STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official title: A Phase 1-2 Multi-Center Study to Assess the Efficacy and Safety of Abiraterone Acetate as Adjunctive Therapy in Pre-Pubescent Children with Classic 21-Hydroxylase Deficiency

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A Phase 1-2 Multi-Center Study to Assess the Efficacy and Safety of Abiraterone Acetate as Adjunctive Therapy in Pre-Pubescent Children with Classic 21-Hydroxylase Deficiency

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1. INTRODUCTION AND PURPOSE

1.1. Synopsis

Children with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency tend to have elevated circulating levels of androgens, which can accelerate skeletal maturation and adversely impact adult height (reviewed in (1-3)). Supraphysiologic doses of hydrocortisone are required to suppress secretion of adrenal androgen precursors, and this treatment can retard linear growth. Abiraterone acetate is a prodrug of abiraterone, an irreversible inhibitor of 17α hydroxylase/C17, 20-lyase (cytochrome P450c17 [CYP17]), a key enzyme required for testosterone synthesis (4;5). Phase 1 of this study is designed to determine the minimal dose of abiraterone acetate dispersed tablets formulated from Active Pharmaceutical Ingredient (API)) needed to decrease serum androstenedione to age-appropriate levels in pre-pubescent children with classic 21-hydroxylase deficiency in order to reduce daily requirement of hydrocortisone in these patients. Phase 2 will determine if, over 24 months, this treatment retards bone age advancement and thus improves adult height prognosis. Phase 1 and Phase 2 will determine safety and tolerability in a pediatric population over the short and long term, respectively.

1.2. Primary Outcome Measures

1.2.1. Phase 1

The minimal dose of abiraterone acetate required to suppress excess androgens as indicated by a normalization of androstenedione in pre-pubescent children with classic 21-hydroxylase deficiency on physiologic replacement doses of hydrocortisone.

1.2.2. Phase 2

Retardation of bone age advancement in growing pre-pubescent children with classic 21-hydroxylase deficiency during treatment with abiraterone acetate for 24 months.

1.3. Secondary Outcome Measures

1.3.1. Phase 1

The pharmacokinetic (PK) profile of abiraterone.

1.3.2. Phase 2

Changes in height, weight, body mass index (Z-score for age, predicted adult height, laboratory parameters and hydrocortisone dose after treatment with abiraterone acetate; the safety profile of abiraterone acetate after multiple dosing in this patient population.

1.4. Hypotheses (Phase 2)

1.4.1. Primary Hypothesis

Abiraterone acetate retards the advancement of skeletal maturity (bone age) over the study period in pre-pubescent children with classic 21-hydroxylase deficiency.

1.4.2. Secondary Hypotheses

- Abiraterone acetate reduces the daily requirement of hydrocortisone to normalize androstenedione concentrations in pre-pubescent children with classic 21-hydroxylase deficiency.

- Abiraterone acetate is associated with less weight gain than placebo.
- Abiraterone acetate is associated with lower age-adjusted BMI Z-score than placebo.
- Abiraterone acetate is associated with higher predicted adult height (adjusted for midparental height) than placebo.

1.5. Overall Rationale for the Study

As noted, children with 21-hydroxylase deficiency require supraphysiologic replacement doses of glucocorticoids to suppress adrenocorticotropic hormone (ACTH)-driven adrenal androgen synthesis (3). Excessive glucocorticoids are associated with excessive weight gain and slowing of linear growth (6). It would be desirable in pre-pubertal children to decrease the exposure to excess glucocorticoids while avoiding the adverse effects of inappropriate exposure to androgens. The present study is the first clinical trial to explore the utility of abiraterone acetate as a means for decreasing daily requirements for glucocorticoids in pre-pubertal children with 21-hydroxylase deficiency. See section 2.2 for approved indications for abiraterone acetate.

1.6. Safety endpoints

The potential benefits to the subjects would be some retardation in bone age advancement and thus improvement in adult height, and avoidance of supraphysiologic glucocorticoid dosing, which itself carries many risks including reduced linear growth, excessive weight gain, and abnormal glucose tolerance (also see Section 13). The main risks to abiraterone acetate are abnormal liver function tests, which should be avoidable with periodic monitoring. Patients taking abiraterone acetate who have normally functioning adrenal glands secrete increased amounts of deoxycorticosterone, an active mineralocorticoid, and consequently are at risk of developing signs of mineralocorticoid excess such as hypertension or heart failure (see Sections 10.1.1.1 and 11.2.1), but patients with 21-hydroxylase deficiency are unable to synthesize this steroid and are not at risk for these problems. Cataracts were observed in preclinical studies in rats but have not been seen in other nonhuman species including monkeys, and have not been observed at an increased rate in clinical trials. Subjects will have yearly ophthalmologic exams to monitor for this problem.

2. BACKGROUND

2.1. 21-Hydroxylase Deficiency

2.1.1. Clinical Presentation

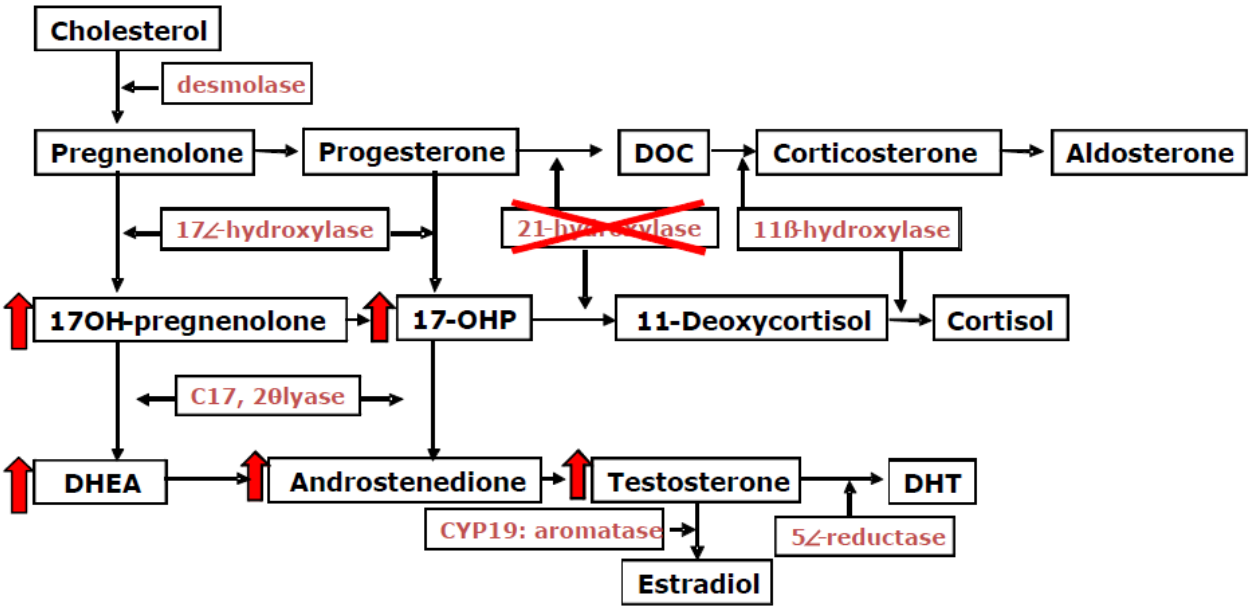
Congenital adrenal hyperplasia (CAH) is an inherited inability to synthesize cortisol in the adrenal gland (Figure 1).

More than 90% of cases are caused by deficiency of steroid 21-hydroxylase (CYP21, also termed CYP21A2, P450c21); in this protocol we will generally use the terms CAH and 21-hydroxylase deficiency interchangeably. CYP21 is a cytochrome P450 enzyme located in the endoplasmic reticulum. It catalyzes conversion of 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol, a precursor for cortisol, and progesterone to deoxycorticosterone, a precursor for aldosterone. Thus, patients with 21-hydroxylase deficiency cannot synthesize cortisol efficiently, and so the adrenal cortex is stimulated by corticotropin

(ACTH) and overproduces cortisol precursors. Some of these precursors are diverted to sex hormone biosynthesis, which may cause signs of androgen excess including ambiguous genitalia in newborn females and rapid postnatal growth in both sexes. Concomitant aldosterone deficiency may lead to salt wasting with consequent failure to thrive, hypovolemia and shock.

There is a range of phenotypes. A severely affected form with a concurrent severe defect in aldosterone biosynthesis ("salt wasting" type) and a form with less impairment of aldosterone biosynthesis ("simple virilizing" type), are together termed “classic” 21-hydroxylase deficiency. A mild "nonclassic" form may be asymptomatic or associated with signs of postnatal androgen excess (1;2). Classic 21-hydroxylase deficiency is detected in approximately 1/16,000 births in most populations (reviewed in (7)). The nonclassic form occurs in approximately 0.2 percent in the general Caucasian population.

Figure 1: Pathways of Steroid Biosynthesis in Adrenal Glands in CYP21 Deficiency



17-OHP=17-hydroxyprogesterone; CYP=cytochrome; DHEA=dehydroepiandrosterone; DHT=dihydrotestosterone
DOC=deoxycorticosterone

Figure 1 Pathways of steroid biosynthesis in 21-hydroxylase deficiency. Enzymes are indicated by their activities rather than by systematic names. Steroids that are typically increased in this disorder are denoted by upward-pointing arrows. Aromatase and 5α-reductase are located mainly in extra-adrenal sites.

Approximately 75 percent of classic 21-hydroxylase deficiency patients cannot adequately synthesize aldosterone. Since aldosterone regulates urinary sodium resorption, untreated individuals excrete excessive sodium and develop hypovolemia and hyperreninemia. They cannot excrete potassium efficiently and are prone to hyperkalemia, especially in infancy. Cortisol deficiency contributes to poor cardiac function, poor vascular response to catecholamines, decreased glomerular filtration, and

increased secretion of antidiuretic hormone (reviewed in (8)). Thus, cortisol and aldosterone deficiency together cause hyponatremic dehydration and shock in inadequately treated patients.

Excess 17-OHP, 17-hydroxypregnenolone, and progesterone are further metabolized to dehydroepiandrosterone and androstenedione. Once secreted, these substances are further metabolized to active androgens (testosterone and dihydrotestosterone). Adrenal secretion of excess androgen precursors does not significantly affect male sexual differentiation. In affected female fetuses, androgens inhibit the formation of separate vaginal and urethral canals and cause clitoral enlargement, fusion of the labial folds, and rostral migration of the urethral/vaginal perineal orifice (reviewed in (9)). Thus, severely affected girls typically have ambiguous or male appearing external genitalia with perineal hypospadias and chordee, but without palpable testes.

Most importantly for the present study, in inadequately treated patients, postnatal chronic exposure to high levels of sex hormones promotes rapid somatic growth (predominantly an androgen effect) and advanced skeletal age leading to premature epiphyseal fusion (predominantly an effect of extragonadal aromatization of androgens to estrogens)(10). Pubic and axillary hair may develop early. Clitoral growth may continue in girls. Young boys may have penile growth despite small testes, since the androgens are adrenal in origin. Chronic exposure to androgens may activate the hypothalamic-pituitary-gonadal axis causing centrally-mediated precocious puberty (2). Linear growth is affected even with close therapeutic monitoring. Based on meta-analysis of data from over 30 centers, adult heights in classic patients average 1.4 standard deviations below the population mean, or 1.0 standard deviations below expectations adjusted for parental heights (6). Both under-treatment and over-treatment put patients at risk for short stature, the former owing to premature epiphyseal closure induced by sex steroids, and the latter to glucocorticoid-induced inhibition of growth (11). The present study will test whether pharmacologic blockade of sex steroid biosynthesis will improve growth expectations in children with CAH.

2.1.2. Genetics

We will discuss the genetics of this disorder because it is relevant to subject selection. Steroid 21-hydroxylase deficiency is an autosomal recessive disorder caused by mutations in the CYP21 (CYP21A2) gene, which is located on chromosome 6p21.3 along with a pseudogene, CYP21P (CYP21A1P) (reviewed in (1;2)). Although CYP21 and CYP21P are 98 percent identical in nucleotide sequence, the latter has accumulated several mutations that totally inactivate its gene product (Figure 2). Other mutations in CYP21P affect pre-mRNA splicing or amino acid sequence. Most mutations causing 21-hydroxylase deficiency arise from two types of recombination between CYP21 and CYP21P.

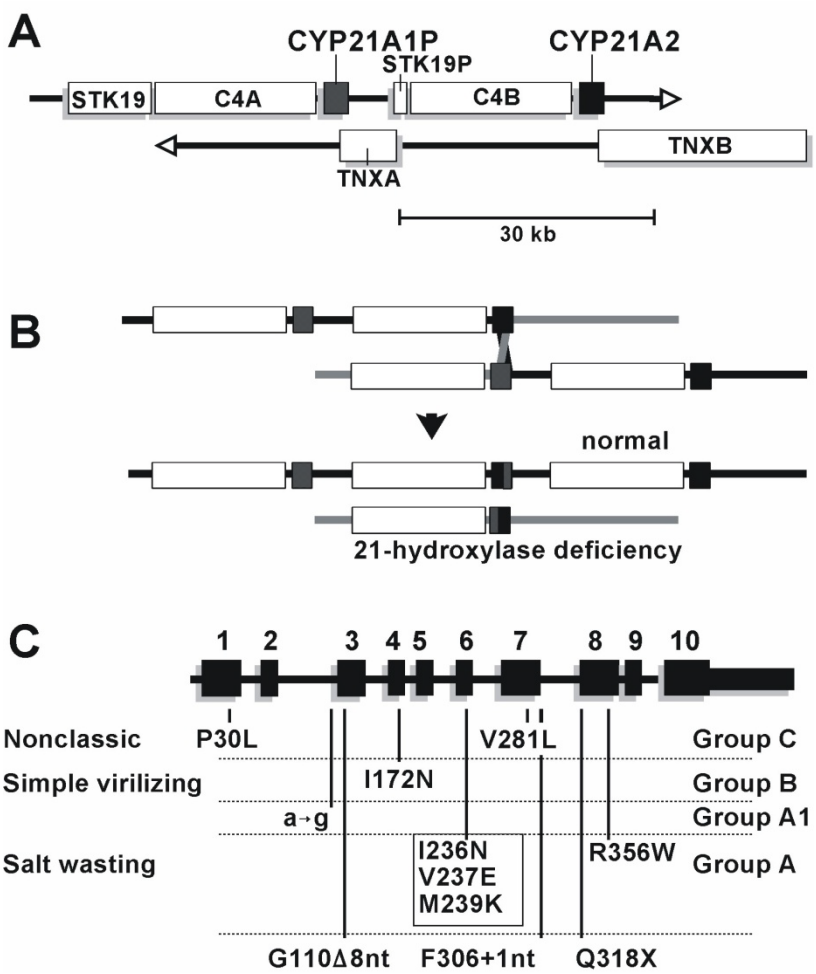


Figure 2. Genetics of 21-hydroxylase deficiency. A, Diagram of the chromosomal region on 6p21.3 containing the 21-hydroxylase genes. *CYP21P* and *CYP21* are the steroid 21-hydroxylase pseudogene and active gene, respectively. *C4A* and *C4B* encode the fourth component of serum complement. *STK19* encodes a serine/threonine kinase

, and STK19P is the corresponding truncated pseudogene. On the opposite chromosomal strand, *TNXB* encodes tenascin-X and *TNXA* is the corresponding truncated pseudogene. A bar delineates the 30 kb region that is deleted in approximately 20 percent of 21-hydroxylase deficiency chromosomes.

B, illustration of unequal crossing-over events causing deletions of CYP21

C, **Diagram of *CYP21*. Numbered boxes represent exons; a 1 kb scale is indicated. The positions of mutations normally found in *CYP21P* are shown; any of these can be transferred to *CYP21* in gene conversion events. Recombinant enzymes carrying each missense mutation have been expressed in cultured cells. The percent of normal activity seen in each mutant enzyme is denoted by the position of each mutation on a vertical scale, with the mutations most severely affecting activity at the bottom of the figure. Mutations are: P30L, Pro30Leu; a6g, mutation in intron 2 activating a cryptic splice site; Δ8nt, 8 nucleotide deletion; I172N, Ile172Asn; I236N,V237E, and M239K are a cluster of three mutations invariably inherited together, Ile236Asn, Val237Glu, Met239Lys; V281L, Val281Leu; +1nt, single nucleotide insertion; Q318X, nonsense mutation of Gln318; R356W, Arg356Trp; P453S, Pro453Ser.**

Approximately 75 percent represent deleterious mutations found in the pseudogene that are transferred to CYP21 during mitosis by a process termed gene conversion. About 20 percent are meiotic recombinations that delete a 30 kilobase gene segment encompassing the 3' end of the CYP21P pseudogene, all of the adjacent C4B complement gene, and the 5' end of CYP21. This produces a non-functional chimeric pseudogene. Over 165 additional mutations comprise the remaining 5 percent (12). In patients, 1 to 2 percent of affected alleles are *de novo* mutations not carried by either parent (1). Moreover, many patients carry more than one mutation on each allele because of the high rate of gene conversion. It is therefore important to ascertain parental genotypes for prenatal counseling and to set phase on detected mutations (i.e., determine which mutations are on each allele).

Correlations between CYP21 genotype and phenotype have been studied in various ethnic and racial groups (13)(and reviewed in (1;2)). CYP21 mutations can be grouped into three categories according to the level of enzymatic activity predicted from in vitro mutagenesis and expression. Group A consists of mutations such as deletions or nonsense mutations that totally ablate enzyme activity; these are most often associated with salt-wasting disease. Group B consists mainly of the missense mutation Ile172Asn (I172N,999T>A), which

yields an enzyme with 1 to 2 percent normal activity. This permits some aldosterone synthesis and is characteristic of patients with simple virilizing disease. A mutation in the second intron (nucleotide 656A to G, transferred from CYP21P by gene conversion, 655A/C>G) comprises 25 percent of all classic 21-hydroxylase deficiency alleles and usually results in abnormally spliced mRNA transcripts. However, a small amount of the mRNA is normally spliced, and thus this mutation is associated with both salt-wasting and simple virilizing disease. This is the only mutation in Group A1.

The final group of mutations includes Val281Leu (V281L, 1683G>T) and Pro30Leu (P30L, 89C>T), which produce enzymes retaining 20 to 60 percent of normal activity; these are associated with nonclassic disease. However, if the P30L mutation is present as part of a larger gene conversion encompassing at least the first 167 bases of the CYP21A1P/CYP21A2 promoter, it is associated with simple virilizing disease. Such gene conversions will be classified as mutation group B for purposes of this study (14).When 21-hydroxylase deficiency phenotype is quantitated using 17-OHP levels or scores for signs of androgen excess or salt wasting, 80 to 90 percent of phenotypic variation is accounted for by CYP21 genotype (i.e., allelic variation). Compound heterozygotes for two different CYP21 mutations usually have a phenotype compatible with the milder of the gene defects, and are therefore classified into groups A, A1, B or C depending on the more mildly affected allele.

2.1.3. Standard of Care

Patients with classic 21-hydroxylase deficiency require chronic glucocorticoid treatment to inhibit excessive secretion of CRH and ACTH by the hypothalamus and pituitary and reduce elevated adrenal sex steroids (reviewed in (3)). In children, the preferred drug is hydrocortisone (i.e., cortisol itself) in maintenance doses of 10 to 15 mg/M^2/day in three divided doses. Hydrocortisone's short half-life minimizes growth suppression and other adverse side effects of longer acting, more potent glucocorticoids such as prednisone and dexamethasone. Because of the short half-life, a single daily dose of hydrocortisone is ineffective in regulating adrenocortical secretion. There is divergence of opinion regarding whether to administer three equal doses over the day, or provide more hydrocortisone in the morning (the time of the normal diurnal ACTH and cortisol peaks) or the evening, to attempt to suppress the morning ACTH peak. There appears to be little difference between such regimens in practice (15). Stress doses of up to 100 mg/M^2/day are given during adrenal crises and life-threatening situations.

Even maintenance doses exceed physiologic cortisol secretion (7 to 9 mg/M^2/day in neonates and 6 to 8 mg/M^2/day in children and adolescents (16)). Treatment efficacy is best monitored by measuring 17-OHP and androstenedione levels at a consistent time in relation to medication dosing. Children should also have an annual bone age x-ray and careful monitoring of linear growth. The goal is to use the lowest glucocorticoid dose that adequately suppresses adrenal androgens and maintains normal growth and weight gain, generally <17 mg/M^2/24h of hydrocortisone (11). One should not strive to normalize 17-OHP since this often requires excessive glucocorticoid doses. Rather, 17-OHP levels should be partially suppressed to the range of 100 to 1200 ng/dl (3 to 30 nmol/L). Androstenedione and testosterone levels (the latter useful only in women and pre-pubertal children) should be maintained at a level appropriate for age and sex.

