a dosing and symptom diary at home starting after visit 1 until the end of the study.

Adverse events (AEs)

Information regarding the occurrence of AEs will be captured throughout the study from Visit 0 until the final visit. Subjects will be given a phone number to notify the study coordinator regarding an asthma exacerbation or other adverse event.

8 DESCRIPTION OF VISITS

Below are the visits and the interventions that may occur at each of the visits. In addition to the following scheduled visits, we are also including an unscheduled visit that may be used for any reason when a subject needs to return to the study site to complete study activities.

Visit 0 (Screening Visit)

1. Review the study with the subject and obtain written informed consent and HIPAA authorization
2. Assign the subject a unique subject id number
3. Complete asthma control test and asthma control questionnaire
4. Record demographics and other baseline data

5. Record medical and surgical history, including a history of asthma, diagnosis date, and asthma signs and symptoms
6. Record concomitant medications
7. Review inclusion/exclusion criteria
8. Measure and record height and weight without shoes
9. Perform and record vital signs, including blood pressure after the subject has been seated for 5 minutes
10. Perform and record oximetry
11. Perform abbreviated physical exam
12. Obtain urine to perform urine pregnancy test (when applicable) and urine cotinine test
13. Obtain blood for prostate specific antigen test (when applicable)
14. Perform spirometry with maximum bronchodilator response
15. Perform FeNO
16. Obtain blood
17. Record any adverse events (AEs) that may have occurred since signing consent
18. Schedule MCT or Visit 1

<u>MCT Visit, if needed (Anytime between days 1-7, must be at least 3 days prior to Visit 1)</u>

1. Confirm ongoing consent to participate
2. Collect urine for pregnancy test if applicable
3. Record vital signs and weight
4. Complete MCT checklist
5. Perform and record MCT
6. Confirm eligibility criteria
7. Record adverse events
8. Schedule Visit 1

<u>Visit 1 (Day 7 ± 3)</u>

1. Complete asthma control test and asthma control questionnaire
2. Review and record any changes to concomitant medications
3. Record any adverse events (AEs) that may have occurred since last visit
4. Measure and record weight without shoes
5. Perform and record vital signs, including blood pressure after the subject has been seated for 5 minutes
6. Perform and record oximetry
7. Perform abbreviated physical exam
8. Obtain urine to perform urine pregnancy test (when applicable)
9. Perform spirometry
10. Perform FeNO
11. Obtain blood
12. Give subject a dosing and symptom diary and instructions on dosing intervals
13. Randomize to receive placebo or DHEA-S
14. Send home with 28 days of DHEA-S or placebo capsules
15. Schedule visit 2

Visit 2 (Day 21 ± 3) phone visit

1. Complete asthma control test and asthma control questionnaire
2. Review and record any changes to concomitant medications
3. Record any adverse events (AEs) that may have occurred since last visit
4. Schedule visit 3

Visit 3 (Day 35 ± 3)

1. Complete asthma control test and asthma control questionnaire
2. Review and record any changes to concomitant medications
3. Record any adverse events (AEs) that may have occurred since last visit
4. Review inclusion/exclusion criteria
5. Measure and record weight without shoes
6. Perform and record vital signs, including blood pressure after the subject has been seated for 5 minutes
7. Perform and record oximetry
8. Perform abbreviated physical exam
9. Obtain urine to perform urine pregnancy test (when applicable)
10. Perform spirometry
11. Perform FeNO
12. Obtain blood
13. Collect any unused capsules from visit 1
14. Collect dosing and symptom diary
15. Schedule visit 4

Visit 4 (Day 63 ± 3)

1. Complete asthma control test and asthma control questionnaire
2. Review and record any changes to concomitant medications
3. Record any adverse events (AEs) that may have occurred since last visit
4. Measure and record weight without shoes
5. Perform and record vital signs, including blood pressure after the subject has been seated for 5 minutes
6. Perform and record oximetry
7. Perform abbreviated physical exam
8. Obtain urine to perform urine pregnancy test (when applicable)
9. Perform spirometry
10. Perform FeNO
11. Obtain blood
12. Give subject a dosing and symptom diary and instructions on dosing intervals
13. Randomize to receive placebo or DHEA-S (will enter whatever did not receive in visits 1-3)
14. Send subject home with 28 days of 100 mg DHEA-S or placebo capsules to take daily
15. Schedule visit 5

Visit 5 (Day 77 ± 3) phone visit

1. Complete asthma control test and asthma control questionnaire

2. Review and record any changes to concomitant medications
3. Record any adverse events (AEs) that may have occurred since last visit
4. Schedule visit 6

