Clinical Study Protocol

Study Title: A Phase 2, Multicenter Study of ATR-101 for the Treatment of Congenital Adrenal Hyperplasia
Study Number: ATR-101-201
Study Phase: 2
Product Name: ATR-101
IND Number: 122745
NCT Number: NCT02804178

Indication: Congenital Adrenal Hyperplasia
Sponsor: Millendo Therapeutics, Inc.

Sponsor Medical Contact: Pharis Mohideen, M.D.

Amendment 1
January 14, 2016

SYNOPSIS

Compound Name/No.	ATR-101
Study Number	ATR-101-201
Study Title	A Phase 2, Multicenter, Study of ATR-101 for the Treatment of Congenital Adrenal Hyperplasia
Phase of Clinical Development	**2**
Objective(s)	**Primary:** The primary objective of this study is to evaluate the efficacy and safety of orally administered ATR-101 in subjects with classic congenital adrenal hyperplasia (CAH). **Secondary:** • To evaluate the changes in adrenal cortical steroids and steroid intermediates • To evaluate the changes to the hypothalamic-pituitary-adrenal axis (via ACTH) • To evaluate the pharmacokinetics (PK) of ATR-101
Study Design	This is a multicenter, single-blind, multiple dose study of ATR-101 with a placebo washout component. The Screening Period will be followed by a placebo, Baseline Lead-in Period. Subjects will then receive the lowest dose of ATR-101 for 14 days followed by a single-blind placebo Washout Period of 14 days. Safety and efficacy assessments will occur at the end of ATR-101 treatment and following the Washout Period. If the primary outcome measure (17-OHP ≤ 2x ULN) is not achieved, the subject will proceed to the next higher dose level. ATR-101 treatment will stop once the primary outcome measure is met. A total of 5 ATR-101 dose levels are possible.
Duration of Study	Approximately 12 months
Number of Centers	5-8 in United States
Number/Type of Subjects	Minimum of 9 with a maximum of 17. Classic CAH due to 21-hydroxylase deficiency (21-OHD).
Study Treatments	ATR-101 tablets twice daily by mouth. ATR-101 tablets will be available in 125, 250 and 500 mg doses with matching placebo tablets. Five dose levels are planned: 125 mg BID, 250 mg BID, 500 mg BID, 750 mg BID and 1000 mg BID.
Duration of Treatment	Treatment duration will range from a minimum of approximately 2 months to 6 months per subject. Subjects will have a Screening Period of up to 21 days and then enter a placebo Baseline Lead-in Period of 14 days. Each dose level

Compound Name/No.	ATR-101
Study Number	ATR-101-201
	will last 28 days and consist of ATR-101 treatment for 14 days followed immediately by 14 days of matching placebo. A subject may receive a minimum of one dose level or up to a maximum of 5 dose levels, in sequentially increasing dose strengths.
Key Inclusion Criteria	Subjects meeting the following criteria may be included in the study: • Subjects aged 18 to 80 years at the time of signing the informed consent form (ICF) • Men or women with classic CAH due to 21-OHD • Subject must have a documented historical diagnosis of CAH due to 21-OHD based on any one of the following criteria: o Documented genetic mutation in the CYP21A2 enzyme consistent with a diagnosis of classic CAH o Historical documentation of elevated 17-OHP (e.g. in infancy or following a cosyntropin (ACTH) stimulation test) • Biochemical marker of disease status at Screening and Baseline Lead-in Period o 17-OHP $\geq$ 4 x ULN • Chronic glucocorticoid replacement therapy for at least 6 consecutive months prior to signing ICF • Stable glucocorticoid and mineralocorticoid regimen for at least 1 month prior to signing ICF (per Investigator discretion) • Female subjects of childbearing potential must consent to use two medically acceptable methods of contraception throughout the study period and for 30 days after the last dose of study treatment • Males must be sterile (e.g. status-post vasectomy) for 6 months prior to informed consent or agree to use two approved methods of contraception where one method must include a barrier method

Compound Name/No.	ATR-101
Study Number	ATR-101-201
Key Exclusion Criteria	Subjects will be excluded from participation in the study if any of the following criteria are met: • Non-classic CAH • Other causes of adrenal insufficiency such as Addison's disease; adrenalectomy, etc. • Surgery within the previous 3 months prior to screening or planned surgery during study participation. Minor procedures are permitted (e.g. removal of skin tags or other minor dermatological procedures) • Abnormal laboratory tests at Screening: o ALT or AST > 2 x ULN o Bilirubin > 1.5 x ULN o Serum Creatinine >1.5 x ULN • History of active cancer requiring medical or surgical therapy within the past 6 months (with the exception of successfully treated non-metastatic basal cell or squamous cell carcinoma of the skin and carcinoma in-situ of the cervix) • Significant comorbid medical condition(s) that may preclude compliance with the study protocol or such that study participation may not be in the subject's best medical interest. Medical conditions may include (but are not limited to) those of the cardiovascular, respiratory, gastrointestinal, renal, hepatic, central nervous system (CNS) or immune system (e.g., human immunodeficiency virus), Myocardial infarction (MI) or cerebrovascular accident/transient ischemic attack (CVA/TIA) within the past 6 months. • Psychiatric illness such that comprehension of the informed consent or compliance with the study protocol may be impaired • Treatment with another investigational drug or device within 3 months prior to Screening

Compound Name/No.	ATR-101
Study Number	ATR-101-201
Criteria for Evaluation	**Pharmacokinetics:** ATR-101 (and its metabolites) pharmacokinetic parameters will be assessed.
	Pharmacodynamics: Changes in adrenal cortical steroids and steroid intermediates (e.g. 17-OHP, androstenedione, testosterone, free testosterone, sex hormone binding globulin (SHBG), dehydroepiandrosterone (DHEA), DHEA-S, aldosterone, PRA); Changes in ACTH
	Safety: Safety assessment will consist of monitoring and recording: adverse events (AE) and serious adverse events (SAE); changes in physical examinations, vital signs, electrocardiograms (ECGs); regular monitoring of hematology, prothrombin time (PT)/activated partial thromboplastin time (aPTT), INR, blood chemistry, steroid hormones and urine analysis values.
Stopping Criteria	Investigational Medicinal Product (IMP) may be discontinued due to a safety event. Once a subject has met the efficacy endpoint, no further administration of study drug will be permitted.
Study Endpoints	**Primary Efficacy Endpoint:** The primary efficacy endpoint will be the overall response rate defined by the percentage of subjects meeting the primary outcome measure as follows: • 17-OHP $\leq$ 2 x ULN **Safety Endpoints:** Safety parameters (AEs, vital signs, physical examination, laboratory measures, ECG) **Pharmacokinetic Endpoints:** • Area under the curve ($AUC_{0\text{-}4\ hr}$) • Maximum plasma concentration (Cmax) • Time to maximum concentration (Tmax)
Statistical Methods	Qualitative statistical analyses will be performed for both safety and efficacy parameters.