In addition to glucocorticoid treatment, children with the salt wasting form of 21-hydroxylase deficiency require mineralocorticoid (fludrocortisone acetate, usually 0.05 to 0.2 mg daily but up to 0.4 mg daily in sick neonates) and infants often require sodium chloride supplements. Blood pressure and plasma renin activity or direct renin assays may be used to monitor mineralocorticoid and sodium replacement. Hypertension, edema, tachycardia and suppressed plasma renin signify overtreatment with mineralocorticoids. Excessive fludrocortisone may also retard growth.

2.1.4. Potential Improvement in Care From This Study

Pharmacologic blockade of sex steroid synthesis in prepubertal children with 21-hydroxylase deficiency would retard skeletal maturation and afford more years in which such children could grow. Moreover, if glucocorticoid dosing could be reduced to a level sufficient to prevent adrenal insufficiency (but not itself suppress secretion of adrenal androgen precursors) this would minimize glucocorticoid-related linear growth retardation. The overall effect would be improved adult height.

2.2. Status of Study Drug

Abiraterone acetate tablet formulations (ZYTIGA® brand and several generics) in combination with prednisone/prednisolone (hereafter referred to as prednisone) have been approved for the treatment of men with metastatic castration-resistant prostate cancer (mCRPC). See section 3.2 for details.

2.3. Previous Research on Blockade of Sex Steroids in CAH

2.3.1. Testolactone and flutamide in children with CAH

The hypothesis that blockade of sex steroid synthesis or action might permit glucocorticoid doses to be decreased in CAH patients has been previously tested. A four-drug regimen consisting of low dose hydrocortisone, fludrocortisone, testolactone (an aromatase inhibitor to minimize estrogen-induced skeletal maturation), and flutamide (an androgen receptor blocker) reduced the rate of bone age advancement and slowed weight and height velocity, compared with a standard regimen of higher dose hydrocortisone and fludrocortisone (17). No serious adverse effects were observed. This experimental therapy is not currently recommended as standard of care (3).

2.3.2. Phase 1 Study of Abiraterone Acetate in Adult Women With CAH

A phase 1 study of abiraterone acetate has been conducted in adult women with 21-hydroxylase deficiency (Study 212082HPL1002, hereafter referred to as Study HPL1002)(18). Six subjects were treated with each of two doses of abiraterone acetate suspension (100 mg or 250 mg/day) for 6 days, which is equivalent to about 1.5 or 4 mg/kg for a typical 60 kg woman). Androstenedione was decreased at nadir 4-6 h after the last dose by 90% or 96%, respectively, at 100 mg or 250 mg/d (mean decrease from 621 to 41 ng/dl at the higher dose, **Figure 3**). 24h after the final dose, the androstenedione level was still less than 20% of baseline (114 ng/dl) and it was only 30% of baseline (215 ng/dl) after 48h.

Treatment with abiraterone acetate also decreased 17-OHP levels, but the inhibition was not as complete and was more transient. At nadir 4h after administration of 250 mg on day 6 of treatment, 17-OHP had decreased from 9273 ng/dl at baseline to 1362 ng/dl (85% decrease, **Figure 3**) but it was back

to or above baseline levels by 24h after the last dose. The implications of these findings for the design of the present study are discussed in section 11.1.1

The mean testosterone concentration also decreased 75% from baseline on Day 6 and remained under 50 ng/dL 2 days after the last dose. In addition, concentrations of urine testosterone metabolites, etiocholanolone and androsterone glucuronides, decreased as well. Abiraterone acetate was safe and well tolerated.

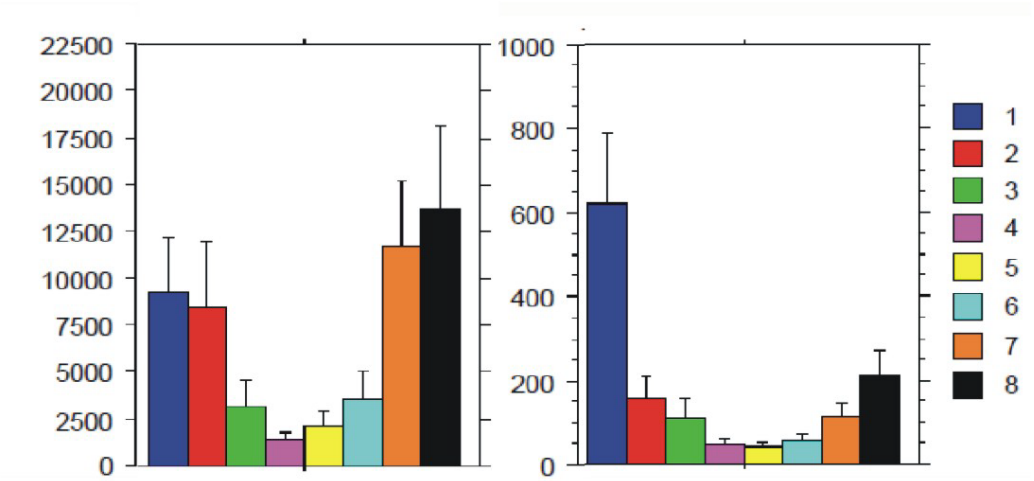


Figure 3. Pharmacodynamics of abiraterone acetate in adult women with CAH given 250 mg daily of abiraterone acetate suspension. *Left panel*, 17-hydroxyprogesterone. *Right panel*, androstenedione. Scales are ng/dl. Bars are means of determinations on six subjects; error bars are 1 standard error. Samples are numbered as follows: 1, baseline; 2, morning of day 6 at time of administration; 3-6 2h, 4h, 6h and 8h after dose, respectively; 7, morning of day 7, 24h after last dose; 8, morning of day 8, 48 after last dose. The time courses with 100 mg daily were very similar (not shown).

2.4. Previous Pediatric Use of Abiraterone Acetate

We are aware of use of abiraterone acetate in a single pediatric patient, a 7 year old boy with central precocious puberty (19). This child was treated with 250 mg daily of abiraterone acetate and 8.5 mg/M2/24h of hydrocortisone under single patient IND 121950, held by a co-investigator on the present project, Mitchell Geffner. This dose of abiraterone acetate, which is higher than that anticipated in the present study, was well tolerated after 1.8 years of treatment with no serious adverse effects, and normal blood pressure, electrolytes and liver function tests. Additionally, three children were treated in the present IND for one week each with a previous product, encapsulated powder prepared from pulverized commercial abiraterone acetate (Zytiga®) tablets. Two subjects received 1 mg/kg/day, and one subject received 2 mg/kg/d. No adverse events were reported.

3. CONCISE SUMMARY OF PROJECT

3.1. Overview of Study Design

This study consists of Phase 1 and Phase 2 portions.

3.1.1. Phase 1 Dose-Finding

Phase 1 is a dose-finding study which will consist of a Screening Period, a Lead-in Period of 7-9 days with a possible 7-9 day extension, followed by a 7-day Treatment Period during which patients will receive abiraterone acetate dispersed tablets. Subjects will take protocol-specified doses of hydrocortisone and fludrocortisone during the Lead-in Period and through the Treatment Period. Androstenedione normalization will be determined based on morning androstenedione concentration on Day 8 at each dose level. If eligible, subjects have the option to enroll into the randomized Phase 2 study.

3.1.2. Phase 2 Double-Blind

The Phase 2 portion of the study is a double-blind 2:1 randomization of abiraterone acetate versus placebo with duration of up to 109 weeks.

3.2. Study Drug Information

3.2.1. Mechanism of action

Abiraterone acetate is a prodrug of abiraterone (17-[3-pyridyl] androsta-5,16-dien-3β-ol), an androgen biosynthesis inhibitor. The mechanism of action of abiraterone is selective inhibition of cytochrome P450 17α-hydroxylase/17,20-lyase (CYP17). CYP17 catalyzes the conversion of pregnenolone and progesterone into testosterone precursors, dehydroepiandrosterone (DHEA) and androstenedione, respectively, by 17α-hydroxylation and cleavage of the C17,20 bond. Once absorbed after oral administration, abiraterone acetate is rapidly converted to abiraterone, the predominant active metabolite detected in nonclinical and clinical studies (4;20).

3.2.2. Formulation

Abiraterone acetate active pharmaceutical ingredient (API)will be formulated by Sharp Clinical Services (Bethlehem, PA 18020) into 10 mg tablets. The 10 mg tablets will each contain:

Abiraterone acetate	10 mg
Avicel PH-102 (microcrystalline cellulose)	23.2 mg
Lactose, MONO 316	46 mg
Magnesium stearate	0.8 mg

Microcrystalline cellulose and lactose are the two excipients in the original Zytiga abiraterone acetate tablets. For Phase 2, Sharp will also prepare placebo tablets, which will contain 26.5 mg of microcrystalline cellulose and 52.6 mg of lactose. To maximize consistency in Phase 1, tablets should be

dispersed into a small amount of water or apple juice immediately before administration, and not swallowed whole. Note that, no food is permitted until 30 minutes after the medication is administered; see section 3.3.1 for details. For the most comprehensive nonclinical and clinical information regarding the efficacy and safety of abiraterone acetate, refer to the latest version of the United States Prescribing Information (USPI) (21). For warnings regarding handling of study drug, see section 3.2.5.

3.2.3. Physical Description of Study Drug(s)

The test formulation of abiraterone acetate supplied for this study are tablets compounded from API. In Phase 2, hydrocortisone and fludrocortisone will be supplied by the sponsor (as noted on the face page, the Sponsor of this study is UT Southwestern Medical Center and the Sponsor-Investigator, Perrin C White, MD; also see section 11.4.8).

3.2.4. Packaging and Labeling

Abiraterone acetate will be provided in tablets containing 10 mg of abiraterone acetate. In Phase 2, placebo tablets will be identical in appearance to those containing active drug. Families will be instructed to disperse the tablets in a small volume of water or apple juice. Study drug labels will contain information to meet the applicable regulatory requirements.

3.2.5. Preparation, Handling, and Storage

The tablets must be stored at controlled temperatures ranging from 20°C to 25°C in a secure facility with appropriate alarms and backup storage plans in place. Storage temperatures 15°C to 30°C are allowed for pharmacies, hospitals, and warehouses. Records of storage conditions must be maintained and the sponsor notified immediately if conditions exceed the range specified.

3.2.6. Warning Regarding the Handling of Abiraterone Acetate Tablets or Powder

This medicine may cause harm to the unborn child if taken by women who are pregnant. It should not be taken by women who are breast-feeding. Women who are pregnant or who may be pregnant should wear gloves if they need to touch abiraterone acetate tablets**.** To minimize the risk of aerosolization, dry tablets should not be crushed, but instead dispersed directly in liquid. Study investigators should notify any caregivers of this information, to ensure the appropriate precautions are taken.

3.2.7. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject, must be documented on the drug accountability form. All participants in this study will be minors and references to study subjects refer to the legally acceptable representatives (LAR) as appropriate. The subject must be instructed to return all original containers, whether empty or containing study drug. All study drugs will be stored and disposed of according to the sponsor's instructions. Site staff must not combine contents of the study drug containers. Abiraterone acetate must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions.

Unused study drug and study drug returned by the subject (including empty bottles), must be available for verification by the sponsor's site monitor during monitoring visits. Unused study drug will be destroyed on site according to institutional policies. This must be documented on the drug accounting form. Abiraterone acetate should be dispensed under the supervision of the investigator or a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

3.3. Dosage and Administration

3.3.1. Phase 1 Dose-Finding

In Phase 1, 8 subjects in succession will be given 2 or 4 mg/kg/d of abiraterone acetate, respectively, rounded to the nearest 10 mg. By comparison, adult women with CAH in a Phase 1 study were given 100 mg or 250 mg, equivalent to 1.5 or 4 mg/kg for a typical 60 kg woman (see section 2.3.2). Abiraterone acetate will be taken every morning on Study Days 1 through 7 (section 4.1) on an empty stomach, at least 30 minutes before a low-fat breakfast (<3 grams of fat; see Appendix A for guidelines and suggestions to be provided to parents. Ingested fat increases absorption of abiraterone acetate; the US Prescribing Information calls for the patient to have abstained from eating two hours before and one hour after dosing, but there are no limits on the composition of the next meal. The schedule in this study is set in deference to the typical morning schedules of school age children. The doses used in this study are well below those employed for prostate cancer (the standard dose of 1000 mg/d is 13 mg/kg/d for a typical 75 kg man), so any increased drug absorption owing to a food effect (as well as the use of abiraterone acetate dispersed tablets instead of intact tablets) will be accounted for by the dose finding in Phase 1. Hydrocortisone 8 ± 1 mg/m^2/day divided into 3 doses, and the patient's usual dose of fludrocortisone (typically 0.05- 0.2 mg/day in one or two doses) taken with food will be given during the Lead-in Period and continued through the Treatment Period.

Once 2 subjects have failed to normalize their androstenedione levels at a given dose, advancement to the next dose level will be considered by the Sponsor with the approval of the Data Safety and Monitoring Board (DSMB, see Section 11.3). The DSMB will determine whether or not to advance to the next dose in Phase 1 based on safety and androstenedione normalization (the lowest dose that results in normalization of androstenedione levels at least 7 of 8 subjects will be used for all subjects in Phase 2). As discussed, this was already done for the 1 mg/kg/d dose level.Possible adverse effects of abiraterone acetate are discussed in Sections 10.1 and 11.2. In particular, abnormal liver function tests (as defined in Section 11.2.2) in >1 of 8 subjects in a dose cohort, if judged by the site investigator and the DSMB to be related to the study drug, will preclude escalation to a higher dose. As discussed in Sections 10.1.1.1 and 11.2.1, the mechanism-based toxicities of hypertension, hypokalemia, edema and cardiac failure are not anticipated to occur in this study. To the extent they do occur, the DSMB may mandate a prospective decrease in fludrocortisone dose upon enrollment of additional subjects. Any serious adverse events in Phase 1 will be reviewed by the DSMB for relatedness to study treatment, with the consideration that subjects will have taken study drug for only one week. The occurrence of an SAE in a subject that is probably related to study treatment will preclude participation in Phase 2. The

occurrence of >1 SAE in a dose cohort judged probably related to treatment will preclude escalation to a higher dose. The maximum tolerated dose (MTD) for the study will be declared at the dose level below where ≥ 2 SAEs related to study drug occur. If this occurs at the lowest dose level (1 mg/kg/d), the DSMB may mandate a cohort at a lower dose level (0.5 mg/kg/d). Note that this will not apply to SAEs typically associated with CAH including episodes of adrenal insufficiency, hypotension, or electrolyte abnormalities. SAEs associated with mineralocorticoid excess (hypertension, hypokalemia) may, at the discretion of the DSMB, prompt a protocol modification to reduce fludrocortisone doses upon starting abiraterone acetate (also see Section 11.2.1).

3.3.2. Phase 2 Double-Blind

Hydrocortisone and fludrocortisone will be given each day throughout the study. Hydrocortisone 8 ± 1 mg/m^2/day divided into 3 doses, and the patient's usual dose of fludrocortisone (typically 0.05-0.2 mg/day in one or two doses) taken with food will be given during the Lead-in Period. Once the administration of blinded study drug begins, the hydrocortisone dose will first be titrated after 4 weeks, then approximately every 12-13 weeks to achieve the desired androstenedione concentration, and also avoid excessively high or low 17-hydroxyprogesterone or ACTH levels (discussed in detail in Section 11.1.1). Blinded study drug will be administered in the morning on an empty stomach (at least 30 minutes before a low-fat breakfast or 1 hour before any breakfast).

3.3.3. Dose Reductions

Generally, no dose reductions of the study drug are allowed during the dose-finding and double-blind portions of the study (see Section 11.2 for exceptions in Phase 2).

3.3.4. Dose Determination for Phase 2

The following criteria will be used to set the abiraterone acetate dose for Phase 2.

- For each subject in Phase 1, the serum androstenedione level on Day 8 at each dose level will be used for determination of normalization. If a dose of abiraterone acetate is missed, then the Treatment Period at that dose will be repeated and the androstenedione value on Day 8 from the repeated period will be used (also see section 3.3.7.1). The percentage for normalization is based on all subjects who received 7 consecutive doses of abiraterone acetate administered from Days 1 through 7 at each dose level.
- If the highest planned dose (4mg/kg/d) does not result in normalization of androstenedione levels on Day 8 at least 7 of 8 subjects, the DSMB (see Section 11.3) will determine whether to authorize testing of one or more additional dose levels (e.g., 8 mg/mg/d). This remains less on a body weight basis than the standard adult dosing of 1000 mg/d (13 mg/kg/d for a typical 75 kg man).
- The lowest dose that results in normalization of androstenedione levels at least 7 of 8 subjects will be used for Phase 2. See Section 14.3.1 for a discussion of sample size in Phase 1.
- Except as discussed in Section 11.3.2, no dose escalations of abiraterone acetate are allowed during the Phase 2 double-blind portion of the study.

- PD data will be examined and exposure compared with that seen in adult women with CAH (see section 2.3.2)

3.3.5. Dose Adjustments of Study Drug for Weight Increases During Phase 2

Study drug will be dispensed in 10 mg tablets. Whereas study drug dose will be adjusted at every clinic visit (approximately every 13 weeks) as necessary, the frequency at which adjustments are actually made will depend on the per-kg dose selected for Phase 2; e.g., a dose of 2 mg/kg/d can be adjusted with every 5 kg weight gain, whereas a dose of 4 mg/kg/d can be adjusted with every 2.5 kg weight gain.

3.3.6. Treatment compliance

The investigative site will instruct the subject as to the proper procedure for taking all study required medications (which may include printed instructions) and recording the dosing of study drug (abiraterone acetate or placebo) in the dosing diary, which will include the date, time and dose of study drug. The site will confirm that the study drug was taken on an empty stomach each day (at least 2 hours since last meal, and at least 30 minutes before a low fat breakfast, or 1 hour before a meal with unspecified composition). Subjects will be instructed to bring study medications (including empty vials) to their next visit. The site will review the dosing diary, confirm with the subject that it is correct and will confirm that the study drug (vials) returned is consistent with the diary.

3.3.7. Missed Doses

3.3.7.1. Phase 1 Dose-Finding

Missed doses of abiraterone acetate will need to be reported to the investigator immediately. If a dose of abiraterone acetate is missed, then the Treatment Period at that dose will be repeated, and the androstenedione value on Day 8 from the repeated period will be used. If a missed dose of abiraterone acetate occurs, the site will initiate Visit 4A. During Visit 4A the patient/parent/legally authorized representative will be re-educated on study drug administration and provided instructions on when to recommence the abiraterone acetate (Repeat treatment period should only begin once PV4A is completed). Because abiraterone concentrations and pharmacodynamics effects should reach steady state within 6 days (18), we do not expect the prior, interrupted Treatment Period to influence the results, and we will not attempt to mandate a particular time interval or to monitor washout prior to repeating the Treatment Period. However, to ensure safety, we will obtain the following tests prior to commencing the repeat Treatment Period (also see Sections 4.1.3.2 and 4.1.7): Hematology (CBC, diff, platelets), comprehensive metabolic profile (to include serum electrolytes, kidney function tests (BUN,Creatinine), liver function tests (aspartate aminotransferase (AST,) and alanine aminotransferase (ALT), bilirubin)).

If a dose is missed in the repeated Treatment Period, the subject will be dropped from the study. The continuation of treatment may be granted only after a discussion with the sponsor.

One dose of hydrocortisone may be missed during the first 4 days of abiraterone acetate dosing, but no missed doses are allowed 1 day prior to PK/PD assessment.

3.3.7.2. Phase 2 Double-Blind

The importance of treatment compliance should be stressed to the subjects prior to the study start, and they should be counseled appropriately regarding any noted deviation from the dosing schedule. Subjects will be instructed to bring study medications (including empty vials) to their next visit. Dosing diaries will be issued and reviewed at each visit and reconciled with returned study drug (vials). Accurate recording of hydrocortisone dosing during double-blind Phase 2 should be stressed to the subject.

Three consecutive missed doses of blinded study drug per month are allowed in the Phase 2 in the absence of an adverse event. Subjects who missed more than this for reasons other than adverse events may have study treatments discontinued due to non-compliance. The sponsor should be notified if any subject meets the criteria for discontinuation of study treatments due to non-compliance. The continuation of treatment with blinded study drug for such subjects may be granted only after a discussion with the sponsor. Any subjects withdrawn from study treatment should continue follow-up for scheduled assessments, see Section 4.5.3.

There is a possibility that subjects receiving placebo may become aware of this fact (see section 4.5.2). Such subjects should continue receiving the assigned treatment and return for scheduled evaluations.

3.3.8. Missed Study Visits

3.3.8.1. Phase 1

See Section 4.1 for description of study visits. The following deviations from the timeline are permitted: Visit 2 may be postponed up to 2 days (i.e., scheduled 7-9 days after reducing the hydrocortisone dose). An exact time interval between Visits 2 and 3 is not specified, but Visit 3 should occur within 42 days (6 weeks) of Visit 1. Visit 4 must be 24h after Visit 3. Visit 5 may be postponed for up to 2 days, but the final daily dose of abiraterone acetate must be 24h before the visit (i.e., up to 9 days of abiraterone acetate treatment is permitted under the protocol. Visits outside mandated intervals will be logged as protocol deviations. In light of the centrality of PK data for Phase 1, a missed Visit 4 should be discussed with the sponsor to determine the best course of action.