Visit 6 (Day 91 ± 3)

1. Complete asthma control test and asthma control questionnaire
2. Review and record any changes to concomitant medications
3. Record any adverse events (AEs) that may have occurred since last visit
4. Measure and record weight without shoes
5. Perform and record vital signs, including blood pressure after the subject has been seated for 5 minutes
6. Perform and record oximetry
7. Perform abbreviated physical exam
8. Obtain urine to perform urine pregnancy test (when applicable)
9. Perform spirometry
10. Perform FeNO
11. Obtain blood
12. Collect any unused capsules from visit 4
13. Collect dosing and symptom diary

9 STUDY RISKS

DHEA: DHEA is commercially available without a prescription. The DHEA capsules used in this study are formulated for slow release. Most of the known data pertaining to risks come from studies in adults with adrenal insufficiency who were treated with long courses of DHEA (e.g. 3-12 months). Many of these trials were included in a recent meta-analysis (27). This paper included 10 trials where 264 women treated with 20-50mg (most were 50mg) daily for 3-12 months (most were 4-6 months). None of the trials reported any serious adverse effects from prolonged therapy with DHEA. Minor side effects reported include greasy skin, hirsutism, acne, scalp itching and increased sweating. In two trials including 36 men, reported side effects included diarrhea (n=1), mild acne (n=1) and increased facial hair (n=1) (28, 29). In a study of 23 adolescent girls and young women (ages 13-25) treated with 25mg of DHEA for 1 year, adverse events were similar between DHEA and placebo (30). One girl developed mild hirsutism, and no subjects developed acne. We are aware of a single case report of a 55-year-old patient developing palpitations after 2 weeks of DHEA therapy (50mg/day) that were found to represent premature atrial and ventricular contractions (PACs and PVCs) that resolved with an oral beta-blocker therapy (31). Finally, we recently completed a pilot study of DHEA repletion in female asthma patients with DHEA-S levels <200 µg/dl. The short-term (2 week) regimen was associated with a significant improvement in post-bronchodilator FEV_1, and no major side effects were observed (5). These results support feasibility of the proposed trial and suggest that asthma patients with low DHEA-S plasma levels will tolerate DHEA treatment.

Blood collection and genotyping: When blood samples are taken from a vein, subjects may have discomfort or pain where the blood was taken. Sometimes a person may become dizzy or faint when blood is taken. There is also a risk of infection (rare), bleeding, redness or bruising at the skin puncture.

Bleeding and bruising can usually be reduced by putting pressure on the place where the blood was taken. The chance of infection is lowered by using standard skin cleaning and sterile needles.

Genotype data is obtained from blood analysis. The only risk specifically associated with genotyping is breach of confidentiality. Every effort will be made to maintain confidentiality and all study data will be treated as confidential information. No identifiable information released or shared with individuals outside the study team.

Spirometry: There is a small risk of lightheadedness, wheezing, shortness of breath or increased cough when performing spirometry. These symptoms usually resolve quickly without the need for treatment. Withholding short-acting/long-acting beta-agonists prior to study visits: There is a risk of shortness of breath or breathing difficulty. Subjects will be advised that if they experience any worsening symptoms during the pre-visit withholding period, they should use their usual medication as needed and call the study team to cancel or reschedule the study visit.

Methacholine Challenge Test (MCT): The volunteer may experience coughing, chest tightness, shortness of breath, and/or wheezing during this procedure. These symptoms typically resolve spontaneously 10-15 minutes after testing without active intervention – recovery can be hastened as needed with administration of albuterol.

FeNO: Such testing can cause a subject to become light-headed, dizzy or tired. In asthmatic subjects, testing may also induce or worsen wheeze, shortness of breath, and/or chest tightness. Rescue therapy with Albuterol will be administered as needed. The chance of these symptoms occurring is low and treatment will be readily available.

Medication Withhold: Withholding medications may cause subjects to experience increased symptoms of the condition for which the medication is taken. Subjects will be advised that if they experience any unmanageable, worsening symptoms during the pre-visit withholding period, they should use their usual medication(s) as needed and call the study team to cancel or reschedule the visit.

Urine Collection: Urine will be collected by clean-catch. There are no foreseeable risks to its collection. However, there is the risk of emotional distress if a subject discovers that she is pregnant. Our study coordinators are highly trained and experienced regarding advising women who discover that they are pregnant as part of a research protocol.

Questionnaires: At any time during the study, subjects can stop answering or skip questions that feel too personal or make them uncomfortable.