Schedule of Assessments for ATR-101

Procedure	Screening (Day -21 to Day -1)[a]	Baseline Lead-In[b]	Dose Level 1[c]		Dose Levels 2 - 5		Final Study Visit or Early Termination Visit (Day 29)	Follow-up Visit (Telephone)
		Placebo (Day 1)	ATR-101 Treatment (Day 1-14)	Placebo Washout (Day 15-28)	ATR-101 Treatment (Day 1-14)	Placebo Washout (Day 15-28)		(Final Study Visit/Early Termination Visit + 2 weeks)
Informed Consent	X							
Dose Assessment[d]					X			
Inclusion/Exclusion Criteria	X	X	X[e]					
Medical History & Demographics	X							
Physical Examination[f]	X	X	X	X	X	X	X	
Vital Signs[g] and Weight	X	X	X	X	X	X	X	
12-lead ECG[h]	X		X	X	X	X	X	
Hematology Panel	X	X[q]	X	X	X	X	X	
Serum Chemistry Panel	X	X[q]	X	X	X	X	X	
PT, aPTT, INR	X	X[q]	X	X	X	X	X	
Urinalysis	X						X	
Serology (HBsAg, Hepatitis C antibody, HIV)	X							
Steroid Hormones[i]	X	X	X	X	X	X	X	
Exogenous Glucocorticoid Levels[j]	X	X	X	X	X	X	X	
Pregnancy Test[k]	X		X		X		X	
PK ATR-101 Plasma Levels[l]			X	X	X	X	X	
Prior/Concomitant Medications	X	X	X	X	X	X	X	X
Dispense IMP[m]		X	X	X	X	X		
Collect IMP[n]/Drug Accountability			X	X	X	X	X	
Assess IMP Compliance[o]			X	X	X	X	X	
Adverse Events[p]	X	X	X	X	X	X	X	X

[a] Day -21 to Day -1 will be used to collect data from the Screening assessments.

[b] Baseline Lead-In with placebo will be a minimum of 14 days but an additional 3 days is allowed.

[c] For each Dose Level there will be 14 days of treatment with ATR-101 and 14 days of treatment with placebo. For each portion there should be a minimum of 11 days of treatment and a maximum of +3 days is allowed beyond the scheduled 14 days.

[d] Dose assessment will be performed prior to dosing on Day 1 of Dose Levels 2, 3, 4 and 5 as needed. The PI or SI will review the 17-OHP results obtained on Day 15 and determine whether the Final Study Visit will be conducted (17-OHP ≤2 x ULN on Day 15) or whether the next Dose Level, Day 1 Visit will be conducted (17-OHP > 2 x ULN on Day 15).

[e] 17-OHP results from Screening and Baseline Lead-In Period will be used in this evaluation of inclusion criteria.

[f] Complete physical examinations will be performed at Screening and the Final Study Visit or Early Termination Visit. An abbreviated (brief) physical exam will be performed at Day 1 of Baseline Lead-In Period, pre-dose on Day 1 and Day 15 of each dose level.

[g] Vital signs (blood pressure, pulse, respiration rate, and temperature) and body weight will be measured at Screening, Day 1 of the Baseline Lead-In Period, pre-dose and 1, 2, and 4 hour post-dose on Day 1 of each dose level, Day 15 for each dose level, and at the Final Study Visit or Early Termination Visit. Height will be measured at Screening.

[h] All subjects will have 12-lead ECG assessments at Screening, Day 1 pre-dose and 2 hours post-dose for each dose level, Day 15 pre-dose for each dose level, and at the completion of the Placebo Washout Period on Day 29.

[i] Blood samples for steroid hormones and steroid intermediates including 17-OHP, androstenedione, cortisol, testosterone, ACTH, free testosterone, SHBG, aldosterone, 11-DOC, PRA, DHEA and DHEAS will be obtained at Screening, Day 1 of Baseline Lead-In Period, pre-dose on Day 1 and Day 15 of each dose level and at the Final Study Visit or Early Termination Visit. All samples will be collected prior to 10 AM.

[j] Blood samples for exogenous glucocorticoid levels (Betamethasone, Budesonide, Dexamethasone, Fludrocortisone, Flunisolide, Fluorometholone, Hydrocortisone, Megestrol acetate, Methylprednisolone, Prednisolone, Prednisone, Triamcinolone, Triamcinolone acetonide) will be obtained as appropriate for each subject.

[k] Obtained for females of childbearing potential who are not surgically sterile or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who have had menses any time in the preceding 12 consecutive months). A serum pregnancy test will be performed at Screening. A urine pregnancy test will be performed prior to dosing on Day 1 of each Dose Level and at the Final Study Visit or Early Termination Visit.

[l] Blood for PK analysis of ATR101 and its metabolites in plasma will be obtained on Day 1 of each Dose Level at pre-dose and 1, 2, 3, and 4 hours post-dose; on Day 15 of each Dose Level at pre-dose and at the Final Study Visit or Early Termination Visit. A window of ± 10 minutes is permitted around each sampling time-point.

[m] The first dose will be administered on site on Day 1 and Day 15 of each dose level.

[n] All bottles and unused tablets must be returned to the study site on Day 1 and Day 15 of each dose level and at the Final Study Visit or Early Termination Visit.

[o] IMP compliance will be assessed by counting the number of tablets returned and determining if the correct number were taken within the window of 80% to 120%.

[p] AEs will be collected from the time the subject signs the informed consent form until 30 days after the last dose of IMP.

[q] Tests do not need to be repeated on Day 1 of Baseline Lead-In if the subject's clinical condition has not changed and these tests were done ≤ 14 days prior to Day 1

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11-DOC	11-deoxycorticosterone
17-OHP	17-hydroxyprogesterone
21-OHD	21-hydroxylase deficiency
21-OHP	21-hydroxyprogresterone
ACC	Adrenal cortical carcinoma
ACTH	Adrenocorticotropic hormone
ACAT1	Acyl-CoA: cholesterol acyltransferase 1
AE	Adverse event
ALB	Albumin
ALK-P	Alkaline phosphatase
ALT; SGPT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST; SGOT	Aspartate aminotransferase
AUC	Area under the concentration-time curve
β-hCG	Beta human chorionic gonadotropin
BID	Twice daily
BUN	Blood urea nitrogen
Ca	Calcium
CAH	Congenital adrenal hyperplasia
CE	Cholesterol ester
CFR	Code of Federal Regulations
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CQA	Clinical quality assurance
CRA	Clinical research associate
CS	Cushing's syndrome
CSR	Clinical study report
CVA	Cerebrovascular accident
CYP	Cytochrome P450 enzymes
DHEA	Dehydroepiandrosterone
DHEA-S	Dehydroepiandrosterone sulfate
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic Data Capture
eCRF	Electronic case report form
FC	Free cholesterol
FDA	Food and Drug Administration
GC	Glucocorticoid
GCP	Good clinical practices
HBsAg	Hepatitis B surface antigen
Hct	Hematocrit