3.3.8.2. Phase 2

Study visits in Phase 2 may be scheduled within a one-week interval. Visits outside mandated intervals will be logged as protocol deviations.

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3.3.9. Rationales for Endpoints

3.3.9.1. Phase 1 Dose-Finding

This study is designed to explore the use of abiraterone acetate in pre-pubertal children with 21-hydroxylase deficiency as a means for decreasing excess adrenal androgen secretion and daily requirements for glucocorticoids. Currently, abiraterone acetate is not indicated for use in pediatric patients, and evidence of safety of daily administration of abiraterone acetate in children is limited to a

single published patient (19) plus two patients treated thus far in Phase 1. Additionally it is necessary to account for possibly altered PK owing to [a] the use of abiraterone acetate API in custom-formulated tablets, rather than using Zytiga brand tablets or FDA-approved generic tablets, [b] the use of dispersed rather than intact tablets, and [c] the instruction to take the study medication 30 minutes before a low fat breakfast, rather than one hour before a breakfast of unspecified composition (also see section 3.3.1).

Therefore, the study is designed to assess abiraterone acetate exposure and response to treatment and to ensure that risks to subjects are minimized. The disposition pathways of abiraterone are not anticipated to be different between children (≥2 years of age) and adults. In the proposed study, the PK assessments will be used to characterize drug exposure in children. In addition, pharmacokinetics/pharmacodynamics (PK/PD) relationships will be explored.

The most commonly used steroid precursors or androgens for glucocorticoid titration in CAH are 17-OHP and androstenedione. 17-OHP is subject to greater diurnal variation and is thus more sensitive to time of sampling. The inhibitory effect of abiraterone acetate on 17-OHP levels is relatively transient (see Figure 3 in section 2.3.2) and would require titration several hours after a dose, rather than the next morning, which would increase the length of study visits and be burdensome for subjects. Moreover, 17-OHP is not a direct precursor for androgens in humans whereas androstenedione is converted to testosterone, mostly outside the adrenal, in a single enzymatic step. Thus, androstenedione is a more appropriate endpoint for dose titration if the aim is to minimize inappropriate androgen secretion. Dihydrotestosterone will be a secondary endpoint in addition to 17-hydroxyprogesterone. This is necessary because 17-hydroxyprogesterone can be indirectly metabolized to dihydrotestosterone, the most active known androgen (via the so-called “backdoor pathway”), without using androstenedione as an intermediate, and biologically significant levels of dihydrotestosterone might be attained if 17-hydroxyprogesterone levels are very elevated (22-24). However, although dihydrotestosterone is normally synthesized mainly from testosterone, testosterone would itself be a redundant endpoint because it is synthesized only from androstenedione and not via the backdoor pathway.

3.3.9.2. Phase 2

3.3.9.2.1. Bone age advancement

The Phase 2 primary endpoint is advancement in bone age per year advancement in chronologic age, which will be determined by repeated measure every 6 months for the 24-month duration of Phase 2. This will test the primary hypothesis that blockade of androgen synthesis in prepubertal children with 21-hydroxylase deficiency will retard skeletal maturation. The duration of the study will not allow testing of a treatment effect on final adult height, which would be the ultimate aim of such treatment, so bone age maturation is considered the best available surrogate measure (these will be read centrally by an automated program, see section 4.3.5).

3.3.9.2.2. Hydrocortisone dose

The difference in the mean daily hydrocortisone dose between subjects who received abiraterone acetate compared with placebo is a secondary endpoint. This is clinically meaningful since titration of hydrocortisone to minimize effects of inappropriately high concentrations of androgens can be a challenge in growing children (3). This often requires supraphysiologic doses of hydrocortisone, which

can themselves adversely affect linear growth. Final adult height in CAH patients is inversely related to mean glucocorticoid dose (6;11). Therefore, this endpoint is an additional surrogate measure for potential beneficial effects of abiraterone acetate treatment on final height in these patients.

3.3.9.2.3. Weight

Treatment with high doses of glucocorticoids can cause excessive weight gain. Patients with CAH have increased fat mass. This may have unfavorable metabolic consequence including increased insulin resistance (25;26). Therefore, this secondary endpoint will assess whether any reduction in glucocorticoid dose with abiraterone acetate treatment is physiologically significant.

3.3.9.2.4. Height

We will measure height (i.e., linear growth rate) in our subjects, but will interpret these data cautiously. As noted above in section 3.3.9.2.2, high glucocorticoids can retard linear growth, and so if glucocorticoid doses can be reduced in subjects treated with abiraterone acetate, this might be expected to increase the growth rate. However, high androgen levels accelerate linear growth (at the expense of even faster skeletal maturation) and therefore if high androgen levels can be decreased with abiraterone acetate, this might actually slow linear growth. This is indeed what was observed with a four-drug regimen consisting of low-dose hydrocortisone, fludrocortisone, testolactone and flutamide (17). The net effect of abiraterone acetate treatment on linear growth rate is thus difficult to predict.

3.3.9.2.5. Body mass index

Body mass index will be calculated from each subject's height and weight using the formula mass(kg)/height(m)^2. This will be converted to age-specific Z-scores using 2000 Center for Disease Control data (27).

3.3.10. Study drug dose rationale

A dose-finding study in adults with classic 21-hydroxylase deficiency (Study HPL1002) has been completed (see Section 2.3.2). The primary objective of the study in adults was to determine the minimum dose of abiraterone acetate required to normalize serum androstenedione in premenopausal women on hormonal contraceptive therapy. This study represents the most appropriate human model for pre-pubescent children with the same disease.

As noted in section 3.3.1, subjects in Phase 1 of the present study will be dosed at 2 or 4 mg/kg/d. These doses have been selected to be similar to the effective doses per kg for normalization of androstenedione in adult women with CAH, as determined in Study HPL1002 (100-250 mg/d, corresponding to ~1.5-4 mg/kg/d for a typical 60 kg woman; note however, that HPL1002 utilized a suspension--not available for the present study—which may have different bioavailability than the dispersed tablets to be used herein). The maximum dose is nominally ~30% of the dose per kg used in men with prostate cancer (1000 mg/d, or ~13 mg/kg/d for a 75 kg man).

As multiple blood samples are drawn for PK and PD in adults, a PK/PD association in adults may be extrapolated to children by modeling and simulation. The possibility of extrapolating the PK/PD relationship from adult to children will be evaluated further after data from Phase 1 become available. We do not anticipate a difference in the model between adults and children at the age range to be studied.

3.3.11. Hydrocortisone Dose Rationale

The suggested daily dose of hydrocortisone in children with salt-wasting 21-hydroxylase deficiency is 10-15 mg/m^2 ((3), but the average dose that is actually required to achieve adequate control is at the high end of this range (28). Hydrocortisone doses in excess of 15-17 mg/m^2/day in adolescents have been associated with shorter adult height (3). Only those children who are receiving ≥10 mg/m^2 of daily hydrocortisone are being included in the study. Normal adrenal glands in children between 2 to 9 years secrete the equivalent of 6 to 9 mg/m^2 of hydrocortisone per day (16). Thus, the starting hydrocortisone dose of 8 $\pm$ 1 mg/m^2 approximates physiologic secretion by the adrenals. This dose is not expected to be associated with signs of adrenal insufficiency (3;17). Monitoring of dosing adequacy and rules for dose adjustment are discussed in detail in section 11.1.1

3.3.12. Age Rationale

Children as young as 2 years old will also be included in this study. Children under the age of 2 will not be treated with abiraterone acetate because:

- Due to the blood volume required for monitoring, there will be a 12 kg weight requirement as part of the eligibility criteria. Children younger than 2 years will be unlikely to meet the weight requirement.

- Standard radiology practice is to use radiographs of a hemiskeleton for bone age determination in children younger than 2 years, whereas radiographs of the left hand and wrist are used for older children. There is increased radiation exposure with the hemiskeleton films, and moreover it will be very difficult to compare changes in films over time in each subject if some are of the hemiskeleton, and later ones of the left hand and wrist.

- Abiraterone acetate has a well-characterized food effect (29). US Prescribing Information calls for the patient to have abstained from eating two hours before and one hour after dosing, with no limitation on the composition of the meal. This schedule is difficult for school age children; hence subjects in this study are allowed a low fat breakfast 30 minutes after the dose. But even this scheduling may be too challenging for children under 2 years old.

Children after the onset of age-appropriate central puberty will not be included in this study because:

- It is not desirable to interfere with normal age-appropriate effects of puberty including bone mineralization, development of secondary sexual characteristics, and the pubertal growth spurt.

- Children in true puberty have activation of the hypothalamus-pituitary axis, and as a result, will have very high gonadotropin secretion if sex steroid synthesis is blocked with abiraterone acetate. This may have undesirable effects such as polycystic ovaries in females. Note, however, that in children who have central precocious puberty triggered by CAH therapy during this study (see section 11.1.4), this problem will be treated with a gonadotropin releasing hormone agonist.

Randomization will be stratified by age (2 to 5 years and 6 years or greater) to achieve an approximately equal number of subjects within each age group among the 2 treatment groups, because:

- Skeletal maturation is not a truly linear process with age, and it will be desirable to compare treatment effects in groups with similar age composition.

- The risk of inducing central precocious puberty may increase with age, and it is desirable to compare this risk between treatment groups.

- The data do not exist to derive predicted heights for children with bone age < 6 years.

3.3.13. Rationale for Pharmacokinetic Sampling Scheme

The sampling scheme is intended to minimize blood draws in this pediatric population while providing sufficient PK and PD information. We will assess single-dose PK with samples at 0, 1, 2, 4 hours (Day 1) and 24 hours (Day 2), which should be adequate to determine maximum plasma concentration (Cmax) and elimination half-life. We will not obtain an 8 hour sample on Day 1 because such a long visit would be burdensome for these young subjects and their families. The sample on day 8 can be used to predict abiraterone steady-state accumulation. As regards pharmacodynamics, the Phase 1 study in adult women with CAH (HPL-1002, see Figure 3 in section 2.3.2) demonstrates that the pharmacodynamic peaks for suppression of 17-hydroxyprogesterone or androstenedione levels are each at 4 hours post-dose. Because of blood volume limitations in small children, we will limit PD samples to 4 and 24 hours after the first dose, and the sample on Day 8. The 4 hour sample will be near Cmax, and our main interest is the efficacy of steady-state inhibition of androstenedione levels, which we will determine from the 24h and particularly the 8d samples.

3.3.14. Other Considerations

Contraceptive therapy is not required in this study of pre-pubescent children. However, physicians are expected to be vigilant about following children closely for hints of onset of puberty. Frequent physical examinations, as well as frequent LH (luteinizing hormone) and FSH (follicle-stimulating hormone) assessments will enable physicians to closely monitor the onset of puberty so that contraception will not be an issue.

3.3.15. Sample size

3.3.15.1. Phase 1

This is a Phase 1 study; the sample size is one of convenience (also see section 14.3.1). Phase 1 will study up to 8 evaluable subjects at each of two dose levels. To allow for screen failures and early withdrawals, a maximum of 36 subjects will be consented. Additional enrollment beyond this number will require review and approval by the DSMB.

3.3.15.2. Phase 2

The primary endpoint In Phase 2 is bone age advancement (change in bone age per year of chronologic age). In a study of flutamide and testolactone as adjunctive therapy in CAH (18), the rate of bone age maturation declined from 1.9 ± 0.3 to 0.7 ± 0.2 (mean + SEM) bone age year/chronological year in the children receiving the regimen with flutamide and testolactone. As there were 14 subjects per arm, this implies standard deviations of ~1.0. A sample size of 48 subjects (32 in the abiraterone acetate arm and 16 in the placebo arm) will have 90% power to detect a difference in bone age advancement of 1 year over the 2 year period of the study with a 0.05 2-sided significance level. To allow for ~10% early withdrawals, 54 subjects will be randomized (36 to abiraterone acetate and 18 to placebo) and data from all subjects will be used for the primary (intent to treat) analysis. Up to 65 subjects will be consented to allow for ~15% screen failures. It is anticipated that approximately 13 subjects will be consented at each of 5 study sites. These will include UT Southwestern Medical Center, National Institutes of Health, Children's Hospital of Los Angeles, Cohen Children's Medical Center of New York, and University of Michigan. Data will be collected and stored within a common Redcap database for all study sites.

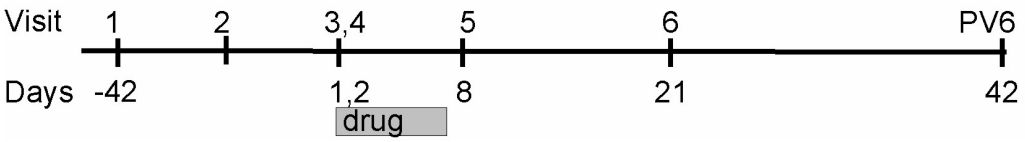
3.3.15.3. Estimate of number of eligible subjects

The lead site (UT Southwestern Medical Center/Children's Medical Center Dallas) currently follows 41 female and 35 male patients with CAH ages 2-9. The NIH Clinical Center follows 60 children in this age range. The other participating centers will likely follow similar numbers of patients. Charts on all such patients will be reviewed by each site investigator under a HIPAA waiver to identify those with classic CAH who might be potentially eligible for this study, and eliminate those with nonclassic CAH.

4. STUDY PROCEDURES

4.1. Phase 1, Dose Finding Study

Phase 1 consists of 9 study visits (6 clinic visits and 3 telephone calls) over up to 86 days, but may have up to 13 visits (up to 8 clinic visits and up to 5 telephone calls)over 93 days if Optional Visits and Phone Visits 2A and 4A are all utilized (see Sections 4.1.2.2 and 4.1.3.3) . Because the screening period may vary in length, study days prior to the Treatment Period are numbered negatively. See Table 1 (and figure below) for scheduled study activities.



4.1.1. Visit 1, Up to Day -42

4.1.1.1. Consent and Screening

All subjects must sign the informed consent/assent (see Section 9) prior to the conduct of any study procedures. Each parent who is participating in DNA testing must also sign a separate informed consent.

The following screening procedures will be performed:

- Vital signs, height, weight and temperature
- Review initial inclusion/exclusion criteria
- Physical Examination including Tanner staging
- Medical history and demographics, and concomitant medications.
- Blood samples for DNA confirmation of diagnosis (including at least one parent), if not already available
- Complete blood count (CBC), Comprehensive Metabolic Panel (CMP), hormone levels (LH, FSH), serum 17-OHP, testosterone, dihydrotestosterone, androstenedione, plasma renin activity and ACTH.
- Urinalysis
- 12-lead ECG
- Cataract examination (may be postponed to Visit 2).
- Skeletal age assessment (radiograph of left hand and wrist). An existing radiograph completed within 3 months of Visit 1 may be used as long as it was clinically read as <10 years (girls) or <11 years (boys).
- Subject will be registered in the central database after signing consent

Subjects must satisfy the initial inclusion and exclusion criteria listed in Sections 0 and 7 respectively, except criteria to be evaluated during screening period, prior to initiating the Lead-in Period.

This clinic visit will take approximately 3 hours.

Up to 16-21 mL of blood will be drawn (see Section 10.5 for discussion of blood volume limits).

4.1.1.2. Phone Visit 1: Lead-in Period

When screening laboratory test results are available and the subject has satisfied all inclusion criteria (it is acceptable that DNA testing be pending) and no exclusion criteria (it is acceptable that the cataract exam be pending), the subject will be instructed to reduce hydrocortisone dose to 8 ± 1 mg/m^2/d (see section 3.3.11) and continue the subject's usual fludrocortisone dose. The subject will then be instructed to schedule lab work to be done for Visit 2, 7-9 days after reducing the hydrocortisone dose.

Adverse events and concomitant medications will be reviewed by study staff.

4.1.2. Visit 2: Clinic/Laboratory Visit

The subject will be instructed to come to Visit 2 having not yet taken his/her morning hydrocortisone and fludrocortisone medication. The subject will have a blood sample obtained for androstenedione level between 0800 and 1000.

This clinic visit will take approximately 40 minutes. Alternatively, this visit may be conducted by prior arrangements made by the Sponsor at a local Quest lab.

Up to 2 mL of blood will be drawn.

Adverse events and concomitant medications will be reviewed by study staff.

4.1.2.1. Phone Visit 2

The androstenedione level from Visit 2 will be reviewed to ensure that it is >1.5 times the upper limit of normal (ULN) for age, and the subject will be contacted by phone. If it is not, the subject will continue in the Lead-In Period for an additional 7-9 days and Optional Visit 2A will be scheduled for a repeat sample.

If the subject meets the androstenedione inclusion criterion, s/he will advance to the Treatment Period and Visit 3 will be scheduled.

Adverse events and concomitant medications will be reviewed by study staff.

4.1.2.2. Optional Visit 2A: Clinic/Laboratory Visit

This visit will only occur if an extended Lead-In Period is required. The subject will be instructed to come to Visit 2A having not yet taken his/her morning hydrocortisone and fludrocortisone medication. The subject will have a blood sample obtained for androstenedione level between 0800 and 1000.

This clinic visit will take approximately 40 minutes. Alternatively, this visit may be conducted by prior arrangements made by the Sponsor at a local Quest lab.

Up to 2 mL of blood will be drawn.

Adverse events and concomitant medications will be reviewed by study staff.

4.1.2.3. Optional Phone Visit 2A

The androstenedione level from Visit 2A will be reviewed to ensure that it is >1.5 times the upper limit of normal (ULN) for age, and the subject will be contacted by phone.

If the androstenedione level at Visit 2A remains $\leq$1.5 x ULN, the subject will be counted as a screen failure and will be replaced; all study procedures will cease, and the subject will be instructed to resume their usual hydrocortisone dosing.

If the subject meets the androstenedione inclusion criterion, s/he will advance to the Treatment Period and Visit 3 will be scheduled.

Adverse events and concomitant medications will be reviewed by study staff.

4.1.3. Visit 3, Day 1: Clinic Visit

4.1.3.1. Treatment Period

The subject will be instructed to come to Visit 3 fasting and having not yet taken his/her morning hydrocortisone and fludrocortisone medication. Baseline fasting blood samples will be drawn between 0800 and 1000.

The following procedures will be performed:

- Review inclusion and exclusion criteria
- Obtain vital signs, height, weight and temperature
- Review adverse events and concomitant medications
- Placement of saline-locked IV catheter to allow repeated blood draws
- Fasting blood sample to test (Pre-dose labs): Serum 17-OHP, androstenedione, testosterone, dihydrotestosterone, plasma renin activity and ACTH
- Baseline PK sample (Pre-dose PK)
- Dispense medications: study drug (abiraterone acetate), and provide education for at home dosing of study drug, hydrocortisone and fludrocortisone
- Provide Subject Diary and instructions
- Subject will be given first dose of study drug in clinic and wait at least 30 minutes before eating a low fat (only) breakfast/snack if they choose
- PK blood samples at 60, 120 and 240 minutes after study drug dose. and repeated serum 17-OHP, androstenedione and dihydrotestosterone at 240 minutes after study drug dose. Each time point can vary plus or minus 5 minutes.
- Following PK blood sample at 240 minutes, the morning doses of hydrocortisone and fludrocortisone will be given, and the IV catheter will be removed.

Subjects will be furnished with Study Drug (see section 3.2). Phase 1 of this study is an open-label study. No randomization or blinding will occur in Phase 1. Subjects will be instructed to take a daily dose of abiraterone acetate on an empty stomach (at least 2 hours since last meal, and at least 30 minutes before a low fat breakfast, or 1 hour before a meal with unspecified composition) in the morning (see section 3.3.1). The first dose will be administered in the clinic as noted.

This clinic visit will take approximately -5 hours.
Up to 23 mL of blood will be drawn.

4.1.3.2. Visit 4, Day 2: Clinic Visit

The subject will be instructed to come to Visit 4 fasting and having not yet taken his/her morning study drug, hydrocortisone and fludrocortisone medication.

- A fasting blood sample will be drawn 24h (plus or minus 20 minutes after the Study Drug for: Serum 17-OHP, androstenedione, testosterone, dihydrotestosterone, and a simultaneous sample for PK.
- Following blood sample, daily doses of hydrocortisone and fludrocortisone will be given. The subject will take the daily dose of study drug in clinic and wait at least 30 minutes before eating a low fat (only) breakfast/snack if they choose

Up to 8 ml of blood will be drawn.

Adverse events and concomitant medications will be reviewed by study staff.

4.1.3.3. Optional Visit 4A: Clinic/Laboratory Visit

This visit will occur if the subject misses a dose of abiraterone during the Treatment Period (see Section 3.3.7.1). The following procedures will be performed:

- The subject will have a blood sample obtained between 0800 and 1000 for: CBC and Comprehensive Metabolic Panel.
- Dispense new bottle of study drug (abiraterone acetate). The subject will be instructed to wait until Optional Phone Visit 4A to commence taking study drug.
- Provide a new subject diary and instructions.
- Re-educate subject/parent/legally authorized representative on study drug administration instructions.