10 STUDY BENEFITS

There are no expected direct benefits to individual subjects participating in this research. The information obtained from this research study may prove helpful for future asthma patients and other pulmonary research projects.

11 WITHDRAWAL FROM STUDY PARTICIPATION

An individual subject will be withdrawn from the trial if the subject withdraws consent (the subject is not required to justify this decision). All withdrawals will be documented and the reason (if provided) for withdrawal will be recorded. There is no need to follow subjects after withdrawal. If a subject wishes to withdraw consent, the PI will have his/her stored specimens discarded. Specimens already tested or used by another researcher will not be destroyed. Information already learned from the testing of the sample will not be destroyed. If a subject starts taking the DHEA-S or placebo and then calls in prior to completion of the study to say that they want to stop taking it/withdraw from the study, we will ask the subject to come back for their final lab draw and return their unused capsules.

In addition, a subject may be withdrawn from the study at any time if the PI feels that it is not in the subject's best interest to continue. Possible reasons for study withdrawal include but are not limited to:

- Subject withdrawal of consent
- Subject is not compliant with or tolerating study procedures
- Subject is not adherent to study drug schedule
- Adverse event that, in the opinion of the PI, places the subject at increased risk
- Lost to follow-up
- Physician request for early termination of study
- Subject becomes pregnant

Being a part of this clinical trial while pregnant may expose the unborn child to significant risks. Therefore, pregnant women will be excluded from the study. A pregnancy test will be done at the beginning at every study visit for any women of childbearing potential, and it must be negative before they can enter and continue in this study. All subjects must agree to use appropriate contraceptive measures during the study. Medically acceptable contraceptives include: (1) surgical sterilization, (2) approved hormonal contraceptives such as birth control pills, (3) barrier methods (such as a condom or diaphragm) used with a spermicide, (4) abstinence, or (5) an intrauterine device (IUD). If they become pregnant during this study, they must inform a member of the research team immediately. In this scenario, study drug will be discontinued immediately, and the subject will be monitored throughout the pregnancy and for 1 year after study drug was discontinued. The baby will be monitored for adverse events for 1 year after birth.

12 DATA AND SAFETY MONITORING

This study will have a Data and Safety Monitoring Board (DSMB). The DSMB will meet regularly to review reports of all adverse events. The DSMB may review all procedures, protocol changes, ICFs and annual reports. Notification of all Serious AEs will be sent to DSMB, the principal investigator and the study's Steering Committee (comprised of research project leaders). The DSMB Chair also will function as an independent medical monitor and AE adjudicator. AEs will be reviewed and categorized as serious, non-serious, drug related, or procedure related. Based on the safety data, the DSMB has the authority to request a modification to the study design. This overview is only meant to be used as a guideline by the DSMB to review the study and to make a recommendation to continue or modify the protocol, not necessarily a mandate to the board for study termination. The members will not be involved in the planned study but will have the requisite clinical expertise to oversee subject safety. The DSMB will meet at least once per year, will review a written report prepared annually by the study team, and in response, will prepare a written report of the results of these meetings. The PI will alert the DSMB,

along with the IRB, the study's Steering Committee, and the NHLBI Program Officer of any serious AEs. Procedures and requirements for prompt reporting of AEs and unanticipated problems involving risk to subjects or others have been established by our IRB and will be adhered to for all aspects of this project. Any member of the study team will report any unexpected event or problem and any AE, either serious or non-serious, to the PI immediately upon discovery. The PI will then proceed to report the event within the specified timeframes mandated by the DSMB Charter, the IRB and the NHLBI. Any non-serious AE, either study or not study related, can be reported by the research team at the date of the next continuing review. Current regulations require that any AE that is (1) unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the study-related documents, and (b) the characteristics of the subject population being studied, (2) related or possibly related to study participation, AND (3) suggesting that the research places subjects or others at greater risk of harm than was previously known must be reported to the IRB within 5 business days. A SAE that is non-study related can be reported at the next continuing review.

13 SAFETY ASSESSMENTS

The monitoring in place for assessing the subject's responses will ensure that any untoward change in physiologic status is immediately known.

This includes the following:

1. Measuring pulmonary function at the beginning of each visit and measuring bronchodilator response if there is a drop ≥ 10% from baseline.
2. Obtaining ACT scores at each visit to assess subjects' asthma control.
3. Performing an abbreviated physical exam at all visits.
4. Checking vital signs, including pulse oximetry, to ensure the subject is at their baseline.
5. Asking about interim history to ensure the subject has not had an asthma exacerbation since the previous visit.