HEENT	Head, eyes, ears, nose, and throat
Hgb	Hemoglobin
HIPPA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic pituitary adrenal
ICF	Informed consent form
ICH	International Conference on Harmonization
ID	Identification number
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
INR	International normalizedrRatio
IRB	Institutional Review Board
mg	Milligram
MC	Mineralocorticoid
MI	Myocardial Infarction
MTD	Maximum tolerated dose
PCOS	Polycystic ovarian syndrome
PI	Principal investigator
PD	Progressive disease
PK	Pharmacokinetics
PRA	Plasma Renin Activity
PT	Prothrombin time
RBC	Red blood cell
SAE	Serious adverse event
SI	Sub-investigator
StAR	Steroidogenic acute regulatory protein
TIA	Transient ischemic attack
T_{max}	Time to maximum concentration
TMF	Trial master file
ULN	Upper limit of normal
UPT	Urine pregnancy test
US	United States
WBC	White blood cell
WHO	World Health Organization

1 INTRODUCTION

1.1 Description of Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) consists of genetic disorders affecting the synthesis of cortisol from the adrenal glands. More than 90% of all CAH cases are due to defects in the cytochrome P450 enzyme steroid 21-hydroxylase, also known as 21-hydroxylase or CYP21A2.[1] The enzyme 21-hydroxylase facilitates the conversion of 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol, the immediate precursor of cortisol. Additionally, 21-hydroxylase is responsible for the conversion of progesterone to 11-deoxycorticosterone, the precursor of aldosterone.[1] Depending on the severity of the enzyme defect, partial or complete glucocorticoid (GC) and mineralocorticoid (MC) deficiency may exist. Two forms of 21-hydroxylase deficiency (21-OHD) have been defined: "classic" 21-OHD is associated with cortisol insufficiency and "nonclassic" 21-OHD is associated with mild subclinical impairment of cortisol synthesis.[2] The remaining cases (<10%) of CAH are mainly due to four other enzyme deficiencies (i.e. P450scc, P450c17, 11β-hydroxylase, 3β-hydroysteroid dehydrogenase), a cholesterol protein defect (StAR) and one electron-transfer protein.[3]

In the US, Newborn screening for CAH began in the late 1970's with the ability to readily measure 17-OHP.[4] Elevated 17-OHP, the hallmark of CAH due to 21-OHD, occurs in the setting of impaired ability to convert 11-deoxycortisol to cortisol and progesterone to deoxycorticosterone. Prior to screening measures to identify CAH patients and treatment with GC therapy, undiagnosed/untreated CAH was associated with significant morbidity and mortality.

Replacement GC and MC therapy are the mainstays of CAH treatment. In spite of many decades of GC replacement therapy and CAH patients surviving into adulthood, CAH remains a challenging and difficult disease to manage. Lack of cortisol feedback inhibition results in markedly increased ACTH production which over time results in enlarged adrenal glands. The adrenals of adult patients with CAH produce a large amount of only a few steroids: progesterone, 17-OHP, dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S).[5] Management of classic CAH entails a difficult balance between GC replacement required for survival versus higher, supra-physiologic (pharmacologic) doses needed to suppress ACTH levels and decrease androgen production without causing iatrogenic Cushing's syndrome (CS). Women have the added challenges of androgen excess (e.g., hirsutism, acne and alopecia) and potentially the inability to conceive.[5] Women may also develop a secondary polycystic ovary syndrome (PCOS) since androgens and 17-OHP also derive from the ovaries and may persist even after adrenal suppression.[6] Men may have complications of androgen excess manifesting as suppression of gonadotropins leading to testicular atrophy and infertility.[7] Additionally, up to 50% of men may have testicular adrenal rest tumors which can become quite large and painful along with causing testicular dysfunction.[8] Thus, there are three major concerns for the management of adults with 21-OHD: (1) prevention of adrenal and gonadal hyperplasia and neoplasia, (2) prevention of long-term consequences of adrenal replacement therapies, and (3) restoration of fertility in those who desire to have children.[5]

1.2 Rationale for Use of ATR-101 in Congenital Adrenal Hyperplasia

ATR-101 inhibition of adrenal steroid and steroid intermediate synthesis may provide an extremely valuable tool for the clinician managing CAH. Inhibition of adrenal steroidogenesis across the androgen pathway would negate the need to suppress ACTH with supra-physiologic doses of GC and prevent the risk of iatrogenic CS. CAH patients may then require only physiologic doses of GC replacement. Use of ATR-101 in the treatment of CAH is supported by extensive mechanism of action studies, robust non-clinical proof of concept data and exposure of approximately 50 patients with adrenocortical carcinoma (ACC) in a Phase 1 study.

The mechanism of action of ATR-101 has been studied extensively *in vitro* and *in vivo.* ACAT1, the molecular target of ATR-101, is highly expressed in the adrenal glands compared with other tissues[9] and ATR-101 is found at higher levels in the adrenal glands compared to other sites in the body,[10] both of which are likely to contribute to the selectivity of ATR-101's effects on the adrenal glands. ATR-101 disrupts adrenal cholesterol homeostasis via ACAT1, an enzyme that catalyzes the esterification of free cholesterol (FC) to cholesterol ester (CE). In the adrenal glands, CE serves as a substrate reservoir for steroid biosynthesis. At low doses/exposures, ATR-101 treatment results in reduction of the CE reservoir and leads to reduced synthesis of adrenal steroids. Higher doses/exposures of ATR-101 cause further disruption of the normal FC/CE ratio which leads to endoplasmic reticulum stress and activation of the unfolded protein response. If left unresolved, this cascade results in apoptosis. The results present a clear molecular understanding of the dose-dependent, novel mechanism of action of ATR-101.

Two proof of concept dog studies have been conducted which validate the mechanism of action studies.[10] The first study in normal beagle dogs (N=3) were administered ATR-101 at 3 mg/kg/day for 7 days, followed by 30 mg/kg/day for 7 days. At the conclusion of the study, adrenal CE levels were markedly decreased and there were dose-and time-dependent decreases in the levels of all adrenal steroids and steroid intermediates tested. The second study was conducted in dogs with naturally-occurring CS. Ten dogs with confirmed CS (three adrenal and seven pituitary etiology) were treated as follows: four dogs received 2 weeks of treatment (3 mg/kg/day x 1 week, followed by 30 mg/kg/day x 1 week); six dogs received 4 weeks of treatment (3 mg/kg/day x 1 week, followed by 30 mg/kg/day x 3 weeks). Nine out of 10 dogs experienced reductions in ACTH-stimulated cortisol concentrations. The mean reduction in post-ACTH stimulated cortisol concentration was 51.5% at the time of study completion. ATR-101 was well tolerated in both dog studies with no meaningful safety issues identified. These studies, along with the *in vitro* mechanism of action studies, support the use of ATR-101 in endocrine diseases of adrenal dysfunction.