Up to 4 mL of blood will be drawn.
Adverse events and concomitant medications will be reviewed by study staff.

4.1.3.4. Optional Phone Visit 4A

This visit will occur when the results of laboratory tests from Optional Visit 4A have been reviewed to ensure that no new exclusion criteria have been met. The subject will be instructed to begin taking study drug.

4.1.4. Visit 5, Day 8: Clinic Visit; 24h After End of Treatment Period

The subject will take the last daily dose of abiraterone acetate on Day 7. Visit 5 may be postponed for up to 2 days, but the final daily dose of abiraterone acetate must be 24h before the visit (i.e., up to 9 days of abiraterone acetate treatment is permitted under the protocol). The subject will be instructed to come to Visit 5 having not yet taken his/her morning hydrocortisone or fludrocortisone doses. A blood sample will be drawn between 0700 and 1000. This may require caution in timing of the final dose of study drug on Day 7 to ensure that the subject is present in the clinic 24 h after the dose.

If it becomes apparent at Visit 5 that a dose of abiraterone acetate was missed, this Visit becomes Visit 4A (see above) and Visit 5 is rescheduled.

The following procedures will be performed:

- Obtain vital signs, height, weight and temperature
- Physical examination

- Review adverse events, and concomitant medications
- Blood sample drawn between 0700 and 1000 (but 24h plus or minus 20 minutes after the final dose of study drug) to test: Serum 17-OHP, androstenedione, testosterone, dihydrotestosterone, plasma renin activity, ACTH, and a simultaneous sample for PK.
- Provide education for at home dosing of hydrocortisone and fludrocortisone.
- 12-lead ECG.
- Review diary
- Drug accountability

The subject will be instructed to resume his/her usual hydrocortisone dosing (as at entry into the study) as of the day of the screening visit. The subject will then take his/her morning hydrocortisone and fludrocortisone doses.

This clinic visit will take approximately 2 hours.

Up to 12 mL of blood will be drawn.

4.1.5. Visit 6, Day 21 (19-23 days): Clinic Visit; Monitoring of Washout

The subject will be instructed to come to Visit 6 having not yet taken his/her morning hydrocortisone and fludrocortisone medication. The subject will have a blood sample obtained between 0800 and 1000 for:

- CBC, Comprehensive Metabolic Panel, Serum 17-OHP, androstenedione, testosterone, LH, FSH, dihydrotestosterone, plasma renin activity and ACTH
- A urinalysis will be performed.

Adverse events and concomitant medications will be reviewed by study staff.

This clinic visit will take approximately 40 minutes. Alternatively, this visit may be conducted by prior arrangements made by the Sponsor at a local Quest lab.

Up to 16 mL of blood will be drawn.

4.1.6. Phone Visit 6, Day 42 (40-44 days); Final Study Visit

Interval medical history, including adverse events and concomitant medication will be reviewed with the subject. Laboratory values from Visit 6 will be reviewed by the site investigator and hydrocortisone and fludrocortisone doses adjusted as necessary (see section 11.1). This telephone call will take approximately 30 minutes. This is the final study visit. The subject will be encouraged to schedule a follow-up visit with his or her usual endocrinologist.

4.1.7. Discontinuation of Treatment in Phase 1

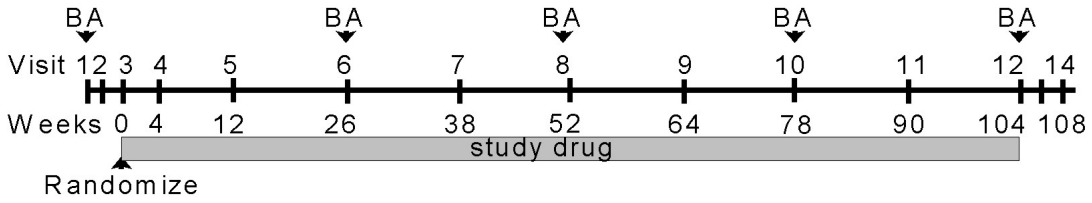
The Phase 1 study has only a 1 week treatment period making adverse events unlikely. A subject's study treatment should be discontinued if:

- Entry into treatment phase in error (not fulfilling the inclusion and/or exclusion criteria)
- Consent is withdrawn.
- The subject misses a dose of study medication in both the original treatment period and the optional retreatment period (see Section3.3.7.1).
- Non-compliance
- Lost to follow-up
- The investigator believes that for safety reasons (eg, adverse events) it is in the best interest of the subject to stop treatment. Safety concerns that may warrant discontinuation of abiraterone acetate include:
  - AST and/or ALT >3x of Study Day 1 levels in the absence of evidence of liver obstruction or other explanations for the increase in LFTs,
  - Serum bilirubin to >2x of Study Day 1 levels without any evidence of liver obstruction or glucuronidation capacity caused by Gilbert syndrome or some other explanation.
  - Total bilirubin ≥1.5 x ULN accompanied by any AST or ALT elevation.
  - Persistent nausea and vomiting not amenable to medical therapy and lasting more than 72 hours and not explainable by other causes than abiraterone acetate treatment.
- Administration of prohibited medications (see section 7)
- Signs of central puberty

Subjects who are withdrawn early should be scheduled for an Early Termination Visit that includes all of the study assessments listed in section 4.1.5. The subject should be instructed to resume the hydrocortisone dose used at study entry.

4.2. Phase 2, Randomized Double-Blind Study

Phase 2 consists of up to 30 study visits (including up to 15 clinic visits and up to 15 telephone calls) over up to 113 weeks (approximately 2 years). Because the screening period may vary in length, study days prior to the Treatment Period will be numbered negatively. See Table 2 (and figure below) for scheduled study activities.



4.2.1. Visit 1, Up to Day -30

4.2.1.1. Consent and Screening

Phase 1 subjects entering Phase 2 must be re-consented. Genetic (DNA) testing to confirm diagnosis will not be repeated for subjects who participated in Phase 1. All subjects must sign the informed

consent/assent (see Section 9) prior to the conduct of any study procedures. Each parent who is participating in DNA testing must also sign a separate informed consent.

The following screening procedures will be performed:

- Review inclusion and exclusion criteria
- Obtain vital signs, height, weight and temperature
- Physical Examination
- Medical history and demographics, including adverse events, history and concomitant medications
- Blood samples for DNA confirmation of diagnosis (including parents), if not already available
- Hematology (CBC, diff, platelets), serum electrolytes, kidney function tests (BUN, creatinine), liver function tests (AST, ALT, bilirubin), hormone levels (LH, FSH), serum 17-OHP, testosterone, dihydrotestosterone, androstenedione and plasma renin activity and ACTH.
- Urinalysis 12-lead ECG
- Cataract examination
- Skeletal age assessment (radiograph of left hand and wrist)
- Pelvic Ultrasound for girls
- Testicular Ultrasound for boys
- Subject will be registered in the central database after signing consent

Subjects must satisfy the inclusion and none of the exclusion criteria listed in Sections 0 and 7 respectively, prior to initiating the Treatment Phase.

This clinic visit will take approximately 3 hours.

Volume of blood draw: 9-12 mL (pending necessity of DNA confirmation of diagnosis).

4.2.1.2. Phone Visit 1; Lead-in Period

When screening laboratory test results are available and the subject has satisfied all inclusion criteria and no exclusion criteria, the subject will be instructed to reduce hydrocortisone dose to 8 ± 1 mg/m^2/d (see section 3.3.11) and continue his/her usual fludrocortisone dose. If the subject is taking an increased dose of hydrocortisone for the stress of an intercurrent illness (see Section 11.1.2) the dose reduction will be postponed until the illness has resolved and the subject has been afebrile for at least 24 hours. The subject will then be instructed to schedule lab work to be done for Visit 2.

Adverse events and concomitant medications will be reviewed by study staff.

4.2.2. Visit 2: Clinic/laboratory Visit

The subject will be instructed to come to Visit 2 having not yet taken his/her morning hydrocortisone and fludrocortisone medication. The patient will have a blood sample obtained for androstenedione level between 0800 and 1000.

This clinic visit will take approximately 40 minutes.

Up to 1 mL of blood will be drawn.

4.2.2.1. Phone Visit 2

The androstenedione level from Visit 2 will be reviewed to ensure that it is >1.5 times the upper limit of normal (ULN) for age, and the subject will be contacted by phone. If it is not, the subject will continue in the Lead-In Period and Optional Visit 2A will be scheduled for a repeat sample.

If the subject meets the androstenedione inclusion criterion, s/he will advance to the Treatment Period and Visit 3 will be scheduled.

Adverse events and concomitant medications will be reviewed by study staff.

4.2.2.2. Optional Visit 2A: Clinic/laboratory Visit

The subject will be instructed to come to Visit 2A having not yet taken his/her morning hydrocortisone and fludrocortisone medication. The patient will have a blood sample obtained for androstenedione level between 0800 and 1000.

This clinic visit will take approximately 40 minutes.

Up to 1 mL of blood will be drawn.

4.2.2.3. Optional Phone Visit 2A

The androstenedione level from Visit 2A will be reviewed to ensure that it is >1.5 times the upper limit of normal (ULN) for age, and the subject will be contacted by phone.

If the androstenedione level at Visit 2A remains $\leq$1.5 x ULN, the subject will be counted as a screen failure and will be replaced; all study procedures will cease, and the subject will be instructed to resume their usual hydrocortisone dosing.

If the subject meets the androstenedione inclusion criterion, s/he will advance to the Treatment Period and Visit 3 will be scheduled.

Adverse events and concomitant medications will be reviewed by study staff.

4.2.3. Visit 3, Day 0: Clinic Visit

4.2.3.1. Randomization

A 2-stage stratified randomization procedure will be applied with stratification factors of age group (2 to 5 year vs. 6 to 9 year) and study site. Within each stratum, subjects are then assigned to 1 of 2 treatment groups at a 2:1 allocation ratio (active drug to placebo) based on the randomization schedule. The randomization schedule will be balanced using randomly permuted blocks. All subjects must commence treatment within 3 calendar days of randomization.

The treatment to which a subject is assigned will be determined by consecutive envelopes provided to the research pharmacist at each study site by the sponsor-investigator's statistician. All other study personnel will be blinded to the subjects' treatment assignments.

4.2.3.2. Treatment Period

The subject will be instructed to come to Visit 3 fasting and having not yet taken his/her morning hydrocortisone and fludrocortisone medication. A baseline fasting blood sample will be drawn between 0800 and 1000.The following procedures will be performed:

- Review adverse events, exclusion criteria, interval medical history and concomitant medications
- Obtain vital signs, height, weight and temperature
- Fasting blood sample to test: hematology CBC, diff, platelets), serum electrolytes, kidney function tests (BUN, Creatinine), liver function tests (AST, ALT and bilirubin), lipid panel, insulin, hormone levels (LH, FSH), Serum 17-OHP, androstenedione, testosterone, dihydrotestosterone, plasma renin activity and ACTH, and baseline PK sample
- Dispense medications: study drug (abiraterone acetate or placebo), hydrocortisone and fludrocortisone and provide education for at home dosing. To ensure standardization, hydrocortisone and fludrocortisone will be provided to study pharmacies from a single source.
- Provide Subject Diary and instructions
- Subject will be given first dose of study drug in clinic and wait at least 30 minutes before eating a low fat (only) breakfast/snack if they choose
- PK blood sample 120 minutes after study drug dose
- Following PK blood sample at 120 minutes, daily dose of hydrocortisone and fludrocortisone will be given

Subjects will be furnished with Study Drug as well as hydrocortisone and fludrocortisone as part of the study. The drugs will be dispensed by the local study pharmacist and dosed as determined in Phase 1. Subjects will be instructed to take the Study Drug on an empty stomach (at least 2h since last meal) in the morning (see section 3.3.1). The first dose will be administered in the clinic as noted.

This clinic visit will take approximately 2.5-3 hours. Up to 13 mL of blood will be drawn (11 ml at first blood draw, 2 ml at second).

4.2.4. Phone Visit 3, Week 2

Interval medical history, including adverse events, will be reviewed with the subject. Laboratory values from Visit 3 (the previous clinic visit) will be reviewed by the site investigator and hydrocortisone and fludrocortisone doses adjusted as necessary (see section 11.1). This telephone call will take approximately 30 minutes.

4.2.5. Visit 4, Week 4: Clinic Visit

The subject will be instructed to come to Visit 4 fasting and having not yet taken his/her morning Study Drug, hydrocortisone or fludrocortisone medication. A baseline fasting blood sample will be drawn between 0800 and 1000.

The following procedures will be performed:

- Physical examination
- Obtain vital signs, height, weight and temperature
- Review adverse events exclusion criteria, interval medical history and concomitant medications
- Hematology (CBC, differential, platelets), serum electrolytes, kidney function tests (BUN,Creatinine), liver function tests (AST, ALT, bilirubin), hormone levels (LH, FSH), lipid panel, insulin, serum 17-OHP, androstenedione, testosterone, dihydrotestosterone and plasma renin activity and ACTH.
- Trough PK sample
- Dispense medications: study drug (abiraterone acetate or placebo), hydrocortisone and fludrocortisone and provide education for at home dosing
- Adjust study medication as needed depending on weight gain of subject.
- Provide Subject Diary and instructions
- Subject will be given dose of study drug in clinic and wait at least 30 minutes before eating a low fat (only) breakfast/snack if they choose
- PK blood sample and repeated serum 17-OHP, androstenedione and dihydrotestosterone 120 minutes after study drug dose
- Following PK blood sample at 120 minutes, daily dose of hydrocortisone and fludrocortisone will be given

Subjects will be furnished with Study Drug (see section 3.2) as well as hydrocortisone and fludrocortisone as part of the study. The drugs will be dispensed by the local study pharmacist and dosed as determined in Phase 1 (see section 3.3.2). Subjects will be instructed to take the Study Drug on an empty stomach in the morning (see section 3.3.1). The first dose will be administered in the clinic as noted.

This clinic visit will take approximately 2.5-3 hours.

Up to 16 mL of blood will be drawn (14 ml at first blood draw, 2 ml at second).

4.2.6. Phone Visit 4, Week 6-7

Interval medical history, including adverse events, will be reviewed with the subject. Laboratory values from Visit 4 will be reviewed by the site investigator and hydrocortisone and fludrocortisone doses adjusted as necessary (see section 11.1). This telephone call will take approximately 30 minutes.

4.2.7. Visit 5, Week 12: Clinic Visit

The subject will be instructed to come to Visit 5 fasting and having not yet taken his/her morning Study Drug, hydrocortisone and fludrocortisone medication. The 2-hour blood sample will be omitted. The subject will take the morning hydrocortisone, fludrocortisone and Study Drug doses after the blood sample is drawn between 0800 and 1000.

The following procedures will be performed:

- Physical examination
- Obtain vital signs, height, weight and temperature
- Review adverse events exclusion criteria, interval medical history and concomitant medications
- Hematology (CBC, diff, platelets), serum electrolytes, kidney function tests (BUN, Creatinine), liver function tests (AST, ALT, bilirubin), lipid panel, insulin, hormone levels (LH, FSH), serum 17-OHP, androstenedione, testosterone, dihydrotestosterone and plasma renin activity and ACTH.
- Trough PK sample
- Dispense medications: study drug (abiraterone acetate or placebo), hydrocortisone and fludrocortisone and provide education for at home dosing
- Adjust medication depending on weight gain of subject as needed (see Section3.3.5)
- Provide Subject Diary and instructions
- Study Drug and daily dose of hydrocortisone and fludrocortisone will be given after blood sample is drawn.

This clinic visit will take approximately 1.5 hours.

Up to 12 mL of blood will be drawn.

4.2.8. Phone Visit 5, Week 13-14

Interval medical history, including adverse events, will be reviewed with the subject. Laboratory values from Visit 5 will be reviewed by the site investigator and hydrocortisone and fludrocortisone doses adjusted as necessary (see section 11.1). This telephone call will take approximately 30 minutes.

4.2.9. Visit 6, Week 26: Clinic Visit

The subject will be instructed to come to Visit 6 fasting and having not yet taken his/her morning Study Drug, hydrocortisone or fludrocortisone medication. A baseline fasting blood sample will be drawn between 0800 and 1000.

The following procedures will be performed:

- Physical examination

- Obtain vital signs, height, weight and temperature
- Review adverse events exclusion criteria, interval medical history and concomitant medications
- Hematology (CBC, differential, platelets), serum electrolytes, kidney function tests (BUN, Creatinine), liver function tests (AST, ALT, bilirubin), lipid panel, insulin, hormone levels (LH, FSH), serum 17-OHP, androstenedione, testosterone, dihydrotestosterone and plasma renin activity and ACTH.
- Trough PK sample
- Dispense medications: study drug (abiraterone acetate or placebo), hydrocortisone and fludrocortisone and provide education for at home dosing
- Adjust medication depending on weight gain of subject as needed (see Section3.3.5)
- Provide Subject Diary and instructions
- Subject will be given first dose of study drug in clinic and wait at least 30 minutes before eating a low fat (only) breakfast/snack if they choose
- PK blood sample and repeated serum 17-OHP, androstenedione, and dihydrotestosterone 120 minutes after study drug dose
- Urinalysis
- Following PK blood sample at 120 minutes, daily dose of hydrocortisone and fludrocortisone will be given
- Skeletal age assessment (radiograph of left hand and wrist)

Subjects will be furnished with Study Drug (see section 3.2) as well as hydrocortisone and fludrocortisone as part of the study. The drugs will be dispensed by the local study pharmacist and dosed as determined in Phase 1 (see section 3.3.2). Subjects will be instructed to take the Study Drug on an empty stomach in the morning (see section 3.3.1). The first dose will be administered in the clinic as noted.

This clinic visit will take approximately 2.5-3 hours.

Up to 16 mL of blood will be drawn (14 ml at first blood draw, 2 ml at second).

4.2.10. Phone Visit 6, Week 27-28

Interval medical history, including adverse events, will be reviewed with the subject. Laboratory values from Visit 6 will be reviewed by the site investigator and hydrocortisone and fludrocortisone doses adjusted as necessary (see section 11.1). This telephone call will take approximately 30 minutes.

4.2.11. Visit 7, Week38: Clinic Visit

The subject will be instructed to come to Visit 7 fasting and having not yet taken his/her morning Study Drug, hydrocortisone and fludrocortisone medication. The 2 hour blood sample will be omitted. The subject will take the morning hydrocortisone, fludrocortisone and Study Drug doses after the blood sample is drawn between 0800 and 1000.

The following procedures will be performed:

- Physical exam by provider

- Obtain vital signs, height and weight
- Review adverse events exclusion criteria, interval medical history and concomitant medications
- Hematology (CBC, differential, platelets), serum electrolytes, kidney function tests (BUN, Creatinine), liver function tests (AST, ALT, bilirubin), lipid panel, insulin, hormone levels (LH, FSH), serum 17-OHP, androstenedione, testosterone and dihydrotestosterone, and plasma renin activity and ACTH
- PK blood sample prior to abiraterone acetate
- Adjust study medication depending on weight gain of subject (see Section3.3.5)
- Dispense medications: study drug (abiraterone acetate or placebo), hydrocortisone and fludrocortisone and provide education for at home dosing
- Provide Subject Diary and instructions
- Subject will be given dose of study drug in clinic and wait at least 30 minutes before eating a low fat (only) breakfast/snack if they choose
- PK blood sample and repeated serum 17-OHP, androstenedione and dihydrotestosterone 120 minutes after study drug dose

This clinic visit will take approximately 1.5 hours.

Up to 12 mL of blood will be drawn.

4.2.12. Phone Visit 7, Week 39-40

Interval medical history, including adverse events, will be reviewed with the subject. Laboratory values from Visit 7 will be reviewed by the site investigator and hydrocortisone and fludrocortisone doses adjusted as necessary (see section 11.1). This telephone call will take approximately 30 minutes.

4.2.13. Visit 8, Week 52: Clinic Visit

The subject will be instructed to come to Visit 8 fasting and having not yet taken his/her morning Study Drug, hydrocortisone or fludrocortisone medication. A baseline fasting blood sample will be drawn between 0800 and 1000.

The following procedures will be performed:

- Physical examination
- Obtain vital signs, height, weight and temperature
- Review adverse events exclusion criteria, interval medical history and concomitant medications
- Hematology (CBC, differential, platelets), serum electrolytes, kidney function tests (BUN, Creatinine), liver function tests (AST, ALT, bilirubin), lipid panel, insulin, hormone levels (LH, FSH), serum 17-OHP, androstenedione, testosterone, dihydrotestosterone and plasma renin activity and ACTH.
- Trough PK sample
- Dispense medications: study drug (abiraterone acetate or placebo), hydrocortisone and fludrocortisone and provide education for at home dosing

- Adjust medication depending on weight gain of subject as needed (see Section3.3.5)
- Provide Subject Diary and instructions
- Subject will be given dose of study drug in clinic and wait at least 30 minutes before eating a low fat (only) breakfast/snack if they choose
- PK blood sample and repeated serum 17-OHP, androstenedione and dihydrotestosterone 120 minutes after study drug dose
- Urinalysis
- Following blood sample at 120 minutes, daily dose of hydrocortisone and fludrocortisone will be given
- Cataract examination
- Skeletal age assessment (radiograph of left hand and wrist)
- Pelvic Ultrasound for girls
- Testicular Ultrasound for boys

Subjects will be furnished with Study Drug (see section 3.2) as well as hydrocortisone and fludrocortisone as part of the study. The drugs will be dispensed by the local study pharmacist and dosed as determined in Phase 1 (see section 3.3.2). Subjects will be instructed to take the Study Drug on an empty stomach in the morning (see section 3.3.1). The first dose will be administered in the clinic as noted.