As a result of the study design, subjects will be monitored on a case-by-case basis by the study coordinator. The experimental design has each subject extensively monitored; any manner of medical intervention is immediately available, and the appearance of any suspected untoward effect will result in cessation of protocol procedures if decided by the principal investigator.

Any applicable safety concerns will be reported as described above.

14 ADVERSE EVENTS AND SEVERITY GRADING

The IU IRB and the FDA have well-established policies (and means) for prompt reporting of AEs and unanticipated problems involving risk to subjects and these policies will be strictly followed.

Adverse and serious adverse events (AE and SAE, respectively) will be defined according to FDA and OHRP guidelines as per IU IRB and NIH requirements.

14.1 ADVERSE EVENT ASSESSMENT

All adverse events will be reported to the Indiana University IRB and FDA as required per their adverse event reporting policies. At the time of the annual review of the study, adverse events will be reported as per the Indiana University HRPP Reportable Events Policy and Guidance. An Adverse Reaction Reporting Form will be completed for any serious and unexpected adverse reaction associated with the study, and the Indiana University IRB will be notified per IU HRPP Reportable Events Policy and Guidance.

An IND safety report will be submitted to the FDA for an event that is a (1) suspected adverse reaction, (2) serious, and (3) unexpected, per FDA guidance.

> Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event.
>
> An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
>
> An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the protocol.

Any unexpected fatal or life-threatening suspected adverse reaction will be submitted as an IND safety report to the FDA within seven (7) calendar days after initial receipt of information. Any potential serious risks (serious and unexpected suspected adverse reactions, findings from other studies, findings from animal or in vitro testing, or increased rate of occurrence of serious suspected adverse reactions) will be submitted as an IND safety report to the FDA within fifteen (15) calendar days after initial receipt of the information.

All adverse events will be classified and recorded according to the NCI Toxicity Grading Scale. All study related toxicities will be graded (Grades 1, 2, 3 or 4) according to the Toxicity Grading Scale and will be employed along with potential study drug specific toxicities in the individual subject stopping rules. Subject and study stopping rules will be determined by the DSMB. If the DSMB recommends that the study change or be closed early for patient safety reasons or for slow accrual, the PI will act to implement the change as expeditiously as possible. If a recommendation is made to change the study for other than patient safety reasons or slow accrual, the DSMB will provide an adequate rationale for its decision.

Adverse events will be graded as follows:

Grade 0 – No adverse effects
Grade 1 - Mild adverse events
Grade 2 – Moderate adverse events
Grade 3 – Severe adverse events
Grade 4 – Life threatening or disabling adverse events
Grade 5 – Death related to adverse events

Adverse events will be assessed using the NCI Common Toxicity Criteria guidelines listed in (http://ctep.cancer.gov/forms/CTCAEv3.pdf) along with potential study drug specific toxicities in the individual subject stopping rules.

Deaths will be reported to the Indiana University IRB per their institutional guidelines if they occur within 30 days of study intervention. The principal investigator will be responsible for reporting adverse effects to the IRB and other relevant bodies.

14.2 TRACKING OF EVENTS

The following AEs are discussed in the protocol, are discussed with patients as part of the informed consent process, and will be tracked as part of the protocol:

- Complications of venipuncture, blood draw.
- Complications related to study drug

14.3 ADVERSE EVENT REPORTING

- Every event that is reported to either the PI or the designated research associates by the subject or medical staff caring for the subject and which meets the criteria will be documented.
- An AE report will be generated for each event and each report will include: (1) description of the event; (2) when it was reported; (3) severity; and (4) a determination of attribution.
- All SAE's will be reported once the event has been verified, and determination of attribution has been completed in accordance with IU IRB reporting requirements and DSMB requirements. All other AEs will be reported according to the IU IRB reporting requirements.

  DSMB requirements are that SAE's be reported to the board within 24 hours of learning of the confirmed event. DSMB will proceed to review, discuss and convey recommendations.

14.4 FOLLOW UP FOR ADVERSE EVENTS

Subject follow-up will be on a case-by-case basis as directed by the PI and/or the IU IRB and the DSMB as appropriate.

15 STUDY MONITORING

This is a single-site investigator-initiated study, taking place at University Hospital on the IU Indianapolis campus. This site will be monitored by representatives from the Indiana Clinical and Translational Sciences Institute. The Investigator grants permission to the monitoring office, and appropriate

regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

16 SUBJECT RIGHTS AND CONFIDENTIALITY

16.1 ALTERNATIVES TO STUDY PARTICIPATION

This is a voluntary study. The alternative is to choose to not participate. A subject's decision will in no way influence any care a subject might receive at the respective hospital nor will it affect interactions with any of the study personnel.