Additional evidence of the adrenal-specific effects of ATR-101 comes from 4-week and 13-week dog toxicity studies. In the 13-week dog study, nine of 12 animals (four males, five females) at 30/20 mg/kg BID and three of eight animals (one male, two females) at 10/7.5 mg/kg BID exhibited clinical signs consistent with adrenal insufficiency. The earliest presentation occurred on Day 17. Replacement glucocorticoid (GC) and mineralocorticoid (MC) therapy with subcutaneous prednisone and fludrocortisone

resulted in marked clinical improvements. Similar but less robust effects (e.g. no changes in basal cortisol) were observed in the 4-week study and replacement GC/MC therapy was not required. ATR-101-related gross pathologic changes consisted of bilaterally small adrenal glands in both sexes at ≥3 mg/kg BID which correlated with atrophy of the adrenal cortex microscopically. Both 4-week and 13-week studies suggested that the effects of ATR-101, even at the higher doses, are partially reversible. The decreases in adrenal function (decreases in basal and ACTH-stimulated cortisol measurements), decreased adrenal weights and histologic changes, were all anticipated based upon published studies.[11, 12]

In addition to the nonclinical development program, ATR-101 is currently being tested in a Phase 1, first-in-human, maximum tolerated dose (MTD) study, in ACC. ACC is a rare, but highly malignant and aggressive cancer. ATR-101 doses for this indication are markedly higher (i.e. currently approximately 97.9 mg/kg/day) and are targeted for apoptotic effects. Mean AUC_{0-24} values as high as ~45,000 ng·hr/mL have been observed with acceptable toxicity (i.e. MTD has yet to be defined).

In summary, ATR-101 presents an intriguing spectrum of dose-dependent therapeutic options ranging from inhibition of adrenal steroidogenesis at lower doses to apoptotic effects at higher doses. The use of ATR-101 for the treatment of CAH presents a novel therapeutic approach.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the efficacy and safety of orally administered ATR-101 in subjects with CAH.

2.2 Secondary Objectives

The secondary objectives of this study are:

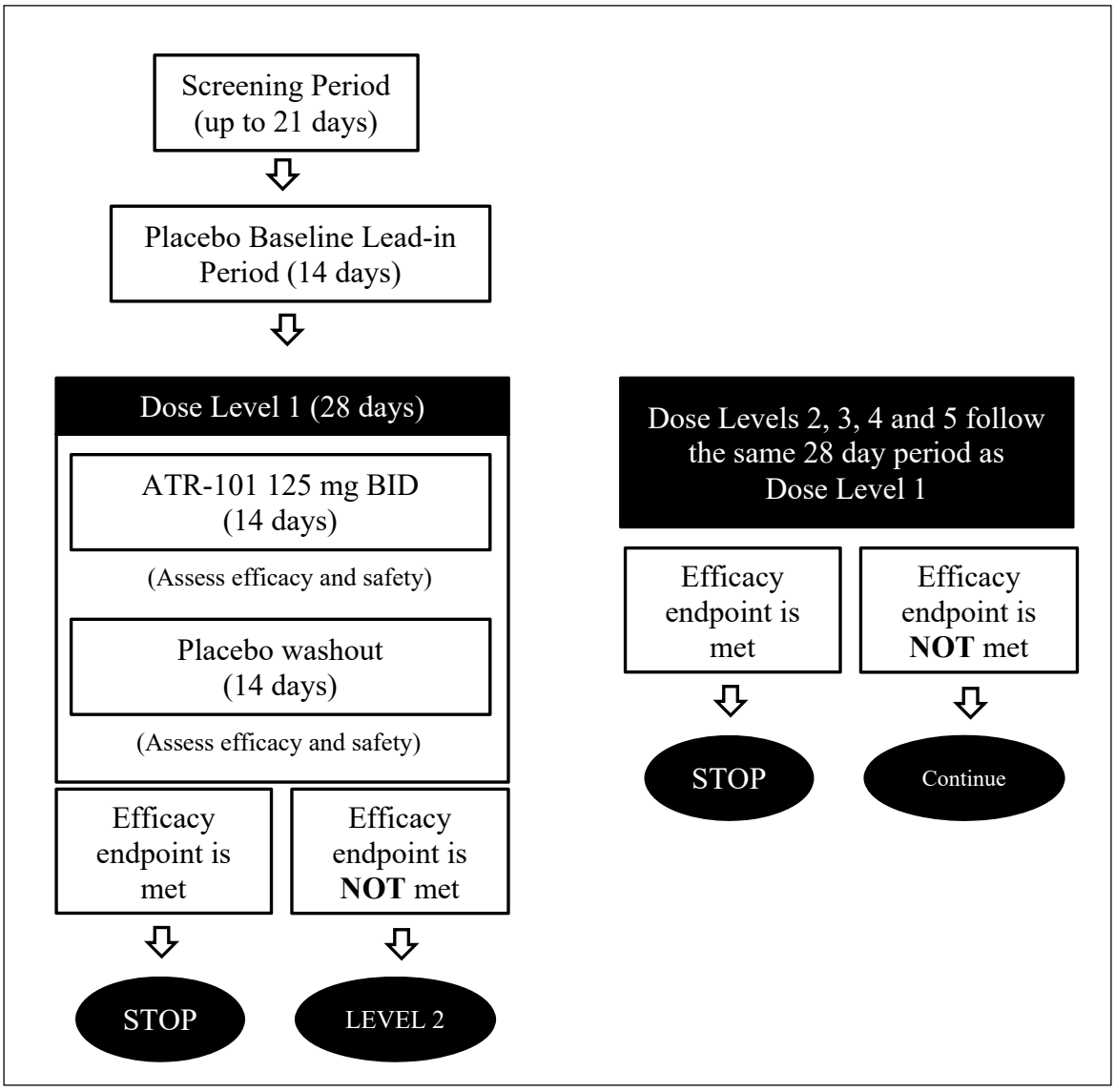
- To evaluate the changes in adrenal cortical steroids and steroid intermediates
- To evaluate the changes to the hypothalamic-pituitary-adrenal axis (via ACTH)
- To evaluate the pharmacokinetics (PK) of ATR-101

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a multicenter, single-blind, multiple dose study of ATR-101 with a placebo washout component. A minimum of nine subjects will be enrolled with the potential to add an additional eight subjects. The study design is presented in Figure 1.

Figure 1 Study Design



Each subject will complete a Screening Period of up to 21 days to assess inclusion and exclusion criteria. Baseline status will be established with a 14 day single-blind, placebo Lead-in Period. Exogenous GC and MC replacement therapy must be maintained

throughout the duration of the study. Each dose level will last for a total of 28 days (see Figure 2). All subjects will start at Dose Level 1, ATR-101 125 mg BID, for 14 days. Efficacy and safety will be assessed after the 14 day ATR-101 treatment period (on the morning of day 15). Immediately after the completion of the ATR-101 treatment period, a 14 day single-blind, placebo Washout Period (placebo matching ATR-101 125 mg) will take place. The efficacy assessment obtained on day 15 will be reviewed by the Principal Investigator (PI) or Sub-investigator (SI) to determine if the subject has met the primary outcome measure or whether the subject should continue to the next dose level (if there are no safety issues).