This clinic visit will take approximately 2.5-3 hours.

Up to 16 mL of blood will be drawn (14 ml at first blood draw, 2 ml at second).

4.2.14. Phone Visit 8, Week 53-54

Interval medical history, including adverse events, will be reviewed with the subject. Laboratory values from Visit 8 will be reviewed by the site investigator and hydrocortisone and fludrocortisone doses adjusted as necessary (see section 11.1). This telephone call will take approximately 30 minutes.

4.2.15. Visit 9, Week 64: Clinic Visit

The subject will be instructed to come to Visit 9 fasting and having not yet taken his/her morning Study Drug, hydrocortisone and fludrocortisone medication.

A baseline fasting blood sample will be drawn between 0800 and 1000.

The following procedures will be performed:

- Physical exam by provider
- Obtain vital signs, height and weight
- Review adverse events exclusion criteria, interval medical history and concomitant medications
- Hematology (CBC, differential, platelets), serum electrolytes, kidney function tests (BUN, creatinine), liver function tests (AST, ALT, bilirubin), lipid panel, insulin, hormone levels (LH, FSH),

serum 17-OHP, androstenedione, testosterone, dihydrotestosterone, and plasma renin activity and ACTH

- Trough PK sample
- Adjust study medication depending on weight gain of subject (see Section3.3.5)
- Dispense medications: study drug (abiraterone acetate or placebo), hydrocortisone and fludrocortisone and provide education for at home dosing
- Provide Subject Diary and instructions
- Subject will be given dose of study drug in clinic and wait at least 30 minutes before eating a low fat (only) breakfast/snack if they choose
- PK blood sample and repeated serum 17-OHP, androstenedione and dihydrotestosterone 120 minutes after study drug dose

Following PK blood sample at 120 minutes, daily dose of hydrocortisone and fludrocortisone will be given.

This clinic visit will take approximately 2.5 hours.

Up to 16mL of blood will be drawn (14 ml at first blood draw, 2 ml at second).

4.2.16. Phone Visit 9, Week 65-66

Interval medical history, including adverse events, will be reviewed with the subject. Laboratory values from Visit 9 will be reviewed by the site investigator and hydrocortisone and fludrocortisone doses adjusted as necessary (see section 11.1). This telephone call will take approximately 30 minutes.

4.2.17. Visit 10, Week 78: Clinic Visit

The subject will be instructed to come to Visit 10 fasting and having not yet taken his/her morning Study Drug, hydrocortisone or fludrocortisone medication. A baseline fasting blood sample will be drawn between 0800 and 1000.

The following procedures will be performed:

- Physical examination
- Obtain vital signs, height, weight and temperature
- Review adverse events exclusion criteria, interval medical history and concomitant medications
- Hematology (CBC, differential, platelets), serum electrolytes, kidney function tests (BUN, Creatinine), liver function tests (AST, ALT, bilirubin), lipid panel, insulin, hormone levels (LH, FSH), serum 17-OHP, androstenedione, testosterone, dihydrotestosterone, and plasma renin activity and ACTH.
- Trough PK sample
- Dispense medications: study drug (abiraterone acetate or placebo), hydrocortisone and fludrocortisone and provide education for at home dosing
- Adjust medication depending on weight gain of subject as needed (see Section3.3.5)
- Provide Subject Diary and instructions

- Subject will be given dose of study drug in clinic and wait at least 30 minutes before eating a low fat (only) breakfast/snack if they choose
- PK blood sample and repeated serum 17-OHP, androstenedione and dihydrotestosterone 120 minutes after study drug dose
- Urinalysis
- Following PK blood sample at 120 minutes, daily dose of hydrocortisone and fludrocortisone will be given
- Skeletal age assessment (radiograph of left hand and wrist)

Subjects will be furnished with Study Drug (see section 3.2) as well as hydrocortisone and fludrocortisone as part of the study. The drugs will be dispensed by the local study pharmacist and dosed as determined in Phase 1 (see section 3.3.2). Subjects will be instructed to take the Study Drug on an empty stomach in the morning (see section 3.3.1). The first dose will be administered in the clinic as noted.

This clinic visit will take approximately 2.5-3 hours.

Up to 16 mL of blood will be drawn (14 ml at first blood draw, 2 ml at second).

4.2.18. Phone Visit 10, Week 77-78

Interval medical history, including adverse events, will be reviewed with the subject. Laboratory values from Visit 10 will be reviewed by the site investigator and hydrocortisone and fludrocortisone doses adjusted as necessary (see section 11.1). This telephone call will take approximately 30 minutes.

4.2.19. Visit 11, Week 90: Clinic Visit

The subject will be instructed to come to Visit 11 fasting and having not yet taken his/her morning Study Drug, hydrocortisone and fludrocortisone medication. A baseline fasting blood sample will be drawn between 0800 and 1000.

The following procedures will be performed:

- Physical exam by provider
- Obtain vital signs, height and weight
- Review adverse events exclusion criteria, interval medical history and concomitant medications
- Hematology (CBC, differential, platelets), serum electrolytes, kidney function tests (BUN, creatinine), liver function tests (AST,ALT, bilirubin), lipid panel, insulin, hormone levels (LH, FSH), serum 17-OHP, androstenedione, testosterone, dihydrotestosterone, and plasma renin activity and ACTH
- Trough PK sample
- Adjust study medication depending on weight gain of subject (see Section3.3.5)
- Dispense medications: study drug (abiraterone acetate or placebo), hydrocortisone and fludrocortisone and provide education for at home dosing
- Provide Subject Diary and instructions

- Subject will be given dose of study drug in clinic and wait at least 30 minutes before eating a low fat (only) breakfast/snack if they choose
- PK blood sample and repeated serum 17-OHP, androstenedione and dihydrotestosterone 120 minutes after study drug dose
- Following PK blood sample at 120 minutes, daily dose of hydrocortisone and fludrocortisone will be given

This clinic visit will take approximately 2.5-3 hours.

Up to 16 mL of blood will be drawn (14 ml at first blood draw, 2 ml at second).

4.2.20. Phone Visit 11, Week 91-92

Interval medical history, including adverse events, will be reviewed with the subject. Laboratory values from Visit 11 will be reviewed by the site investigator and hydrocortisone and fludrocortisone doses adjusted as necessary (see section 11.1). This telephone call will take approximately 30 minutes.

4.2.21. Visit 12, Week 104 Clinic Visit; End of Treatment Period

The subject will be instructed to come to Visit 12 fasting and having not yet taken his/her morning Study Drug, hydrocortisone or fludrocortisone medication. A baseline fasting blood sample will be drawn between 0800 and 1000.

The following procedures will be performed:

- Obtain vital signs, height, weight and temperature
- Physical Examination
- Review adverse events exclusion criteria, interval medical history and concomitant medications
- Hematology (CBC, differential, platelets), serum electrolytes, kidney function tests (BUN, creatinine), liver function tests (AST, ALT, bilirubin), lipid panel, insulin, hormone levels (LH, FSH), serum 17-OHP, androstenedione, testosterone, dihydrotestosterone, and plasma renin activity and ACTH.
- Trough PK sample
- Dispense medications: Final hydrocortisone and fludrocortisone and provide education for at home dosing
- Provide Subject Diary and instructions
- Subject will be given final dose of study drug in clinic and wait at least 30 minutes before eating a low fat (only) breakfast/snack if they choose
- PK blood sample and repeated serum 17-OHP, androstenedione and dihydrotestosterone 120 minutes after study drug dose
- Urinalysis
- Following PK blood sample at 120 minutes, daily dose of hydrocortisone and fludrocortisone will be given
- 12-Lead ECG will be performed immediately before the 120 minute PK blood sample.
- Skeletal age assessment (radiograph of left hand and wrist)

- Testicular ultrasound for boys
- Pelvic ultrasound for girls
- Cataract examination

The subject will be instructed to increase the hydrocortisone dose to the dose (per square meter of body surface area) that the subject was taking at Phase 2 study enrollment. The subject's current fludrocortisone dose will be continued. Subject will be transitioned back to standard of care and given new prescriptions with instructions for post study follow up care.

This clinic visit will take approximately 4 hours.
Up to 16 mL of blood will be drawn (14 ml at first blood draw, 2 ml at second).

4.2.22. Phone Visit 12, Week 105

Interval medical history, including adverse events, will be reviewed with the subject. Laboratory values from Visit 12 will be reviewed by the site investigator and hydrocortisone and fludrocortisone doses adjusted as necessary (see section 11.1). This telephone call will take approximately 30 minutes.

4.2.23. Visit 13, Week 106: Clinic/laboratory Visit; Monitoring of Washout

The subject will be instructed to come to Visit 13 having not yet taken his/her morning hydrocortisone and fludrocortisone medication. The patient will have a blood sample obtained for serum 17-OHP, androstenedione, dihydrotestosterone, and plasma renin and ACTH levels between 0800 and 1000.

This clinic visit will take approximately 40 min.

Up to 5 mL of blood will be drawn.

4.2.24. Phone Visit 13, Week 107

Interval medical history, including adverse events, will be reviewed with the subject. Laboratory values from Visit 13 will be reviewed by the site investigator and hydrocortisone and fludrocortisone doses adjusted as necessary (see section 11.1). This telephone call will take approximately 30 minutes.

4.2.25. Visit 14, Week 108: Clinic/Laboratory Visit; Monitoring of Washout

The subject will be instructed to come to Visit 14 having not yet taken his/her morning hydrocortisone and fludrocortisone medication. The patient will have a blood sample obtained for serum 17-OHP, androstenedione, ACTH, plasma renin activity, and dihydrotestosterone level between 0800 and 1000.

This clinic visit will take approximately 40 minutes.

Up to 5 mL of blood will be drawn.

4.2.26. Phone Visit 14, Week 109; Final Study Visit

Interval medical history, including adverse events, will be reviewed with the subject. Laboratory values from Visit 14 will be reviewed by the site investigator and hydrocortisone and fludrocortisone doses adjusted as necessary (see section 11.1). This telephone call will take approximately 30 minutes.

This is the final study visit.

TABLE 1: Phase 1 Multi-Center Study to Assess the Efficacy and Safety of Abiraterone Acetate as Adjunctive Therapy in

PHASE 1	Screening	Lead -In					Treatment					Follow Up	
Visit Number	1	PV1	2	PV2	2A [5]	PV2A	3	4	4A	PV 4A	V5	6 [5]	PV6
Time (days)	up to -30		up to -20		up to -10		1	2			8	21	42
Visit Type[2]	CLINIC	PHONE	LAB Only	PHONE	Optional LAB Only	Optional PHONE	CLINIC Fasting[5]	CLINIC Fasting[5]	Optional Clinic/lab visit	Optional	Clinic EOT	Monitor of Washout	PHONE Final visit
Informed Consent and Assent (ICF and IAF)	X												
Review of Inclusion/Exclusion criteria	X						X			X	X		
Medical history and demographics	X												X
Review adverse effects		X		X		X	X				X		X
Con Meds		X		X		X	X				X		X
Tanner staging	X												
Physical examination	X										X		
Height and weight	X						X				X		
Vital signs	X						X				X		
Cataract exam	X												
12-lead ECG	X										X		
Blood samples for DNA confirmation of diagnosis	X												
Complete blood count	X								X			X	
Comprehensive metabolic panel	X								X			X	
LH, FSH	X											X	
ACTH	X						X				X	X	
Serum 17-hydroxyprogesterone (17-OHP)	X						X	X			X	X	
Serum androstenedione	X		X		X		X	X			X	X	
Dihydrotestosterone	X						X	X			X	X	
Testosterone	X						X	X			X	X	
Plasma renin activity	X						X				X	X	
PK Blood Sampling							X	X			X		
Urinalysis	X											X	
Skeletal age assessment	X												
Dispense subject diary and instructions							X		X				
Dispense Study Drugs[6]							X		X				
Review Labs (Dose Adjustment of hydrocortisone)[7]		X		X		X				X			
Review Labs (Final off study Dose Adjustment)[7]													X
Blood volumes, ml	16-21		2		2		23	8	4		12	16	

1. Subjects will have an optional Visit 2A only if lab results from Visit 2 indicate that androstenedione level is not at least 1.5 times greater than the upp
Visit 2A indicate that androstendione levels are still less than 1.5 times ULN the subject will be withdrawn from the study. Optional visit 3A and phone
of abiraterone during the Treatment Period (see Section 3.3.7.1).

2. Clinic Visits 3-4 may be up to +2 days. Phone Visits (PV) are required between Clinic Visits and at the End of Study. PV should be completed when lab
Dose adjustment /confirmation for hydrocortisone and fludrocortisone should be completed at time of PV (See protocol section 11.1).

3. Results of previous testing may be used.

4. See Protocol Section 11.2.2 for management of abnormal liver function tests.

5. Blood samples to be drawn between 0800-1000 AM in a fasting state. Morning hydrocortisone and fludrocortisone dosing should be withheld until a

6. Study Drugs include: Abiraterone acetate or placebo, hydrocortisone, and fludrocortisone.
7. See Protocol Section 11.1.1 for dose adjustment parameters.

TABLE 2: Phase 2 Multi-Center Study to Assess the Efficacy and Safety of Abiraterone Acetate as Adjunctive Therapy in Pre-Pubescent Children with Classic 21-Hydroxylase Deficiency

PHASE 2	SCREENING	LEAD-IN					TREATMENT																			WASH OUT			FOLLOW UP	
Visit Number	**1**		**2A[1,6]**		**2[6]**		**3**		**4**		**5**		**6**		**7**		**8**		**9**		**10**		**11**		**12**		**13**		**14[6]**	**EOS**
Time in Weeks (Screening through randomization in Days)	up to -30		up to -20		up to -10		0		4		12		26		38		52		64		78		90		104		106		108	109
Visit Type[2] (PV=PHONE VISIT)	CLINIC	PV	LAB Only	PV	LAB Only	PV	CLINIC Fasting[6]	PV	CLINIC Fasting[6]	PV	CLINIC Fasting[6]	PV	CLINIC Fasting[6]	PV	CLINIC Fasting[6]	PV	CLINIC Fasting[6]	PV	CLINIC Fasting[6]	PV	CLINIC Fasting[6]	PV	CLINIC Fasting[6]	PV	CLINIC EOT Fasting[6]	PV	LAB Only	PV	LAB Only	PV
Informed Consent and Assent (ICF and IAF)	X																													
Review of Inclusion/Exclusion criteria	X						X																							
Medical history and demographics	X																													
Review adverse effects and medical history		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X
Randomization/IWRS							X																							
Physical examination/Tanner Stage[4]	X								X		X		X		X		X		X		X		X		X					
Height and weight	X						X		X		X		X		X		X		X		X		X		X					
Vital signs	X						X		X		X		X		X		X		X		X		X		X					
12-lead ECG	X																								X					
Blood samples for DNA confirmation of diagnosis[3]	X																													
Hematology (CBC, diff, platelets)	X						X		X		X		X		X		X		X		X		X		X					
Serum electrolytes	X						X		X		X		X		X		X		X		X		X		X					
Kidney function tests (BUN,Creatinine)	X						X		X		X		X		X		X		X		X		X		X					
Liver function tests (AST,ALT, bilitrubin)[5]	X						X		X		X		X		X		X		X		X		X		X					
Lipid panel							X		X		X		X		X		X		X		X		X		X					
Insulin							X		X		X		X		X		X		X		X		X		X					
LH, FSH	X						X		X		X		X		X		X		X		X		X		X					
ACTH	X						X		X		X		X		X		X		X		X		X		X		X		X	
Serum 17-hydroxyprogesterone (17-OHP)	X						X		X		X		X		X		X		X		X		X		X		X		X	
Serum androstenedione	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X	
Testosterone	X						X		X		X		X		X		X		X		X		X		X					
Dihydrotestosterone	X						X		X		X		X		X		X		X		X		X		X		X		X	
Plasma renin activity	X						X		X		X		X		X		X		X		X		X		X		X		X	
PK /PD Blood Sampling [7]							X		X		X		X		X		X		X		X		X							
Urinalysis (dipstick)	X												X				X				X				X					
Skeletal age assessment	X												X				X				X				X					
Dispense Study Drug, hydrocortisone and fludrocortisone							X		X		X		X		X		X		X		X		X		X					
Review Labs and adjust dose of hydrocortisone and fludrocortisone)[8]		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X
Review Labs (Final off study Dose Adjustment) [8]																														X
Cataract Examination	X																X								X					
Testicular Ultrasound for boys[4]	X																X								X					
Pelvic Ultrasound for girls[4]	X																X								X					
Blood volumes, ml	**12**		**1**		**1**		**13**		**16**		**12**		**16**		**12**		**16**		**16**		**16**		**16**		**16**		**5**		**5**	

1. Subjects will have an optional Visit 2A only if lab results from Visit 2 indicate that androstenedione level is not at least 1.5 times greater than the upper limit of normal (ULN). If lab results from visit 2A indicate that androstendione levels are still less than 1.5 times ULN the subject will be
2. Clinic Visits 3-14 may be up to +2 days. Phone Visits (PV) are required between Clinic Visits and at the End of Study . PV should be completed when lab results from previous Clinic Visit are available. Dose adjustment /confirmation for hydrocortisone and fludrocortisone should be
3. Results of previous testing may be used.
4. If signs of central precocious puberty present during the study, a gonadotropin releasing hormone agonist may be used for treatment (See Protocol Section 11.1.4).
5.See Protocol Section 11.2.2 for management of abnormal liver function tests.
6. Blood samples to be drawn between 0800-1000 AM in a fasting state. Morning hydrocortisone and fludrocortisone dosing should be withheld until after blood samples are collected.
7. PK/PD blood sampling requires 2 samples 120 minutes apart
8. See Protocol Section 11.1 for dose adjustment parameters.

4.3. Evaluations

4.3.1. Vital Signs

Oral, otic or temporal temperature (same method should be used throughout the study (degrees Celsius)), pulse, respiratory rate, and blood pressure (same method should be used throughout the study) will be measured as outlined in the Time and Events Schedules (Tables 1 and 2) and Sections 4.1 and 4.2. Blood pressure and heart rate measurements will be assessed while subject is sitting with a completely automated device, if available. When vital signs and blood draws are both required, the vital sign measurements will be obtained prior to the scheduled blood draw visit.

4.3.2. Height and weight

Subject height will be measured with a properly calibrated stadiometer. Heights will be measured three times in immediate succession (with subjects instructed to bend and stretch between measurements) and the average used. Weight will be measured in kilograms and with the subject lightly clothed and without shoes.

4.3.3. Physical Examination

Physical examinations, including general appearance, head, eyes, ears, nose and throat (HEENT), chest, cardiac, abdomen, extremities and neurologic and lymph node examinations, and Tanner staging and testicular volume will be conducted at the times specified in the Time and Events Schedules (Tables 1 and 2) and Sections 4.1 and 4.2. Any clinically significant abnormality in physical findings noted during the study should be reported as an adverse event. Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

4.3.4. Clinical Laboratory Tests

Blood samples for serum chemistry and hematology and a random urine sample for urinalysis will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The following tests will be performed by the reference laboratory (Quest):

- Complete Blood Count(includes Differential and Platelets)

White blood cell (WBC)	Red blood cell (RBC)
Hemoglobin	-Hematocrit
MCV	Platelet count
MCH	MCHC
RDW	MPV and Differential (Absolute and Percent - Neutrophils, Lymphocytes, Monocytes, Eosinophils, and Basophils)

*If abnormal cells are noted on a manual review of the peripheral blood smear or if the automated differential information meets specific criteria, a full manual differential will be performed.