16.2 FINANCIAL INFORMATION

Subjects will be paid for their participation in this study. Details are provided in the informed consent form.

16.3 RESEARCH RELATED INJURY

If injury occurs as a result of their involvement in this research, medical treatment is available from the respective hospital or another medical facility but the subject or their medical insurance will be responsible for the cost of this treatment. A research injury is an injury that happens as a result of taking part in this research study. There are no plans for payment of medical expenses or other payments, including lost wages, for any research related injury.

16.4 USE OF SPECIMENS

Test results will not be used to guide clinical care, nor will they be used for purposes outside the scope of this research study.

16.5 CONFIDENTIALITY

All study data will be treated as confidential information. Similarly, the subject's medical history will also be treated as confidential with no identifiable information released or shared with individuals outside the study team. If the study results are published, subject names will not be used. Once all the results are collected any identifiers will be removed and the information assigned a code. The data will be identified by a study number and not by name or identifying information. The code assignment key will be maintained by the study team on a password-secured computer kept in a locked office. Access to the code key will be limited to a need-only basis.

16.6 PRIVACY

Study team members are committed to protecting the privacy of research subjects. Recruitment discussions will be conducted with as much privacy as possible. The consent process will take place in a private room. Subjects will be assured that all study staff working on the study will make every effort to protect their privacy.

16.7 DATA/SAMPLE CONFIDENTIALITY

The study team will make an ongoing effort to keep personal information of the subjects confidential. Personal information will be disclosed only if required by law. Subjects will be informed that they are assigned unique study identification numbers to protect their identity. Any paper and electronic files

containing study data, as well as any specimens, will be coded with the study identification number and not with the subject's name.

Study information, which does not identify the subjects, may be given to regulatory agencies and the Institutional Review Board (IRB). Staff members from these agencies have the right to review each subject's medical and study records only as needed for safety purposes, to verify the data, assess compliance with the protocol and regulation, or to review the results of the study. By signing the study consent, subjects agree to let these organizations see their medical and study records. The records will not be used for any other purposes or disclosed to any other party without subject permission. Some of the records reviewed will contain identifying information; however, the study team are required to keep this information confidential. Efforts will be made to keep personal information in the subject's research record private and confidential, but absolute confidentiality cannot be guaranteed.

16.8 DATA/SAMPLE SECURITY

Health information/specimens will be labeled with subject ID number and any other pertinent information (e.g., study name, visit number, sample date). Subject records will be stored by the study coordinator. Specimens will be stored in the Pediatric Translational Research Lab in the Herman B. Wells Center for Pediatric Research, Pediatric Translational Lab, located in Walther Hall at 980 Walnut St, R3-C115 or in the CCRC Lab, located in the Riley Hospital Children's Clinical Research Center. Only study personnel for this study designated by the PI will have access to the data/specimens. Electronic files will be stored on password-protected IU systems.

16.9 DATA ENTRY & STORAGE

The study team will adhere to 21 CFR Part 11 guidelines and requirements for data entry and storage practices. This study will use a secured, institutional REDCap database for data entry and storage, with original hard copy, paper documents maintained for cross reference. The institutional REDCap will be designed for this study.

17 STATISTICAL ANALYSIS

Descriptive statistics of the study cohort will be summarized and used to determine safety. If an AE occurs, the maximum tolerable dose (MTD) will be determined following a design with intrapatient dose escalation. Mixed-effects models for repeated measures will be considered to test the significance of the difference at various measurement time points.

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18 PROTOCOL SIGNATURE PAGE

Protocol Title:	Phase IIb Clinical Trial to Evaluate Efficacy and Safety of Slow Release DHEA
IRB #:	26427
IND:	162875
Protocol Version/Date:	10Jun2025

The signature below constitutes approval of this study in full accordance with the provisions of this protocol and the attachments. I agree to conduct this study in compliance with the protocol, in-country and local regulatory requirements, applicable United States (US) Code of Federal Regulations (CFR) and ICH Good Clinical Practices (E6).

I agree to conduct the study in accordance with the current protocol and will not make changes to the protocol without obtaining Sponsor and IRB approval, except when necessary to protect the safety, rights, or welfare of subjects.

_____ _____

Printed Name of the Principal Investigator Date

_____

Signature of the Principal Investigator