Figure 2 28 Day Sequence for Each Dose Level

ATR-101 BID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Placebo BID	**Day 15**	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28

Subjects will return to the study center after completion of the 14 day placebo Washout Period and will follow one of two actions based upon **day 15** efficacy results:

- If the primary outcome measure is met (i.e. **17-OHP ≤ 2 x ULN**) the subject completes the Final Study Visit
- If the primary outcome measure is **not** met (i.e. **17-OHP > 2 x ULN**) the subject continues to the next dose level

Table 1 presents the 5 ATR-101 Dose Levels. Dose Levels 2, 3, 4 and 5 will follow the same procedures as Dose Level 1 (i.e. treatment with ATR-101 for 14 days, followed by the placebo Washout Period of 14 days). A subject may receive a minimum of one dose level (Level 1) or a maximum of 5 dose levels (Level 1-5), along with the corresponding placebo Washout Periods.

Table 1 ATR-101 Dose Levels.

Dose Level	ATR-101 Dose	Total Daily Dose
1	125 mg BID	250 mg
2	250 mg BID	500 mg
3	500 mg BID	1000 mg
4	750 mg BID	1500 mg
5	1000 mg BID	2000 mg

3.1.1 Screening Period

Each subject will have a Screening Period of up to 21 days. The Screening Period will assess whether a subject is eligible to participate in the study. All Inclusion and Exclusion criteria will be assessed during this period. The 21 day period provides flexibility to complete laboratory tests and clinical assessments.

3.1.2 Baseline Lead-in Period

Eligible subjects will enter a placebo Baseline Lead-in Period. This 14 day period allows subjects to get accustomed to being in a clinical trial (e.g. avoiding prohibited medications) and taking investigational medicinal product (IMP) on a regular basis. This period also provides an opportunity to develop a more accurate assessment of adrenal steroids and steroid intermediates and documentation of exogenous steroid replacement therapy (GC and MC).

In order to obtain unbiased information, the subjects will not know that the tablets received are placebo and do not contain active drug substance (ATR-101). Placebo tablets for this period will look identical to ATR-101 125 mg tablets (i.e. Dose Level 1). However, the study center personnel will be aware that the tablets are placebo.

At the conclusion of the Baseline Lead-in Period, subjects will be assessed for protocol compliance, including IMP compliance (tablet counts) and whether it is appropriate to proceed in the study.

3.1.3 Dose Level 1 (ATR-101 125 mg BID and matching placebo)

All subjects will start at Dose Level 1 which uses ATR-101 125 mg tablets dosed twice per day (BID). ATR-101 will be taken for 14 consecutive days.

Efficacy and safety (including laboratory measures and clinical assessment) will be assessed during a study visit after the completion of the 14 day ATR-101 treatment period (i.e. morning of day 15). Subjects should take the last dose of ATR-101 Dose Level 1 on the evening of day 14.

Day 15 (of the dosing period) will be the start of the single-blind, placebo Washout Period. The morning dose for day 15 should be taken from the new bottle dispensed at the day 15

visit. Processing of laboratory tests obtained on day 15 will take place during the fourteen day placebo Washout Period.

Subjects will take a placebo tablet BID. Study site personnel will know that this is a placebo period, but subjects should remain blinded (i.e. not know when they are receiving ATR-101 and when they are receiving placebo).

At the end of the 28 day period (i.e. 14 days of ATR-101 and 14 days of single-blind placebo washout), subjects will return to the study center. Laboratory tests and safety assessments will be conducted at this visit. Prior to this visit, the PI or SI will have reviewed the efficacy and safety laboratory values taken at the end of the ATR-101 treatment period (i.e. day 15). If the primary outcome measure is met (i.e. 17-OHP $\leq$ 2 x ULN) this visit will be designated the Final Study Visit and the subject will not continue to Dose Level 2. However, if the primary outcome measure is not met (i.e. 17-OHP > 2 x ULN) and there are no safety concerns, the subject will continue to Dose Level 2.

3.1.4 Dose Levels 2, 3, 4 and 5

Dose Levels 2, 3, 4 and 5 will follow the same procedures as Dose Level 1. Dose Level 2, (ATR-101 250 mg BID) will be taken for 14 consecutive days. At the completion of the 14 day treatment period, subjects will return to the study center for assessment of efficacy and safety (including laboratory measures and clinical assessment). The 14 day single-blind, placebo Washout Period will then start. After completion of the placebo Washout Period, subjects will return to the study center (laboratory testing and safety assessment will occur) and either a Final Study Visit will take place or the subjects will continue to Dose Level 3. Dose Levels 3, 4 and 5 will follow the same course of action.

3.1.5 Final Study Visit

The Final Study Visit will take place once a subject has met the primary outcome measure at the completion of Dose Levels 1-4 or at the completion of Dose Level 5. This visit will be the final visit to the study center.

3.1.6 Follow-up Visit

Two weeks after the Final Study Visit or Early Termination Visit, a Follow-up Visit will take place. This will consist of a telephone interview with the subject to determine if any safety events need to be reported and to record concomitant medications, especially GC and MC.

3.2 Rationale for Study Design and Dose Levels

CAH is a rare disease with a limited number of potential subjects. Therefore, the study design must derive as much information as possible from each subject while simultaneously presenting as little risk as possible. This study protocol provides the potential for each subject to achieve the primary outcome measure at the lowest possible dose with a minimum duration of exposure (i.e. 14 days per dose level). In addition, the placebo Washout Period

ensures that each subject has returned to baseline status prior to receiving the next highest dose of ATR-101. This period also serves to verify that changes in adrenal steroids and steroid intermediates are due to ATR-101 effects. Thus, this protocol design will generate a robust dataset with a limited number of subjects which can establish proof of concept for the use of ATR-101 in CAH.

The starting dose for all subjects will be ATR-101 125 mg taken BID orally with food. This dose corresponds to approximately 3 mg/kg/day for a 75 kg individual and is intended to be a non-effective dose. While the 3 mg/kg/day dose was efficacious in dog studies, the exposures (i.e. $AUC_{0\text{-}24\ hr}$ mean ~4700 ng·hr/mL) were much higher relative to the projected corresponding exposures in humans. Based on pharmacokinetic modeling from the available human data (ACC subjects and healthy volunteer food effect study[13]), the 125 mg BID dose will provide a steady-state $AUC_{0\text{-}24\ hr}$ of ~2308 ng·hr/mL. Dose Level 2 (250 mg BID) will provide an $AUC_{0\text{-}24\ hr}$ of ~4616 ng·hr/mL. Each subsequent dose level (3, 4 and 5) will increase the ATR-101 dose by 500 mg per day, with projected steady-state $AUC_{0\text{-}24\ hr}$ values of ~9234, 13850 and 18467 ng·hr/mL, respectively. Thus, the projected exposures span a non-effective range up to approximately 4-times the effective exposure observed in the dog studies which allows for potential pharmacokinetic/pharmacodynamic differences between dogs and humans.

The Phase 1 ACC study provides tremendous reassurance for the safety of the doses proposed for this protocol in that $AUC_{0\text{-}24\ hr}$ exposures as well as the duration of treatment have already far surpassed those being proposed. The highest exposures observed (to date) in the ACC study have been ~45,000 ng·hr/mL. These exposures have been well-tolerated and the study will continue to dose escalate until the maximum tolerated dose (MTD) or Phase 2/3 dose has been identified.[10] In addition, the average duration of exposure was 60 days across the 11 dose cohorts. ATR-101 has been extremely well tolerated in a patient population that is markedly less robust (all have advanced stage cancer and most have undergone multiple prior treatment regimens) relative to the CAH patient population.