- Comprehensive Metabolic panel

Sodium	Calcium
Potassium	Albumin
Alkaline Phosphatase	Albumin/Globulin Ratio (calculated)
Chloride	TProtein, total
Blood urea nitrogen (BUN)	BUN/Creatinine Ratio (calculated)
Creatinine with GFR Estimated	Carbon Dioxide
Glucose	Globulin (calculated)
-	Total Protein,
ALT	AST
Bilirubin, total	

- Urinalysis, Complete

Appearance	pH
Occult blood	Color
Specific gravity	Protein
Ketones	Glucose
Reducing substances	Bilirubin
Leukocyte esterase	Nitrite
WBC	RBC
Squamous Epithelial cells	Transitional epithelial cells
Renal epithelial cells	Amorphous sediment
Yeast	Microscopic observation
Bacteria	Crystals
Calcium oxalate crystals	Triple phosphate crystals
Uric acid crystals	Hyaline casts
Granular cast	Casts
Comments	Bilirubin ictotest

- Other tests:

Serum Androstenedione	D**ihydro**testosterone
Serum 17-hydroxyprogesterone (17-OHP)	Plasma renin activity
LH	-Banking of frozen serum for subsequent
FSH	determination of abiraterone levels. All banked samples will be destroyed at study conclusion.
ACTH, plasma	Testosterone, total
CAH (21- Hydroxylase Deficiency) Common Mutations	

4.3.5. Skeletal (bone) age

The skeletal age will be assessed by radiograph of the left hand and wrist before initiation of study treatment, and will be done according to the Time and Events Schedule during the study. An existing radiograph obtained within 3 months may be used if clinical read as <9 years (girls) or <10 years (boys). All images must be submitted as anonymized DICOM files either on CD or by secure file transfer. Images will be read by BoneXpert, an automated computer-based bone age analysis program that has been validated on children with precocious puberty and CAH (30;31). Any radiographs that cannot be read by BoneXpert will be evaluated by a blinded group of three readers, with the median value being used.

Note that these automated and blinded readings are for purposes of study outcome. The care team is free to read them independently and communicate them to the family.

4.3.6. ECG Evaluations

ECGs (12-lead) will be recorded until 4 regular consecutive complexes are available. Computer-generated interpretations of ECGs should be reviewed for data integrity and reasonableness by the investigator. Further evaluation of ECG abnormalities will be at the clinical judgment of the investigator but should generally include referral to a pediatric cardiologist.

NOTE: When blood sampling or vital sign measurement is scheduled for the same visit as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood sampling.

4.4.7 Cataract Examinations

Cataract examination using slit lamp will be done by a qualified ophthalmologist or optometrist and will be conducted at the times specified in the Time and Events Schedule. It is not necessary that this be a dilated exam.

4.4. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF and laboratory requisition form. Refer to the Time and Events Schedule for the timing and frequency of all sample collections. Instructions are as follows:

4.4.1. PK sampling will be collected at:

- Visit 3: Pre-abiraterone dosing
- Visit 3: 60 minutes post dosing
- Visit 3: 120 minute post dosing
- Visit 3: 240 minute post dosing
- Visit 4: Pre-abiraterone dosing
- Visit 5: Pre-abiraterone dosing

4.4.2. Collect: 1mL of blood in the plain red top tube. Immediately after collection, invert the tube 8-10 times. Label the tube with Patient number, visit number, date of collection and time of collection. Be sure to record the sample in the PK log found in the regulatory binder.

4.4.3. Processing: Allow sample to clot at room temperature (~45-60 minutes). Centrifuge blood sample at room temperature or in a refrigerated centrifuge set at 4°C to separate the serum (e.g., <1300 rcf for 10-15 minutes.).

4.4.4. Divide serum between the two cryovials supplied with kit. Be sure the cryovials are labeled with the patient number, visit number, date of collection and time of collection. Place one of the vials in the "A" (primary) storage cryobox and the other cryovial into the "B" (backup) storage cryobox.

4.4.5. Store Samples in a -80°C freezer until shipment.

4.5. End of Study

4.5.1. Completion

A subject will be considered to have completed the Phase 1 portion of the study after Phone Visit 6. A subject enrolled in the Phase 2 double-blind portion of the study is considered to have completed the Phase 2 study after Phone Visit 14 (108-109 weeks).

4.5.2. Unblinding

Under normal circumstances, the blind should not be broken until all subjects have completed the week 109 study procedures and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject (e.g., accidental overdose) or if medical necessity is determined by the investigator. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the study pharmacist. In the event the blind is broken, the principal investigator and DSMB must be informed as soon as possible. The date, time, and reason for the unblinding must be documented in the appropriate section of the case report form (CRF), and in the source document. The documentation indicating the code break must be retained with the subject's source documents in a secure manner.

Subjects who have had their treatment assignment unblinded should continue receiving the assigned treatment and return for scheduled evaluations.

It is recognized that the clinical team caring for each patient may be able to infer treatment group assignment based on clinical data available to them including hydrocortisone dose, serum 17-hydroxyprogesterone and androstenedione levels, and the relationship between these levels and levels of ACTH. The clinical team will be encouraged to not share such suppositions with the subject, but

subjects where this has occurred should continue receiving the assigned treatment and return for scheduled evaluations.

4.5.3. Discontinuation of Treatment

If a subject's study treatment must be discontinued before the end of the treatment regimen, this will not result in automatic withdrawal of the subject from the study.

A subject's study treatment should be discontinued if:

- The investigator believes that for safety reasons (eg, adverse events) it is in the best interest of the subject to stop treatment. Safety concerns that may warrant discontinuation of abiraterone acetate include (also see Section 11.2.2):
  - AST and/or ALT >3x of Study Day 1 levels in the absence of evidence of liver obstruction or other explanations for the increase in LFTs,
  - Serum bilirubin to >2x ULN of Study Day 1 levels without any evidence of liver obstruction or glucuronidation capacity caused by Gilbert syndrome or some other explanation.
  - Total bilirubin ≥1.5 x ULN accompanied by any AST or ALT elevation
  - Persistent nausea and vomiting not amenable to medical therapy and lasting more than 72 hours and not explainable by other causes than abiraterone acetate treatment.
  - Development of cataracts during the study
- Administration of prohibited medications (see section 7)
- Dosing noncompliance
- Onset of central puberty during Phase 1.

If a subject discontinues study treatment before the end of the double-blind phase, end-of-treatment assessments (see Sections 4.2.23, 4.2.24, 4.2.25 and 4.2.26) will be obtained. If study treatment is discontinued owing to abnormal liver function, the subject should be monitored until the laboratory abnormalities resolve (see Section 11.2.2). To permit a complete intention-to-treat analysis, follow-up scheduled radiographic bone age assessments should be continued.

4.5.4. Withdrawal from the Study

- A subject will be withdrawn from the study for any of the following reasons: Non-compliance
- Lost to follow-up
- Withdrawal of consent to continue collection of data
- Randomized in error (not fulfilling the inclusion and/or exclusion criteria)

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study an End of Termination Visit should be completed and the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects in Phase 1 who withdraw due to non-compliance may be replaced (see Section 3.3.7). Subjects in Phase 2 who withdraw due to non-compliance will not be replaced.

4.5.5. Transition of Care

At the completion of study treatment, or upon early withdrawal, each subject will be instructed to increase the hydrocortisone dose to the dose (per square meter of body surface area) that the subject was taking at study enrollment. The subject's current fludrocortisone dose will be continued. The subject will be transitioned back to standard of care and given new prescriptions with instructions for post study follow up care.

4.6. Subjects' Financial Responsibility

Subjects will receive all evaluations gratis during the course of the study and (in Phase 2 only) standard of care medications including hydrocortisone and fludrocortisone. If a subject develops precocious central puberty requiring treatment with a gonadotropin-releasing hormone agonist during the study (see section 11.1.4), this will be billed to the patient's insurance. All other medical and dental care is the responsibility of the subject.

5. SUB-STUDY PROCEDURES

Participation in the following substudies is mandatory.

5.1. Pharmacokinetics Evaluations

Phase 1 Dose-Finding: Blood samples will be collected for the determination of abiraterone plasma concentrations predose and 1, 2 and 4 hours postdose on Study Day 1 (Visit 3), predose on Study Day 2 (Visit 4; this is 24 hours postdose from Visit 3), and 24 hours post dose on Study Day 8 (Visit 5). Phase 2 Double-Blind: Blood samples will be collected for the determination of abiraterone plasma concentrations predose and 2 hours postdose on Study Week 4 (Visit 4) and Weeks 52 (Visit 14) and 104 (Visit 22).

5.1.1. Analytical Procedures

The concentrations of abiraterone in plasma will be determined using a validated liquid chromatography-mass spectrometry/mass spectrometry method by the laboratory of Dr Richard Auchus at the University of Michigan. If required, some plasma samples may be analyzed to document the presence of circulating metabolites using a qualified research method (32). Samples will be stored at -80 C at each study site prior to shipment to the University of Michigan.

5.1.2. Pharmacokinetic Parameters

Pharmacokinetic analysis will be restricted to determination of peak and trough drug levels.

5.1.3. Pharmacodynamic Evaluations

Blood samples for determination of androstenedione, dihydrotestosterone and 17-OHP will be collected simultaneously with every sample for abiraterone determination. The exact dates and times of blood sample collection will be recorded. Further information regarding handling and shipment of blood samples will be provided in the laboratory manual.

5.1.4. Pharmacokinetic/Pharmacodynamic Evaluations

The relationship between abiraterone plasma and serum hormone concentrations at all administered doses will be explored using different PK/PD models. Data will be analyzed using non-linear mixed effect models.

5.2. DNA Testing

Blood samples for genotyping will be collected from all subjects who have not already had genetic testing documented. Subjects will be genotyped at Quest Laboratories for CYP21A2 to confirm the diagnosis of classic 21-hydroxylase deficiency. One or both parents will also be genotyped (when permitted by local regulations) to allow setting of phase on the subject's mutations (i.e., determine which mutations are associated with each parental allele); this is necessary because many mutant alleles carry more than one mutation. If no parent is available, the subject will be genotyped and the results reviewed by the Principal Investigator. Subjects with an equivocal clinical history for classic disease (e.g., a male with no history of electrolyte abnormalities and a previously documented maximum 17-OHP level <10,000 ng/dl) and uninterpretable genotypes owing to absent parental data will not be allowed to enter the study. Samples will be discarded once the study is complete.

6. CRITERIA FOR INCLUSION OF SUBJECTS:

Each subject must satisfy all of the following criteria to advance to the Treatment Phase of the study.

1. Pre-pubescent girls (age 2 years [12 kg minimum] to 8 years inclusive (i.e.,prior to the 9th birthday); skeletal age <11 years (Phase 1) or <10 years (Phase 2) or boys (age 2 years [12 kg] to 9 years inclusive; skeletal age <12 years (Phase 1) or <11 years(Phase 2)). The broader bone age criterion in Phase 1 is to assist with recruitment.

2. Confirmed classic 21-hydroxylase deficiency evident by genotype groups A, A1 or B (see section 2.1.2) or clinical course (e.g., adrenal crisis with documented hyperkalemia and hyponatremia, at diagnosis or during a later evaluation; ambiguous genitalia in females). Documentation of one or both parents' genotypes may be required to confirm the subject's genotype.

3. Requirement for standard of care fludrocortisone (any dose) and ≥10 mg/m^2/day of hydrocortisone for at least 1 month prior to the study consent.

4. Morning serum androstenedione concentrations >1.5 x ULN after 7 days of dosing with doses of hydrocortisone required for physiologic replacement.

5. Both parents must sign the informed consent form unless one parent is deceased, unknown, incompetent, or not reasonably available or when only one parent has legal responsibility for the care and custody of the child. Children who are capable of providing assent (typically 10 years of age and older) must sign an assent form before the performance of any study procedures

7. CRITERIA FOR EXCLUSION OF SUBJECTS:

To advance to the Treatment Phase of the study a subject must not meet any of the following criteria.

1. Evidence of central puberty: Tanner Stage $\geq$2 for breast development in girls or testicular volume $\geq$4 mL in boys, or random LH $\geq$0.3 mIU/mL. Subjects with pubic and/or axillary hair as the only sign of puberty onset will be allowed.

2. Current or history of hepatitis from any etiology, including history of active viral hepatitis A, B, or C.

3. Patients with baseline hepatic impairment are excluded from this trial. To be eligible for this protocol, patients must meet all of the following criteria:

- AST, ALT and Total bilirubin $\leq$ ULN
- Albumin > LLN
- No evidence of ascites
- No evidence of encephalopathy

4. Abnormalities of liver function developing during the study are discussed in Section 11.2.2.

5. Abnormal renal function tests, defined as BUN or creatinine >1.5 ULN for age.

6. Significant anemia (hemoglobin < 12 g/dl). If documented to be due to iron deficiency, subjects may be rescreened 3 months after this has been treated.

7. Clinically significant abnormality in the 12-lead electrocardiogram (ECG)

8. A history of a malabsorption syndrome.

9. Evidence of active malignancy.

10. Serious or uncontrolled co-existent disease, including active or uncontrolled infection. Subjects may be rescreened after resolution of any such condition.

11. Concurrent medical condition or disease other than 21-hydroxylase deficiency that may interfere with linear growth or that requires concomitant therapy that is likely to interfere with study procedures or results.

12. Asthma or other condition requiring treatment with systemic corticosteroids within the past 3 months. Asthma treatment with inhaled corticosteroids is permitted.

13. Treatment with potentially hepatotoxic medications (statins); strong inhibitors of CYP3A4 (ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole), or CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital). CYP2C8 substrates (rosiglitazone, pioglitazone, rapaglinide) and CYP2D6 substrates (dextromethorphan, thioridazine) should be avoided,

14. Treatment with medications to affect puberty or synthesis of sex steroids, including gonadotropin releasing hormone agonists, aromatase inhibitors, or androgen receptor blockers (e.g., flutamide, spironolactone). However, a gonadotropin releasing hormone agonist may be started during the study for treatment-emergent central puberty without disqualifying the subject (see section 11.1.4).

15. Treatment with growth hormone at enrollment or during the course of the study.

16. Known allergies, hypersensitivity, or intolerance to abiraterone acetate or its excipients (refer to United States Prescribing Information).

17. Has received an investigational drug within 4 weeks of the planned first dose of study drug or is currently enrolled in an investigational interventional study.

18. Any condition that, in the opinion of the investigator, would make participation not be in the best interest (eg, compromise the well-being) of the subject or that could prevent, limit, or confound the protocol-specified assessments.

19. Presence or history of cataracts.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results) during screening, but prior to the first dose of study drug such that they now meet an exclusion criterion, they should be excluded from participation in the study.

8. SOURCES OF RESEARCH MATERIAL

Existing medical records will be used for screening purposes, including:

8.1. History

- Age
- Neonatal course, including evidence of salt-wasting such as weight loss, hypotension, hyponatremia and hyperkalemia
- Hospitalizations, particularly for vomiting, dehydration, hypotension, and other signs of adrenal crisis
- Surgeries, including (in females) feminizing genitoplasty
- Growth records for both height and weight
- Past and present doses of hydrocortisone, fludrocortisone and sodium chloride
- Past or present use of medications to affect puberty or synthesis of sex steroids, including gonadotropin releasing hormone agonists, aromatase inhibitors, or androgen receptor blockers
- Past or present use of growth hormone

8.2. Physical examination

- Vital signs, particularly blood pressure
- Height and weight

- Presence of clitoromegaly or labial fusion in girls
- Tanner stage: Signs of puberty including presence of adult body odor, axillary or pubic hair, penile or testicular enlargement (boys) or breast development (either sex).

8.3. Laboratory data

- Comprehensive Metabolic panel, CBC, urinalysis
- Steroid levels including 17-hydroxyprogesterone, androstenedione, testosterone, and dihydrotestosterone
- FSH and LH
- Plasma renin activity or direct renin levels and ACTH
- Pharmacokinetics for abiraterone acetate
- Bone age data from skeletal radiographs
- Genotyping, if available

New clinical data will be obtained in this study. Please refer to section 4.3 for a list of these data.

9. RECRUITMENT METHODS AND CONSENTING PROCESS

Subjects may be patients of the investigators, of the investigators' colleagues within each participating institution, patients referred by other physicians, or self-referred. Records at each site will be screened by local study personnel under a HIPAA Waiver to identify potentially eligible subjects. Consistent with local IRB requirements, each potentially eligible patient family will be informed of the study by their physician at a regularly scheduled visit and asked for permission to have study personnel meet with them after the visit to explain the study. Other recruitment materials including posters, brochures, web pages and letters to physicians may be used but must be approved by both the sponsor and by the reviewing IRB.

All subjects in this study are children (minors) who can be enrolled only after obtaining consent of a legally acceptable representative. Each legally acceptable representative must give written consent according to local requirements after the nature of the study has been fully explained. The consent form and assent form must be signed before performance of any study-related activity. The consent and assent forms that are used must be approved by both the sponsor and by the reviewing IRB and be in a language that the subject can read and understand. The informed consent and assent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the investigational staff must explain to potential subjects or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. A certified interpreter must be used for any language in which the person obtaining

consent and the legally acceptable representative are not mutually fluent. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive. Subjects will be told of alternative treatments available if they decline to take part and that such refusal will not prejudice future treatment.

Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor staff without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF (and, if required by the local IRB, a HIPAA consent) the subject or legally acceptable representative is authorizing such access, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed.

The subject's legal guardian or parent representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's or his or her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject/legal guardian or parent.

If the subject or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject or legally acceptable representative is obtained.

Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 10 years of age and older, depending on the institutional policies. Written assent should be obtained from subjects meeting the local minimum age requirement for assent who are able to write.

10. POTENTIAL RISKS

10.1. Study drug (abiraterone acetate) (33-35).

The efficacy and safety of abiraterone acetate (1,000 mg daily tablet dose) and prednisone therapy in adult humans has been studied in men with metastatic, castration-resistant prostate cancer (mCRPC) as detailed below. However, it should be noted that toxicities associated with mineralocorticoid excess (ie, hypertension, fluid retention/edema, cardiac failure and hypokalemia) are not expected in patients with classic 21-hydroxylase deficiency because of such patients cannot synthesize deoxycorticosterone, which is a 21-hydroxylated steroid, or any other mineralocorticoid.

10.1.1. Warnings and precautions

10.1.1.1. Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess

Abiraterone acetate may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. In the two randomized clinical trials grade 3 to 4 hypertension occurred in 2% of patients, grade 3 to 4 hypokalemia in 4% of patients, and grade 3 to 4 edema in 1% of patients treated with abiraterone acetate. Co-administration of a corticosteroid suppresses ACTH drive, resulting in a reduction in the incidence and severity of these adverse reactions. Use caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. These mechanism-based toxicities are not expected to occur in patients with 21-hydroxylase deficiency, who cannot synthesize mineralocorticoids. Also see section 11.2.1.

10.1.1.2. Adrenocortical Insufficiency

Adrenal insufficiency occurred in the two randomized clinical studies in 0.5% of patients taking abiraterone acetate and in 0.2% of patients taking placebo. Adrenocortical insufficiency was reported in patients receiving abiraterone acetate in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. All subjects in the present study have congenital adrenal hyperplasia and thus already have adrenal insufficiency. Adjustments to hydrocortisone dosing during this trial are discussed in sections 11.1.1 and 11.1.2.

10.1.1.3. Hepatotoxicity

In the two randomized clinical trials, grade 3 or 4 ALT or AST increases (at least 5X ULN) were reported in 4% of patients who received abiraterone acetate, typically during the first 3 months after starting treatment. Patients whose baseline ALT or AST were elevated were more likely to experience liver test elevation than those beginning with normal values. Treatment discontinuation due to liver enzyme increases occurred in 1% of patients taking abiraterone acetate. No deaths clearly related to abiraterone acetate were reported due to hepatotoxicity events. We will measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with abiraterone acetate and periodically thereafter (see section 4 and Tables of Assessments). Subjects with baseline hepatic impairment will be excluded from the study (see section 7). We will promptly measure serum total bilirubin, AST, and ALT if clinical

symptoms or signs suggestive of hepatotoxicity develop (see section 11.2.2 for discussion of management of abnormal liver function tests).

10.1.2. Adverse reactions

10.1.2.1. Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. Two randomized placebo-controlled multicenter clinical trials enrolled patients who had metastatic castration-resistant prostate cancer who were using a gonadotropin-releasing hormone (GnRH) agonist or were previously treated with orchiectomy. In both Study 1 and Study 2 abiraterone acetate was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arms. Placebo plus prednisone 5 mg twice daily was given to control patients. The most common adverse drug reactions {≥10%) reported in the two randomized clinical trials that occurred more commonly (>2%) in the abiraterone acetate arm were fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion. The most common laboratory abnormalities (>20%) reported in the two randomized clinical trials that occurred more commonly (≥2%) in the abiraterone acetate arm were anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST,

Table 1: Adverse Reactions due to ZYTIGA in Study 1

System/Organ Class Adverse reaction	ZYTIGA with Prednisone (N=791) All Grades[1] %	 Grade 3-4 %	Placebo with Prednisone (N=394) All Grades %	 Grade 3-4 %
Musculoskeletal and connective tissue disorders				
Joint swelling/discomfort[2]	29.5	4.2	23.4	4.1
Muscle discomfort[3]	26.2	3.0	23.1	2.3
General disorders				
Edema[4]	26.7	1.9	18.3	0.8
Vascular disorders				
Hot flush	19.0	0.3	16.8	0.3
Hypertension	8.5	1.3	6.9	0.3
Gastrointestinal disorders				
Diarrhea	17.6	0.6	13.5	1.3
Dyspepsia	6.1	0	3.3	0
Infections and infestations				
Urinary tract infection	11.5	2.1	7.1	0.5
Upper respiratory tract infection	5.4	0	2.5	0
Respiratory, thoracic and mediastinal disorders				
Cough	10.6	0	7.6	0
Renal and urinary disorders				
Urinary frequency	7.2	0.3	5.1	0.3
Nocturia	6.2	0	4.1	0
Injury, poisoning and procedural complications				
Fractures[5]	5.9	1.4	2.3	0
Cardiac disorders				
Arrhythmia[6]	7.2	1.1	4.6	1.0
Chest pain or chest discomfort[7]	3.8	0.5	2.8	0
Cardiac failure[8]	2.3	1.9	1.0	0.3

[1] Adverse events graded according to CTCAE version 3.0
[2] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness
[3] Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness
[4] Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema
[5] Includes all fractures with the exception of pathological fracture
[6] Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia
[7] Includes terms Angina pectoris, Chest pain, and Angina unstable. Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the ZYTIGA arm (1.3% vs. 1.1% respectively).
[8] Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased

hypophosphatemia, elevated ALT and hypokalemia.