The dosing rationale is further supported by the 13-week dog toxicity study with $AUC_{0\text{-}24\ hr}$ margins relative to the dog No Observed Adverse Effect Level (NOAEL) of 4.0 to 31.9 for the highest (1000 mg BID) and lowest (125 mg BID) ATR-101 doses planned, respectively.

CAH patients will enter the study with elevated 17-OHP values indicating clinical challenges in obtaining optimal GC replacement therapy. CAH patients can have extremely high 17-OHP levels, >300 nmol/L (10,000 ng/dL), relative to reference laboratory normal ranges (<6 nmol/L; <200 ng/dL)[14]. However, complete normalization of 17-OHP is not the therapeutic goal, as this typically results in overtreatment with GC.[14] Acceptably treated CAH patients generally have mildly elevated steroid levels.[14] Thus, the overall goal of the study is to show clinically meaningful decreases in 17-OHP that are aligned with clinical practice goals and to demonstrate similar decreases in the androgen pathway (i.e. androstenedione, testosterone, DHEA, DHEA-S). The study design and dose levels are appropriately supported by existing clinical and nonclinical data.

3.3 Efficacy Assessment

Efficacy will be assessed by changes in adrenal steroids and steroid intermediates. 17-OHP will serve as the **primary outcome measure** as this adrenal steroid intermediate is used diagnostically and to aid in the management of exogenous GC replacement therapy in clinical practice. However, absolute target values for 17-OHP or androgens do not currently exist in treatment guidelines put forth by any of the medical societies. The entry criteria for 17-OHP is set at $\geq$ 4 x ULN which is intended to enroll subjects that are not optimally controlled while on exogenous steroid replacement therapy. It is anticipated that most subjects will enter with 17-OHP levels markedly higher than 4 x ULN. The primary efficacy outcome measure will be aligned to the clinical goal of achieving a mildly elevated 17-OHP level which for this study is defined as $\leq$ 2 x ULN. However, other key efficacy parameters in the androgen pathway (androstenedione, testosterone, DHEA, DHEA-S) will also serve to define efficacy.

The majority of CAH subjects will enter the study on both GC and MC replacement (75% of classic CAH subjects have deficiencies in both pathways). However, plasma renin activity (PRA) and aldosterone will be assessed to determine the potential impact on the MC pathway.

ACTH levels will be assessed to determine potential effects on the hypothalamic-pituitary-adrenal (HPA)-axis. Glucocorticoid replacement doses are expected to remain unchanged so no significant changes in ACTH are anticipated. Confirmation of stable ACTH levels associated with decreases in 17-OHP and androgens will help to establish the ATR-101 pharmacodynamic effects. Increased GC levels, secondary to decreased hepatic metabolism (ATR-101 CYP3A effect; see Section 5.4), could potentially lead to decreased ACTH and subsequently decreased 17-OHP levels. This could potentially confound assessment of direct ATR-101 effects on adrenal steroid and steroid intermediate synthesis. Therefore, assessment of GC levels will also be done during the study.

3.4 Safety Assessment

Safety will be assessed by monitoring adverse events, changes in physical examination (including vital signs), changes in electrocardiograms (ECGs), and changes in laboratory parameters. Safety assessment will take place every 2 weeks during study participation.

CAH subjects will have entered the study on stable GC and MC regimens. Monitoring and management of replacement steroids should continue per usual clinical practice.

4 STUDY POPULATION SELECTION

4.1 Study Population

The study population will consist of adult men and women with a documented history of CAH due to classic 21-OHD. Historical documentation of molecular genetic testing for CYP21A2 deficiency or other appropriate documentation of diagnosis (e.g. elevated 17-OHP) should be provided. The documentation of chronic GC and/or MC replacement therapy should also be provided. The historical biochemical profile for adrenal steroid and steroid intermediates, along with ACTH levels may also provide supportive documentation. Newly diagnosed CAH subjects are not eligible since participation in a clinical study may not be consistent with optimal medical management.

4.2 Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

1. Aged 18 to 80 years at the time of signing the informed consent form
2. Men or women with classic CAH due to 21-OHD
3. Documented historical diagnosis of CAH due to 21-OHD based on any one of the following criteria:
    a. Documented genetic mutation in the CYP21A2 enzyme consistent with a diagnosis of classic CAH
    b. Historical documentation of elevated 17-OHP (e.g. in infancy or following a cosyntropin/ACTH stimulation test)
4. Biochemical marker of disease status at Screening and Baseline Lead-in Period
    a. 17-OHP ≥4 x ULN

        (Note: The test may be repeated one time at the Investigator's discretion if there is reason to suspect the results are inaccurate.)

5. Chronic glucocorticoid replacement therapy for at least 6 consecutive months prior to signing Informed Consent
6. Stable glucocorticoid and mineralocorticoid regimen for at least one month prior to signing Informed Consent (per Investigator discretion)
7. Female subjects of childbearing potential (who are not surgically sterile or who have not been naturally postmenopausal for at least 12 consecutive months) must test negative in the urine pregnancy test prior to the initiation of IMP
8. Female subjects of childbearing potential must consent to use two medically acceptable methods of contraception throughout the study period and for 30 days after the last dose of study treatment
9. Males must be sterile (e.g. status-post vasectomy) for 6 months prior to informed consent or agree to use two approved methods of contraception where one method must include a barrier method
10. Females must have negative serum pregnancy test at Screening

11. Able and willing to sign the informed consent form prior to Screening and be willing to comply with all aspects of the study protocol

4.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participation in the study:

1. Non-classic CAH
2. Other causes of adrenal insufficiency such as Addison's disease; adrenalectomy etc.
3. Surgery within the previous three months prior to screening or planned surgery during study participation. Minor procedures are permitted (e.g. removal of skin tags or other minor dermatological procedures)
4. Abnormal laboratory tests at Screening:
    - ALT or AST >2 x ULN
    - Bilirubin >1.5 x ULN
    - Serum Creatinine >1.5 x ULN
5. History of active cancer requiring medical or surgical therapy within the past 6 months (with the exception of successfully treated non-metastatic basal cell or squamous cell carcinoma of the skin and carcinoma in-situ of the cervix)
6. Significant comorbid medical condition(s) that may preclude compliance with the study protocol or such that study participation may not be in the subject's best medical interest. Medical conditions may include (but are not limited to) those of the cardiovascular, respiratory, gastrointestinal, renal, hepatic, central nervous system (CNS) or immune system [(e.g., human immunodeficiency virus (HIV)], Myocardial infarction (MI) or cerebrovascular accident/transient ischemic attack (CVA/TIA) within the past 6 months
7. An average QTc value (Fridericia correction) of > 470 msec at Screening
8. Psychiatric illness such that comprehension of the informed consent or compliance with the study protocol may be impaired
9. Positive screen for HIV, Hepatitis B surface antigen or Hepatitis C antibody at Screening
10. Pregnant or lactating females
11. Current or ongoing use of any prohibited concomitant medications (Section 5.3)
12. History of substance abuse within the past 2 years prior to informed consent
13. Positive toxicology screening test for substances of abuse
14. Known allergy to ATR-101
15. Treatment with another investigational drug or device within 3 months prior to Screening

5. STUDY TREATMENT

5.1 Assignment of Subject Identification Numbers

Once the subject has signed the ICF at Screening, site personnel will assign a subject identification number (ID). The subject ID will include the site number (3 digits), and 3 digit subject number, assigned sequentially starting with 001. This number and the subject's initials will be utilized to identify the subject throughout the study period. Subject identification numbers will only be assigned to one subject, i.e., if a subject discontinues study treatment early, their subject identification number will not be used for a new subject.