Table 3: Adverse Reactions in ≥5% of Patients on the ZYTIGA Arm in Study 2

System/Organ Class Adverse reaction	ZYTIGA with Prednisone (N=542) All Grades[1] %	 Grade 3-4 %	Placebo with Prednisone (N=540) All Grades %	 Grade 3-4 %
General disorders				
Hypertension	21.6	3.9	13.1	3.0
Respiratory, thoracic and mediastinal disorders				
Cough	17.3	0.0	13.5	0.2
Dyspnea	11.8	2.4	9.6	0.9
Psychiatric disorders				
Insomnia	13.5	0.2	11.3	0.0
Injury, poisoning and procedural complications				
Contusion	13.3	0.0	9.1	0.0
Falls	5.9	0.0	3.3	0.0
Infections and infestations				
Upper respiratory tract infection	12.7	0.0	8.0	0.0
Nasopharyngitis	10.7	0.0	8.1	0.0
Renal and urinary disorders				
Hematuria	10.3	1.3	5.6	0.6
Skin and subcutaneous tissue disorders				
Rash	8.1	0.0	3.7	0.0

[1] Adverse events graded according to CTCAE version 3.0
[2] Includes terms Edema peripheral, Pitting edema, and Generalized edema
[3] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness

Table 2: Laboratory Abnormalities of Interest in Study 1

Laboratory Abnormality	Abiraterone (N=791) All Grades (%)	 Grade 3-4 (%)	Placebo (N=394) All Grades (%)	 Grade 3-4 (%)
Hypertriglyceridemia	62.5	0.4	53.0	0
High AST	30.6	2.1	36.3	1.5
Hypokalemia	28.3	5.3	19.8	1.0
Hypophosphatemia	23.8	7.2	15.7	5.8
High ALT	11.1	1.4	10.4	0.8
High Total Bilirubin	6.6	0.1	4.6	0

Table 4: Laboratory Abnormalities in >15% of Patients in the ZYTIGA Arm of Study 2

Laboratory Abnormality	Abiraterone (N=542) Grade 1-4 %	 Grade 3-4 %	Placebo (N=540) Grade 1-4 %	 Grade 3-4 %
Hematology				
Lymphopenia	38.2	8.7	31.7	7.4
Chemistry				
Hyperglycemia[1]	56.6	6.5	50.9	5.2
High ALT	41.9	6.1	29.1	0.7
High AST	37.3	3.1	28.7	1.1
Hypernatremia	32.8	0.4	25.0	0.2
Hypokalemia	17.2	2.8	10.2	1.7

[1]Based on non-fasting blood draws

Study 1: Metastatic CRPC Following Chemotherapy. Study 1 enrolled 1195 patients with metastatic CRPC who had received prior docetaxel chemotherapy. Patients were not eligible if AST and/or ALT ≥2.5 X ULN in the absence of liver metastases. Patients with liver metastases were excluded if AST and/or ALT >5X ULN. Table 1 shows adverse reactions on the abiraterone acetate arm in Study 1 that occurred with a ≥2% absolute increase in frequency compared to placebo or were events of special interest. The median duration of treatment with abiraterone acetate was 8 months. Table 2 shows laboratory abnormalities of interest from Study 1. Grade 3-4 low serum phosphorus (7%) and low potassium (5%) occurred at a greater than or equal to 5% rate in the abiraterone acetate arm.

Study 2: Metastatic CRPC Prior to Chemotherapy. Study 2 enrolled 1088 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy. Patients were ineligible if AST and/or ALT ≥2.5X ULN and patients were excluded if they had liver metastases. Table 3 shows adverse reactions on the abiraterone acetate arm in Study 2 that occurred with a ≥2% absolute increase in frequency compared to placebo. The median duration of treatment with abiraterone acetate was 13.8 months. Table 4 shows laboratory abnormalities that occurred in greater than 15% of patients, and more frequently (>5%) in the abiraterone acetate arm compared to placebo in

Study 2. Grade 3-4 lymphopenia (9%), hyperglycemia (7%) and high alanine aminotransferase (6%) occurred at a greater than 5% rate in the abiraterone acetate arm.

Cardiovascular Adverse Reactions: In the combined data for studies 1 and 2, cardiac failure occurred more commonly in patients treated with abiraterone compared to patients on the placebo arm (2.1% versus 0.7%). Grade 3-4 cardiac failure occurred in 1.6% of patients taking abiraterone and led to 5 treatment discontinuations and 2 deaths. Grade 3·4 cardiac failure occurred in 0.2% of patients taking placebo. There were no treatment discontinuations and one death due to cardiac failure in the placebo group. In Study 1 and 2, the majority of arrhythmias were grade 1 or 2. There was one death associated with arrhythmia and one patient with sudden death in the abiraterone acetate arms and no deaths in the placebo arms. There were 7 (0.5%) deaths due to cardiorespiratory arrest in the abiraterone acetate arms and 3 (0.3%) deaths in the placebo arms. Myocardial ischemia or myocardial infarction led to death in 3 patients in the placebo arms and 2 deaths in the abiraterone acetate arms. As noted in sections 10.1.1.1 and 11.2.1, mechanism-based cardiovascular toxicity is not expected in the present study.

10.1.3. Post Marketing Experience

The following additional adverse reactions have been identified during post approval use of abiraterone acetate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Respiratory, Thoracic and Mediastinal Disorders: non-infectious pneumonitis. Musculoskeletal and Connective Tissue Disorders: myopathy, including rhabdomyolysis. These adverse effects are presumably mediated by severe hypokalemia which, as discussed in section 11.2.1, should not be encountered in the present study.

10.2. Drug Interactions

10.2.1. Drugs that Inhibit or Induce CYP3A4 Enzymes

Based on in vitro data, abiraterone acetate is a substrate of CYP3A4. In a dedicated drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Strong CYP3A4 inducers represent an exclusion criterion and should be not used during this study. In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

10.2.2. Effects of Abiraterone on Drug Metabolizing Enzymes

ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. In a CYP2D6 drug-drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate

1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug. In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given together with a single dose of 1,000 mg abiraterone acetate. Therefore, patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with abiraterone.

10.3. Increased Abiraterone exposure with food

Abiraterone acetate must be taken on an empty stomach. Abiraterone C_{max} and $AUC_{0-\infty}$ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was ad ministered with a meal compared to a fasted state. The United States Prescribing Information states that no food should be consumed for at least two hours before the dose of abiraterone acetate is taken and for at least one hour after the dose of abiraterone acetate is taken. However, as discussed in sections 3.3.1 and 3.3.9.1, we will permit a low-fat breakfast (see Appendix A) 30 minutes after the dose in deference to the morning schedules of school-age children

10.4. Androgen blockade

This study will be conducted solely in prepubertal children who normally have low levels of sex steroids. Thus adverse effects of blockade of sex steroid synthesis encountered in adults (e.g., decreased bone mineral density, low libido) are not expected in this study.

Children with inadequately treated CAH have high blood levels of androgens, which can condition the hypothalamic-pituitary-gonadal axis such that high levels of gonadotropins will be secreted when androgen levels are finally brought under control. This can cause central precocious puberty, which may then require treatment with a gonadotropin releasing hormone agonist. This was observed in a trial of a four drug regimen consisting of low dose hydrocortisone, fludrocortisone, testolactone (an aromatase inhibitor to prevent estrogen-induced epiphyseal fusion), and flutamide (an androgen receptor blocker to prevent virilization (17). Four children in the experimental treatment arm and two children in the control arm were receiving deslorelin therapy (P = 0.6) after two years of treatment. No serious adverse effects were observed.

10.5. Study procedures

The risks of venipuncture are pain, bleeding and bruising. Patients with CAH ordinarily require blood samples at each visit to monitor their treatment but will require more frequent sampling in this study. Blood volumes will be limited to 2.5 ml/kg body weight for a single blood draw and 5 ml/kg within 30 days. These are half the generally accepted safe volumes for children (36).

Patients with CAH ordinarily have X-rays taken yearly of the left hand and wrist to assess skeletal maturation ("bone age"). They will have this assessment every 6 months as part of the study and will thus receive 2-3 more X-ray exposures over the course of the study than is the standard of care. The effective dose of a pediatric hand X-ray is remarkably small, 0.0001 mSv, corresponding to 30 minutes of the natural background radiation (37). This is a negligible radiation exposure.

10.6. Risks of standard of care

The standard of care for CAH is discussed in section 2.1.3. The risks of venipuncture are discussed in section 10.5. The risks of inadequate dosing of hydrocortisone include hyponatremia, hypoglycemia and hypotension. The risks of excessive dosing of hydrocortisone include excessive weight gain and retarded linear growth. All subjects will continue to receive hydrocortisone, but subjects in the active drug arm may require lower doses of hydrocortisone, thus reducing the risks of overdosing. The risks of hydrocortisone underdosing might be increased in the active drug arm, but doses will be similar to those used to treat other forms of adrenal insufficiency and so the increased risk is low and subjects will be carefully monitored for adequacy of hydrocortisone dosing (section 11.1.1).

Almost all patients in this study will receive fludrocortisone as part of their standard of care. The risks of underdosing fludrocortisone include hyponatremia, hyperkalemia and hypotension. The risks of overdosing include hypertension. Fludrocortisone doses should not differ between the two study arms, and so there should be no difference in these risks between the study arms. Monitoring of fludrocortisone therapy is discussed in section 11.1.3.

11. SUBJECT SAFETY AND DATA MONITORING

11.1. Ensuring Adequate Conventional Therapy

11.1.1. Hydrocortisone

In Phase 2, to ensure standardization, hydrocortisone will be provided to study pharmacies from a single source for dispensing to subjects (see Section 4). As discussed in Section 2.1.3, the goals of glucocorticoid therapy in CAH are to avoid both glucocorticoid insufficiency and androgen excess. The standard of care for monitoring hydrocortisone dosing is to utilize 17-hydroxyprogesterone and androstenedione levels as measures of activation of the hypothalamic-pituitary-adrenal (HPA) axis; glucocorticoid deficiency activates the HPA axis whereas glucocorticoid excess suppresses it. Abiraterone acetate treatment inhibits synthesis of these compounds (indeed, that is the desired therapeutic effect) and renders their levels inaccurate as a measure of HPA axis activation in subjects who are receiving the active drug. Therefore, a more complex monitoring scheme is necessary, with analytes (all to be drawn between 0800-1000) listed in order of consideration. Values over the specified limits will prompt a ~20% increase in hydrocortisone dose with a repeat level to be obtained to be obtained ~4 weeks later.

- Androstenedione. This androgen is routinely monitored in children with CAH. Its synthesis is efficiently inhibited in adult women with CAH (Figure 3). The goal is to maintain it at less than the upper limit of normal (ULN) for prepubertal children, which is ~50 ng/dl.
- Dihydrotestosterone. This potent androgen is not routinely monitored in CAH patients. We will do so in this study because it can be synthesized from 17-hydroxyprogesterone via the so-callled

"backdoor pathway" (22-24) without going through androstenedione as an intermediate. Because the effect of abiraterone acetate on 17-hydroxyprogesterone levels is less complete and more transient than its effect on androstenedione, it is possible that dihydrotestosterone levels might be significantly elevated even if androstenedione levels are normal. Therefore, a dihydrotestosterone level >ULN for prepubertal children (3 ng/dl) will prompt an uptitration of the hydrocortisone dose.

- 17-hydroxyprogesterone. Although monitoring androstenedione and dihydrotestosterone will ensure that subjects are not exposed to excessive androgen levels, these steroids are not very ACTH-responsive and cannot be used to detect marked HPA axis activation, which might indicate potentially dangerous underdosing (or noncompliance) with hydrocortisone. It is unlikely that abiraterone acetate treatment will have a major effect on 17-hydroxyprogesterone levels in the morning, 24 h after the last dose (see Figure 3), and so this steroid can be used to monitor the HPA axis. The standard-of-care upper limit of the target range for this compound is ~1000 ng/dl (3), but that limit is selected to avoid excessive androgen secretion. In children with CAH, a level of ~5000 ng/dl corresponds to an ACTH level of ~400 pg/ml (data not shown**)**, which is the lower end of the range observed in children with untreated but symptomatic Addison's disease (38). It seems prudent to uptitrate the hydrocortisone dose when this level of 17-hydroxyprogesterone is exceeded.
- HPA axis activation will also be assessed directly by periodically measuring ACTH (corticotropin) levels. As discussed in the previous point, the aim will be to maintain morning ACTH levels within the reference range or up to 400 pg/ml (approximately 6-7 times the upper limit of the reference range). In the absence of an obvious physiologic stressor such as a recent intercurrent illness, a value greater than this will prompt uptitration in total daily hydrocortisone dose, followed by a repeat ACTH level 2-4 weeks later. Conversely, a value below the reference range (<10 pg/ml) will prompt approximately a 20% decrease in total daily hydrocortisone dose, followed by a repeat ACTH level 2-4 weeks later. Because 17-hydroxyprogesterone and ACTH levels are correlated, this might seem redundant, but on the one hand we cannot be certain that abiraterone acetate will not suppress 17-hydroxyprogesterone levels to some extent, and on the other hand ACTH levels may take considerably longer to be returned from the laboratory.
- In interpreting the laboratory testing as described above, the clinician should be aware of the subject's physical condition and, even if laboratory tests do not reach thresholds for dose adjustment, increase the hydrocortisone dose for signs and symptoms of adrenal insufficiency such as unexplained fatigue, anorexia, weight loss, or orthostatic hypotension. Conversely, the hydrocortisone dose should be decreased for signs of Cushing syndrome such as poor linear growth or excessive weight gain.

11.1.2. Hydrocortisone Dosing During Illness

- Hydrocortisone doses should be temporarily tripled for febrile illness or other significant physical stress per standard of care and returned to normal dosing when the illness has resolved clinically and the subject is afebrile.
- Intramuscular or intravenous hydrocortisone sodium succinate should be administered according to the study physician's clinical judgment for illnesses causing repeated emesis and/or dehydration and/or hypotension, and for surgical procedures requiring general anesthesia. Typical doses are 100 mg/m^2 bolus followed by 25 mg/m^2 every 6 hours for 24 hours.

- Any study visits should be postponed until the subject has returned to normal hydrocortisone dosing for at least 24 hours.

11.1.3. Fludrocortisone

In Phase 2, to ensure standardization, fludrocortisone will be provided to study pharmacies from a single source for dispensing to subjects (see Section 4). Fludrocortisone dosing will be monitored according to the standard of care with blood pressure, electrolytes, and plasma renin levels. Blood pressure consistently above the reference range for age and/or suppressed plasma renin should prompt consideration of a reduction in fludrocortisone dose of 0.025-0.05 mg/d. Conversely, high serum potassium or low sodium levels, or elevated plasma renin, should prompt consideration of an increase in fludrocortisone dose. The adequacy of any dose adjustment should be confirmed with repeat monitoring labs 2-4 weeks after the adjustment (or sooner at the discretion of the treating physician).

11.1.4. Precocious Puberty

Subjects may be treated with a gonadotropin-releasing hormone agonist (e.g., leuprolide, histrelin) at the discretion of the study physician if there are signs of central precocious puberty (before age 8 years in girls, or at any time in the study in boys) including:

- Physical signs including breast development in girls and testicular enlargement in boys. Pubic or axillary hair might be signs of adrenal androgen secretion and will not be themselves considered to be signs of central precocious puberty.
- Uterine enlargement and ovarian follicular development on pelvic sonogram, or testicular enlargement on testicular sonogram.
- Pubertal response on leuprolide stimulation test (any value for luteinizing hormone [LH] >4.0).

Whereas treatment with a gonadotropin releasing hormone agonist is an exclusion criterion, it is not required to withdraw subjects from the study for such treatment started after enrollment.

11.2. Study Drug Dose Modifications and Management of Toxicity

Dose interruptions can be considered if an adverse event can be attributed to a concurrent illness (i.e., not related or doubtfully related to study drug) or to an alternative explanation. Abiraterone acetate or placebo without a dose modification can be resumed after resolution of the adverse event or if the subject condition has returned to baseline.

11.2.1. Hypokalemia and hypertension.

Although hypokalemia and hypertension are mechanism based adverse effects of abiraterone acetate treatment in patients with intact adrenal glands, they are mediated by increased secretion of deoxycorticosterone, which is not synthesized in patients with 21-hydroxylase deficiency. If these problems occur in subjects in this study, they are most likely a consequence of excessive administration of fludrocortisone and can be readily addressed by decreasing the dose of this agent.

11.2.2. Management of Abnormal Liver Function Tests

Categories of abnormal LFTs are defined as follows:

Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3 x ULN

Total bilirubin ≥2 x ULN (in the absence of Gilbert syndrome)

Total bilirubin ≥1.5 x ULN accompanied by any AST or ALT abnormality (>ULN).

Any AST or ALT elevation associated with nausea, vomiting, anorexia, abdominal pain, or fatigue.

The first incidence of AST or ALT ≥3 x ULN, total bilirubin ≥2 x ULN (in the absence of Gilbert syndrome), or total bilirubin ≥1.5 x ULN accompanied by any AST or ALT elevation below the ranges described in the other categories, or any AST or ALT elevation with associated clinical symptoms, requires that the subject discontinue study treatment immediately and that at least once weekly follow-up continue (measurement of liver enzymes) until resolution of abnormal LFTs. The sponsor should be notified immediately. No rechallenges with study medication will be permitted.

In the case of an AST or ALT <3 x ULN, total bilirubin <2 x ULN (in the absence of Gilbert syndrome), or total bilirubin <1.5 x ULN accompanied by any AST or ALT elevation below the ranges described in the other categories, dosing is allowed to continue provided that the subject has LFTs monitored weekly for 3 weeks. Upon worsening of LFT severity (>10% increase in any laboratory test), the study drug will be discontinued immediately and the site will notify the sponsor. If LFTS are stable or improving after 3 weeks, testing will continue at least monthly for 3 months or until resolution of abnormal LFTs (16).

11.3. Data Safety and Monitoring Board (DSMB)

The DSMB will consist of three pediatric endocrinologists not otherwise involved with the study and the statistician. The principal investigator will attend all meetings and conference calls but will not vote and may be asked to absent himself for confidential discussions by the DSMB.

11.3.1. Phase 1 Dose-Escalation

The DSMB will convene prior to enrollment of the first subject, and after completion of each of the three dose cohorts, but in any case no less frequently than every 6 months. The DSMB may convene at additional times for data review or any safety-related issues. Any DSMB member or site principal investigator has the right to request a DSMB meeting, which will be convened within 3 working days after the request has been made to the study principal investigator. The DSMB will review all safety data and available PK and PD information. This information will be curated by the sponsor/investigator's statistician at UT Southwestern Medical Center.

Decisions regarding changes in the timing of PK sampling, and exploration of alternative doses will be made by the DSMB. Adverse event profile (type, intensity, time of onset, and duration) and PK or PD data will be considered by the DSMB during the decision-making process.

All decisions made by the DSMB will be documented in a DSMB decision document and distributed to investigators before administration of abiraterone acetate to any additional subject. The study site's IRB

will be notified before implementation of any DSMB decision, as required. Completed decision documents will be retained in the study master file and in the study center's files.

11.3.2. Phase 2 Double-Blind

The DSMB will monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study and to meet efficacy objectives. The committee will meet periodically (at least every 6 months) to review interim data. After the review, the DSMB will make recommendations regarding the continuation of the study.

Potential events that would prompt consideration of modifying or terminating the study include, but are not limited to:

- AST, ALT >3x or bilirubin >2x baseline levels in 4 or more subjects.
- Any serious adverse event (see section 11.4) thought to be probably related to study drug.
- Lack of androstenedione normalization in at least 60% of the first 5 subjects on active drug after 3 months. This information will be provided to the DSMB by the study statistician. This would suggest that the abiraterone acetate dose is inadequate and may need to be increased. If 1 or 2 mg/kg/d was originally selected as the dose for Phase 2, the next highest dose will be selected. We will not attempt to expand the size of the study. If, however, 4 mg/kg/d was originally selected for Phase 2 and this dose proves inadequate, the DSMB may mandate reopening Phase 1 to test 8 subjects for a week at 8 mg/kg/d. This dose is still less than the FDA approved dose for abiraterone acetate in adult men with prostate cancer.