5.2 Description of Treatment

ATR-101 Drug Product Tablets are supplied, in doses of 125 mg, 250 mg and 500 mg and ATR-101 Drug Product Placebo Tablets which are identical in size shape and color to the 125 mg, 250 mg and 500 mg ATR-101 Drug Product Tablets.

Each bottle will contain sufficient ATR-101 Drug Product Tablets or ATR-101 Drug Product Placebo Tablets (i.e. 38 tablets) to provide dosing for a 2-week period with extra tablets to account for scheduling visit windows. The tablet formulations are described in Table 2.

Table 2 Tablet Formulations.

ATR-101 Drug Product Tablets	
Study Product:	ATR-101 Drug Product Tablets
Drug Product:	ATR-101 with mannitol, microcrystalline cellulose, croscarmellose sodium, pregelatinized starch, hypromellose, magnesium stearate, and Opadry II white.
Strengths:	125 mg, 250 mg, and 500 mg
Route of administration:	Oral
Manufacturer:	Corealis Pharma, Inc.
ATR-101 Drug Product Placebo Tablets	
Study Product:	ATR-101 Drug Product Placebo Tablets
Drug Product Placebo:	Microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, and Opadry II white in a film-coated tablet
Images:	Exact matching image to ATR-101 Drug Product 125 mg, 250 mg, and 500 mg Tablets
Route of administration:	Oral
Manufacturer:	Corealis Pharma, Inc.

A certificate of analysis for each lot of ATR-101 Drug Product Tablets and ATR-101 Drug Product Placebo Tablets will be provided to the Sponsor prior to shipment. For more information regarding the manufacturer and fill/finish, refer to the most recent version of the Investigator's Brochure.[10]

5.3 Treatments Administered

The Baseline Lead-in Period will administer placebo tablets for 14 days. The tablets will match the ATR-101 125 mg tablets and be administered BID.

Starting with Dose Level 1, each dose level will consist of a 28 day dosing regimen consisting of 14 days of ATR-101 treatment followed immediately by 14 days of matching placebo washout. Bottles containing 38 tablets will be supplied for each 14 day dosing period which allows for 5 extra days of dosing to accommodate visit windows (see Pharmacy Manual). Table 3 presents the tablets and dosing regimen by Dose Levels.

Table 3 ATR-101 Dose Levels and Tablet Doses.

Dose Level	14 day Treatment Period		14 day Washout Period	
	ATR-101 Tablet Strength Dispensed	ATR-101 Dosing	Placebo Tablet Dispensed	Placebo Dosing
1	125 mg	1 tablet BID	Matching 125 mg tablet	1 tablet BID
2	250 mg	1 tablet BID	matching 250 mg tablet	1 tablet BID
3	500 mg	1 tablet BID	matching 500 mg tablet	1 tablet BID
4	250 mg and 500 mg	1 tablet each BID	matching 250 mg and 500 mg tablets	1 tablet each BID
5	500 mg	2 tablets BID	matching 500 mg tablet	2 tablets BID

Only the doses presented in Table 3 will be permitted. No other doses will be allowed.

5.3.1 Timing and Administrative Dosing Conditions

IMP should be taken approximately 12 hours apart (twice per day dosing). The time of day that the dose is taken should be as consistent as possible (e.g. every morning at 8AM and every evening at 8PM).

IMP should be taken immediately after consumption of food. No specific food contents are required and subjects should maintain usual eating practices. If a full meal is not possible or not aligned with a subject's usual eating practices, a light snack should be consumed prior to taking IMP.

The first dose of each bottle will be administered at the site prior to PK sampling. Subjects will be provided with food to consume prior to dose administration. See Pharmacy Manual for more details.

Grapefruit, grapefruit juice and other foods containing grapefruit should be avoided to prohibit possible interactions in the metabolism of ATR-101 or other concomitant medications.

5.3.2 Advancement to the Next Dose Level

If a subject does not meet the primary outcome measure (i.e. 17-OHP $\leq$2 x ULN) at the completion of a given dose level, advancement to the next higher dose level should take

place if there are no safety issues. There is the possibility of receiving a maximum of 5 dose levels (Levels 1-5).

A subject must follow the dose levels in numerical sequence (i.e. Dose Level 1 followed by Dose Level 2 etc.). Skipping a dose level is prohibited and may result in termination from the study.

5.3.3 Changes in Daily Dose are Not Permitted

Subjects must adhere to the daily dose of IMP according to each dose level. Deviation from the protocol regimen is not permitted. Specifically, lower daily doses are not permitted for any reason. If a subject cannot tolerate a given dose due to a safety issue then early termination from the study is the recommended course of action. Decreasing to a lower dose (e.g., once per day dosing or taking fewer tablets at each AM or PM dose) or to the previous dose level is not permitted. Additionally, increased doses are not permitted at any time other than those associated with the protocol design (i.e. advancing to the next dose level). Taking more tablets at a given dose is not permitted under any circumstances.

5.3.4 Missed Doses

If a subject forgets to take a dose on a given day (e.g. the AM dose was not taken), a "make up" dose should not be taken. In general, if more than 4 hours have passed beyond the usual time of day when the dose is taken, that particular dose should not be taken.

5.3.5 Withholding IMP

A "drug holiday" or "dosing break" is not recommended due to the relatively short 28 day period per dose level. However, withholding IMP may be possible under specific conditions. For example, a subject may have a medical event (e.g., dental emergency) that is considered to be transient or reversible within a few days that may potentially have a preferred outcome by withholding IMP. Depending on the specific circumstances, additional days of dosing may be possible to complete a 14 day dosing cycle. The PI or SI should discuss potential events of this nature with the study medical monitor and Sponsor prior to the event if at all possible.

5.3.6 Compliance with IMP

The IMP is to be dispensed by qualified personnel at the study center and only to subjects enrolled in the study. Subject compliance to therapy will be assessed at scheduled study visits by counting the number of tablets returned. Treatment compliance is defined as the subject taking 80% to 120% of the study tablets to be taken during the dosing period for a given dose level. Subjects found to be outside of the definition of compliance may be discontinued from the study at the discretion of the PI or SI.

5.3.7 Blinding

Subjects will be blinded to treatment beginning with the Baseline Lead-in Period that will use placebo tablets that appear identical to ATR-101 125 mg. Dose levels 1 to 5 are split into two weeks of active treatment (ATR-101) followed by two weeks of treatment with matching placebo (Washout Period).