11.4. Adverse Event Reporting

11.4.1. Definitions

11.4.1.1. Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

11.4.1.2. Adverse Drug Reaction (ADR)

A noxious and unintended response to any dose of the drug (or biological) product for which there is a reasonable possibility that the product cause the response. ''Reasonable possibility'' means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

11.4.1.3. **Medicinal Product**

The specific drug under study and any other medicinal product.

11.4.1.4. **Product Quality Complaint (PQC)**

Any discrete concern that questions the identity, quality, durability, reliability, safety, efficacy or intended performance of a drug product.

A complaint may allege an injury or malfunction associated with the use of the drug product. It may also involve the design, literature, packaging, advertising, availability, physical appearance or promotion of the drug product.

11.4.1.5. Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered ''serious'' if, in the view of either the Institution/Principal Investigator it results in any of the following outcomes:

- Death,
- a life-threatening adverse event,
    - *Life-threatening adverse event or life-threatening suspected adverse reaction*.
        - An adverse event or suspected adverse reaction is considered ''life-threatening'' if, in the view of either the Institution/Principal Investigator, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- 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.
- is a suspected transmission of infectious agents by a medicinal product

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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

11.4.1.6. **Special Reporting Situations**

When a report contains a product, an identifiable patient, and identifiable reporter, the following events represent Special Reporting Situations:

- overdose of a medicinal product
- pregnancy exposure (maternal and paternal)

- exposure to a medicinal product from breastfeeding
- suspected abuse/misuse of a medicinal product
- inadvertent or accidental exposure to a medicinal product
- any failure of expected pharmacological action (i.e., lack of effect) of a medicinal product
- unexpected therapeutic or clinical benefit from use of a medicinal product
- medication error involving a product (with or without patient exposure to the medicinal product, e.g., name confusion)
- suspected transmission of any infectious agent via a medicinal product.

11.4.2. Management of Adverse Events, Serious Adverse Events and Special Reporting Situations

For each subject, AEs, SAEs, and Special Reporting Situations should be recorded after informed consent is obtained until the subject has completed participation in the study as follows:

A Serious Adverse event or Special Reporting Situations must be reported to Sponsor if it occurs during a subject's participation in the Study (whether receiving Study Product or not) and within 30 days of receiving the last dose of Study Product.

Any serious adverse event or Special Reporting Situations that is ongoing when a subject completes his/her participation in the Study must be followed until any of the following occurs:

- the event resolves or stabilizes;
- the event returns to baseline condition or value (if a baseline value is available);
- the event can be attributed to agents(s) other than the Study Product, or to factors unrelated to Study conduct.

11.4.3. Recording of Adverse Events, Serious Adverse Events and Special Reporting Situations

Recording should be done in a concise manner using standard, acceptable medical terms.

The adverse event recorded should not be a procedure or a clinical measurement (i.e. a laboratory value or vital sign) but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement.

Preexisting conditions that worsen in severity or frequency during the Study should also be recorded (a preexisting condition that does not worsen is not an adverse event).

Further, a procedure or surgery is not an adverse event; rather, the event leading to the procedure or surgery is considered an adverse event. Any event requiring in-patient hospitalization that occurs during the course of a subject's participation in a trial must be reported as an SAE. Hospitalizations that do not meet the criteria for SAE reporting are:

- Reasons described in the Protocol, e.g. drug administration, Protocol-required testing
- Surgery or procedure planned prior to entry into the Study.

If, in the Principal Investigator's judgment, a clinical significant worsening from baseline is observed in any laboratory or other test parameter (e.g. electrocardiogram (ECG), angiogram), physical exam finding, or vital sign, a corresponding clinical adverse event should be recorded.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the adverse event, whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, "hepatitis" and not "elevated liver function tests" should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an adverse event, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

11.4.4. Maintenance of Safety Information

Safety information will be maintained in a clinical database/repository in a retrievable format. At a minimum, at the end of the treatment phase (="last patient off treatment") as well as the end of the follow-up phase (="last patient out") of the Study, the Institution/Principal Investigator shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent review of the safety data may be necessary, e/g/ to fulfill a regulatory request,.

11.4.5. FDA Reporting Requirements

The Sponsor/Investigator (UT Southwestern) is responsible for reporting serious adverse events to the FDA in accordance with applicable IND Safety Requirements (21 CFR 312.32).

The following safety information SAEs, Adverse Events of Special Interest, Pregnancies, Special Reporting Situations, and PQCs should be reported within **24 hours** of becoming aware of the event(s).

All non-serious AEs should be reported according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

11.4.6. Transmission Methods:

The following methods are acceptable for transmission of safety information to Sponsor:

- Facsimile (fax), receipt of which is evidences in a successful fax transmission report to 1-214-648-9772
- Reporting may be done electronically via an acceptable encrypted email format.
- Telephone (for business continuity purposes, if fax or authorized electronic system is nonfunctional).

11.4.7. Procedures for Reporting Adverse Events (AE), Serious Adverse Events (SAE), Pregnancies, and Special Reporting Situations

11.4.7.1. Serious Adverse Events (SAE), Adverse Events of Special Interest, Pregnancies, and Special Reporting Situations

All available clinical information relevant to the evaluation of an SAE, Adverse Events of Special Interest, and Special Reporting Situations including pregnancy reports (with or without an AE) including paternal exposure are required.

- The Institution and/ or Principal Investigator is responsible for ensuring that these cases from clinical studies are complete and if not are promptly followed-up. This includes ensuring the reports are fully investigated and thoroughly documented by the Principal Investigator and that follow-up information is summarized e.g. hospital records, coroner's reports, autopsy results and recorded on the appropriate forms.
- A study case is not considered complete until all clinical details needed to interpret the case are received and the event has resolved, or otherwise explained, or the patient is lost to follow-up. Reporting of follow-up information should follow the same timeline as initial reports.
- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Study Drug in the course of the Study, by facsimile within 24 hours of such report or correspondence being sent to applicable health authorities.

11.4.7.2. Product Quality Complaints

Any PQC, with or without an AE, (including reports of suspicion of counterfeiting, diversion, or tampering, and suspected transmission of pathogens) will be transmitted to Sponsor, within **24 hours** of becoming aware of the event(s).

11.4.8. Contacting Sponsor Regarding Safety

The Sponsor of this study is University of Texas Southwestern Medical Center, Dallas, TX. The Sponsor-Investigator (Principal Investigator) is Perrin C White, MD, Professor of Pediatrics at this institution. The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

12. PROCEDURES TO MAINTAIN CONFIDENTIALITY

12.1. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study. These data will be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Electronic data will be stored on secure servers that require password protection and maintain audit records of access, and/or on laptops with password-protected encrypted hard drives. All data sent between institutions via e-mail, file transfer protocols or physical media must be encrypted and password protected. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential. Hardcopy

documentation must be stored in locked file cabinets or locked offices secured with either key or badge access.

The informed consent and HIPAA permission obtained from the subject's legally acceptable representative includes explicit consent for the processing of personal data and for the investigator to allow direct access to his or her original medical records for study-related monitoring, audit, IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject's legally acceptable representative has the right to request through the investigator access to the subject's personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

12.2. Disclosure to Outside Entities

All data, whether electronic or hardcopy, will be referenced to a unique patient identifier, with subjects' identifying information kept in separate secure files. The following entities will be granted access to some or all data and specimens from this study:

- Quest Laboratories as the central reference laboratory for this project.
- The UT Southwestern Institutional Review Board (IRB), as the IRB for the sponsor.
- Local IRBs
- Central data management and study monitoring
- Data safety and monitoring board
- Representatives of the Food and Drug Administration (FDA).
- Representatives of other governmental and regulatory agencies.
- Treating endocrinologists

13. POTENTIAL BENEFITS

Benefits to all subjects will include careful medical monitoring of their disease and free study-related medical care for the duration of the study including physical exams, laboratory tests, and medication.

Benefits to subjects randomized to active Study Drug (abiraterone acetate) may include maintenance on a lower dose of hydrocortisone which may minimize excessive weight gain and linear growth delay associated with glucocorticoid excess. Additionally, the hypothesized retardation of skeletal maturation may improve final adult height; patients with classic CAH average ~7 cm shorter than expected for their parental heights.

14. BIOSTATISTICS

14.1. General Considerations

All continuous endpoints will be summarized using descriptive statistics, which will include the number of subjects (n), mean, standard deviation, median, and interquartile range. All categorical endpoints will be summarized using frequencies and percentages. The baseline measurement will be the last value on or before the date of first study treatment.

An interim analysis of safety and efficacy will be performed after 24 subjects have completed 104 weeks of treatment. An interim Clinical Study Report will be written on the basis of this data cutoff.

When all subjects have completed the 109 weeks of Phase 2, a final Clinical Study Report will be written.

14.2. Subject Information

Evaluable subjects at Phase 1 are defined as subjects who have completed all study procedures.

The intent-to-treat (ITT) population includes all subjects randomized into the Phase 2 portion of the study.

All subjects who receive at least 1 dose of study drug will be analyzed for safety.

14.3. Sample Size Determination

14.3.1. Phase 1 Dose-Finding

This is a Phase 1 dose finding study; the sample size is one of convenience. We want to identify a dose that will reliably (0.95 probability) result in normalization of androstenedione levels. With a sample size of 8, the margin of error is 0.16, hence the lower limit of the 95% confidence interval is 0.79. Thus a goal of at least 7/8 subjects (>0.87) to have normalized androstenedione levels is appropriate. Also see section 3.3.15.1.

14.3.2. Phase 2 Double-Blind

The primary endpoint In Phase 2 is bone age advancement (change in bone age per year of chronologic age) (see Section 14.5.1). In a study of flutamide and testolactone as adjunctive therapy in CAH (17), the rate of bone age maturation declined from 1.9 ± 0.3 to 0.7 ± 0.2 (mean $\pm$ SEM) bone age yr/chronological yr in the children receiving the regimen with flutamide and testolactone. As there were 14 subjects per arm, this implies standard deviations of ~1.0. A sample size of 48 subjects (32 in the abiraterone acetate arm and 16 in the placebo arm) will have 90% power to detect a difference in bone age advancement of 1 year over the 2-year period of the study with a 0.05 2-sided significance level. To allow for ~10% attrition, 54 subjects will be randomized (36 to abiraterone acetate and 18 to placebo) and data from all subjects will be used for the primary analysis based on the intent to treat approach.

14.4. Pharmacokinetic and Pharmacodynamic Analyses (Phase 1)

14.4.1. Pharmacokinetic analysis

For each dose level in Phase 1, peak and trough plasma concentrations of abiraterone will be plotted. Plasma concentration data at each time point will be summarized with mean and standard deviation for each dose.

14.4.2. Pharmacodynamic Analyses

The counts and percentages of subjects with serum androstenedione normalization on Day 8 at each dose level will be summarized and the associated exact 2-sided 95% binomial confidence intervals for the percentages will be provided. Mean and mean change from baseline in serum androstenedione and 17-OHP concentrations will be summarized with mean, standard deviation, median, and interquartile range. All Phase 1 PD analysis will be performed on evaluable subjects.

14.5. Outcome Analyses

For Phase 2 double-blind, a mixed linear model (e.g., PROC MIXED in SAS) will be used to fit a linear model for repeated measures and to examine time and treatment effects on:

- bone maturation
- hydrocortisone dose
- height
- BMI percentile
- blood pressure
- hormonal data (see below).

To take age effect on the mean differences into account, an analysis of covariance (ANCOVA) model will be also applied to the primary and secondary efficacy endpoints by including a stratification factor of age group (2 to 5 years vs. 6 to 9 years) and other appropriate covariates to evaluate the differences in mean and mean change from baseline between the 2 treatment groups. All efficacy analysis will be performed on the ITT population by including all subjects randomized into the Phase 2 double-blind portion of the study.

14.5.1. Bone age

Bone age in years will be obtained as output from an automated program (BoneXpert, see section 4.3.5) or, for films that cannot be read by the program due to image quality, the median of 3 investigators' independent readings will be used. The outcome will be expressed as the change in bone age from baseline at each time point, with (as noted above) a repeated measures analysis as the primary outcome.

14.5.2. Hydrocortisone dosing

Hydrocortisone dose at each time point will be expressed in mg per m^2 of body surface area, which will be calculated by the Mosteller formula (39) as $BSA\ (m^2) = SQR\ RT\ (\ [Height(cm) \times Weight(kg)\ ]/\ 3600)$.

14.5.3. Physical Examination

Descriptive statistics of height, height Z-score for age, weight, body mass index (BMI), BMI percentile for age (27), and pubertal (Tanner) stage (at Visit 1), and changes from baseline, will be summarized at each scheduled time point.

14.5.4. Vital Signs

Descriptive statistics of heart rate and blood pressure (systolic and diastolic) sitting values and changes from baseline will be summarized at each scheduled time point. Blood pressure Z scores for age will be calculated. The percentage of subjects with blood pressure values beyond age-adjusted limits (i.e., Z scores >2.0) will be summarized at each scheduled time point.

14.5.5. Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point. Changes from baseline results will be presented in pre- versus posttreatment cross-tabulations (with classes for below, within, and above normal ranges). Preplanned comparisons between treatment groups will include:

- 17-hydroxyprogesterone
- Androstenedione
- ACTH

14.5.6. DNA Analyses

Congenital adrenal hyperplasia subtypes as determined by genotype, will be included as covariates in the statistical analysis. Subjects will be divided into 3 groups. Group A will consist of those who carry null mutations on both alleles (see Figure). Group A1 will include patients who carry at least one intron 2G mutation who are expected to have a slightly milder phenotype. Group B patients, who carry the Ile172Asn mutation as the most severe mutation on at least one allele, generally have a simple virilizing phenotype. Group C patients, who carry Pro30Leu or Val281Leu as the most severe mutation on at least one allele, generally have a nonclassic phenotype and will not be included.

14.6. Safety Analyses

All subjects who receive at least 1 dose of study drug (ie, abiraterone acetate or placebo) will be analyzed for safety. Safety data during Phase 1 will be summarized overall. Safety data collected during Phase 2 will be summarized by treatment groups. Safety variables will be summarized descriptively for vital signs, adverse events, clinical laboratory parameters, and ECG. Serious adverse events, adverse events, and discontinuations from study treatment due to adverse event will be provided in listings.

Adverse events, including laboratory adverse events, will be categorized as mild, moderate, severe (see next Section). Adverse events will be summarized by system organ class and preferred term. Deaths and other serious adverse events will be provided in a listing. Treatment-emergent adverse events resulting in study drug discontinuation, dose modification, dosing interruption or delay will also be listed and

tabulated by preferred term. Other safety endpoints, including vital signs, clinical laboratory parameters, and ECG, will be summarized descriptively. Shift tables for select laboratory parameters will be presented.

14.6.1. Adverse Events

The verbatim terms used in the source and CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.0. All treatment-emergent adverse events reported up to 30 days after the last dose of study drug in each phase of the study will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event

Severity grading is as follows:

Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Moderate; minimal, local or noninvasive intervention indicated;

Severe: hospitalization or prolongation of hospitalization indicated; Disabling or life-threatening;

Death

14.6.2. Cardiac Function Tests

Electrocardiogram parameters will be summarized by treatment groups using descriptive statistics. The percentage of subjects with clinically significant ECG changes will be summarized as appropriate.

15. ADMINISTRATIVE REQUIREMENTS

15.1. Protocol Amendments

All protocol amendments will be issued by the sponsor/Principal Investigator with prior notice to UT Southwestern IRB. Protocol amendments must not be implemented without prior IRB approval except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IRB.. During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information page(s) provided separately). Whenever possible, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it. The local IRB must be notified of any protocol deviation.

15.2. Regulatory Documentation

15.2.1. Required Pre-study Documentation

The following documents must be provided to the sponsor before shipment of study drug to the investigational site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed, written IRB approval of the protocol, amendments, informed consent form, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee.
- Name and address of the IRB, including a current list of the IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IRB, a general statement may be substituted for this list. If an investigator or a member of the investigational staff is a member of the IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.

Regulatory authority approval or notification, and

- Signed and dated statement of investigator and sub-investigators (eg, Form FDA 1572)
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator
- Signed and dated clinical trial agreement, which includes the financial agreement

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all clinical sub-investigators
- Documentation of sub-investigator qualifications (eg, curriculum vitae)

15.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. All reports and communications relating to the study will identify subjects by assigned number.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

15.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the CRF: subject identification, eligibility, and study identification; study discussion and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable. In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a study subject should be consistent with that commonly recorded at the site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines.

15.5. Data Reporting

Data for each patient will be recorded on the eCRF. An eCRF must be completed for every patient enrolled in the study. Data will be entered directly from the source documentation into the eCRF within 2 business days of visit. The eCRF data will be entered by study-site personnel and then reviewed and electronically signed by the Investigator listed on Form FDA 1572, within a reasonable time period after data collection. All study-site personnel must use an electronic signature access method to enter, review, or correct study data. Electronic signature procedures shall comply with the Code of Federal Regulations (CFR) Title 21 Part II and the ICH Guidelines for GCP (Topic E6, April 2000) Section 5.5.3. Passwords and electronic signatures will be strictly confidential.

For all clinical trials, the data should be recorded on the source documents first and not entered directly into the computer. The eCRF will not be regarded as source data for any data points. The investigator must verify that all data entries in the CRFs are accurate and correct. All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel.

15.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, and periodic monitoring visits by the Sponsor. Written instructions will be provided for collection, preparation, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study personnel before the start of the study. The sponsor will review CRFs for accuracy and completeness during monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the clinical study database they will be verified for accuracy and consistency with the data sources.

15.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator must permit access to such reports.

15.8. Monitoring

The sponsor will perform monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and investigational staff and are accessible for verification by the sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents will be discussed with the investigational staff. The sponsor expects that, during monitoring visits, the relevant investigational staff will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

15.9. Study Completion/Termination

15.9.1. Study Completion

The study is considered completed with the last study assessment for the last subject participating in the study. The final data from the investigational site will be sent to the sponsor (or designee) after completion of the final subject assessment at that site, in the time frame specified in the Clinical Trial Agreement.

15.9.2. Study Termination

The sponsor reserves the right to close the investigational site or terminate the study at any time for any reason at the sole discretion of the sponsor. Investigational sites will be closed upon study completion. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigational site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator

15.10. On-Site Audits

The sponsor’s representatives may visit the site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Subject privacy must, however, be respected. The investigator and staff are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

15.11. Use of Information and Publication

Any data generated as a result of this study are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent. The investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain CRF data from all investigational sites that participated in the study, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Results of exploratory analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of exploratory results.

Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law, including registration on the ClinicalTrials.gov website.

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Appendix A-Low Fat Guidelines

A low fat breakfast should contain fewer than 3 grams of fat. When you eat less fat, you eat fewer calories. Your child may need to eat more calories from carbohydrates or proteins.

Choosing Low-fat Foods

Breads, Cereals, Rice, and Pasta

- Choose whole-grain breads
- Avoid foods such as donuts, sweet rolls, muffins, biscuits, cornbread, and pancakes.
- Hot and cold cereals are usually low in fat
- Avoid granola and adding butter to hot cereals
- Avoid anything fried.

Vegetables and Fruit

- Fruits and vegetables are low in fat; they add flavor and variety to your diet
- They contain fiber, vitamins, and minerals
- Avoid adding margarine, butter, full-fat dressings, or sour cream.
- Try using herbs, low-fat yogurt, and low-fat dressings for flavor

Meats

- Baking, broiling, roasting or grilling will minimize fat added to protein sources
- Use either a nonstick pan or nonstick cooking spray
- Trim all visible fat and remove skin before cooking
- Select lean cuts of meat which have the word “loin” or “round” in the name

Milk, Yogurt and Cheese

- Use skim/fat free milk
- Use string cheese as a low-fat, high calcium food source
- Use fat free cottage cheese
- Plain non-fat yogurt can replace sour cream in many recipes

Label Lingo

You may see words on the label that can help you choose lower fat foods. Always read the Nutrition Facts to see exactly how much fat is in the food.

Fat free	½ gram of fat or less per serving
Low saturated fat	1 gram of fat or less per serving
Low fat	3 grams of fat or less per serving
Light or lite	1/3 fewer calories or has 50% less fat than comparable products per serving

Breakfast Selections

1. Oatmeal with berries and 2 oz sliced turkey or ham
    - Season oatmeal with cinnamon, nutmeg, or pumpkin spice
2. Vegetable Omelet and whole wheat bread
    - Egg whites with fresh or frozen vegetables (spinach, peppers, onions, mushrooms, tomatoes)
    - Serve with 1 slice whole wheat toast
3. Egg whites and fruit
    - Ensure to separate the egg and discard yolk portion
    - Serve with any fruit
4. Cereal and skim milk
    - Choose cereals with no more than 2 grams of fat per serving; ensure to measure out 1 serving size
5. Light or Fat-free yogurt and cereal/oats
    - See recommendations for cereal above
    - Yogurt should have no more than 2 grams fat per serving
6. Whole wheat English Muffin and fruit
    - Option to add jelly to English muffin
    - Eat with 1 serving of fruit – banana, apple, berries, etc