5.3.8 Concomitant Therapies

Use of concomitant treatments should be kept to a minimum during the study. Any therapies given other than IMP (including blood transfusions, parental fluids, and other medications) are to be considered a concomitant medication and must be documented on the electronic case report form (eCRF).

GC and MC are critical concomitant medications used in CAH and will be captured on a separate eCRF from other concomitant therapies.

5.3.9 Glucocorticoid and Mineralocorticoid Replacement for CAH

Subjects must continue to receive GC and MC according to individual regimens established prior to entering the study. The regimen should remain as stable and unchanged as possible to minimize potential confounding effects on efficacy outcome measures. However, changes are permitted to ensure subject safety. It is not expected that ATR-101 will have a direct effect on GC replacement therapy as the GC synthetic pathway is already compromised in CAH. Therefore, decreasing cortisol precursors (i.e. 17-OHP) should have no effect on glucocorticoid requirements over the 14 day ATR-101 treatment period.

The timing of glucocorticoid replacement therapy may have an impact on the measurement of 17-OHP. Replacement steroids (GC and MC) must not be taken on the mornings when adrenal steroids/steroid intermediates are being assessed (i.e. Day 15) as this could confound efficacy endpoint measures. GC and MC replacement doses may be given after blood samples are obtained for laboratory assessments.

Approximately 75% of CAH subjects have deficiency in the mineralocorticoid pathway in addition to the GC pathway.[5] Thus, the majority of subjects in this study are anticipated to be on MC replacement. ATR-101 inhibition of the MC pathway for these subjects should not have an effect on MC replacement therapy. Subjects that enter the study with sufficiently intact endogenous MC production may be impacted by suppression of this pathway by ATR-101. However, pharmacological doses of GC, especially shorter acting ones such as hydrocortisone, also confer MC activity and the need for replacement MC is not usually required.[14]

5.3.10 Prohibited Medications

ATR-101 is metabolized by several cytochrome P450 enzymes (CYPs) including CYP3A4. Concurrent use of drugs known to be metabolized by this pathway should be avoided. (Appendix 4).

ATR-101 is most soluble in acidic conditions. Proton pump inhibitors are prohibited and calcium preparations and antacids should not be used 2 hours before to 2 hours after ATR-101 administration.

Grapefruit and grapefruit juice are known to inhibit CYP3A4. Grapefruit products should be avoided.

Concurrent use of medications that are known to prolong the QT/QTc interval at therapeutic exposures are not permitted while on this protocol (Appendix 3, List A). Drugs that only cause prolonged QT intervals in unusual circumstances (e.g., overdosage) may be used with caution (Appendix 3, Lists B and C).

Preclinical data indicate that ATR-101 may compete with certain drugs for P-glycoprotein in the intestinal lumen. The drugs listed in Appendix 5 should be used with caution, as they may have an impact on the level of ATR-101 or vice versa. Note that some of these drugs may also appear in Appendices 3 or 4, and may be contraindicated by those properties.

5.4 Restrictions, Precautions and Warnings

Preclinical studies have identified adrenal suppression with apoptotic histologic changes. Such changes were associated with exposure levels much higher than what is anticipated for this study. However, occurrence of such changes is a possibility. The investigative staff should be familiar with the warnings and precautions for ATR-101 as presented in the Investigator's Brochure.[10]

ATR-101 is metabolized by CYP enzymes and is an inhibitor and inducer of CYP enzymes, and as a consequence, ATR-101 may interfere with the metabolism of other medicines also metabolized by CYP, especially CYP3A4. The metabolism of ATR-101 may be affected by other medicines or foods such as grapefruit products that inhibit CYP3A4. Such medicines and grapefruit products must be avoided. ATR-101 is an inhibitor of P-gp and OATP1B1.

Glucocorticoids are CYP substrates so there is the potential for increased GC levels. Glucocorticoid levels will be measured during the course of the study.

5.5 Packaging and Labeling

The formulation and bulk packaging of ATR-101 will be conducted according to standard procedures. The IMP will be packaged and labeled by the Sponsor's designated contract packager and labelled according to regulatory requirements. IMP will be provided to sites as kits containing a total of 15 bottles. Each kit will provide both ATR-101 and matching placebo for the Baseline Lead-in Period as well as Dose Levels 1-5.

5.6 Storage and Accountability

Study drug must be kept in a secured location and stored at controlled room temperature at the study site within its original container. A daily temperature log for monitoring of proper storage conditions must be maintained by the site.

Access to drug must be restricted to designated study personnel only. Under no circumstances should the PI/SI or site personnel supply study product to other Investigators or clinics, or allow the supplies to be used other than as directed by this protocol without written authorization from the Sponsor. The PI (or delegate) must maintain records of the delivery of the study drug to the study site, the inventory at the site, use for each subject, and return of the study drug to a delegate of the Sponsor or destruction. Total study site accountability will be conducted at the end of the study and the PI/SI (or delegate) must explain all discrepancies. A Site Drug Accountability Log will be supplied by the Sponsor. This log must be kept current and should contain the following information:

- Identification (subject ID number and initials) of subject to whom the study drug was dispensed
- The dates and kit numbers for dispensed study drug
- Initial inventory on receipt of drug at the site
- Final inventory on completion of the study

All records and inventory must be available for inspection by the clinical study monitor. Additional details on the storage and handling of ATR-101 will be provided in the Pharmacy Manual.

5.7 Investigational Product Retention at Study Site

At the time of study close-out, the Sponsor will direct the site regarding the disposition of any unused IMP whether it is to be destroyed or be returned to the Sponsor's designated location. The Sponsor will assure that a final report of drug accountability is prepared and maintained by the investigative site. Additional details on the inventory of IMP will be provided in the Pharmacy Manual.

6 STUDY PROCEDURES

6.1 Allowable Variation in Study Visits

Visits and the protocol defined days for each specific period/procedure should be adhered to as much as possible. However, there is flexibility to allow for logistical considerations and to accommodate scheduling conflicts. Variations to the protocol defined visit dates (i.e. study days) may be allowed depending upon the specific circumstances.

- Screening Visit. Up to 21 days.
- Baseline Lead-in Period. A minimum of 14 days must be completed but an additional 3 days beyond the 14 day period is allowed.
- Dose Levels 1-5
    - ATR-101 Treatment Period
        - A minimum of 11 days (22 doses) of ATR-101 must be taken prior to drawing blood samples for an assessment of efficacy and safety. Therefore, sample collection cannot occur earlier than the 12th day of dosing for a given dose level.
        - A maximum of + 3 days is allowed beyond the scheduled 14 day ATR-101 treatment period.
    - Placebo Washout Period
        - A minimum of 11 days (22 doses) of placebo must be taken prior to drawing blood samples for an assessment of efficacy and safety. Therefore, sample collection cannot occur earlier than the 12th day of dosing for a given dose level.
        - A maximum of + 3 days is allowed beyond the scheduled 14 day placebo treatment period.
- Follow-up visit. A window of $\pm$ 3 days is permitted.

6.2 Informed Consent

Prior to any study specific screening evaluations and clinical trial participation, written informed consent will be obtained from each subject to be involved in the clinical trial by using the Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved ICF. Potential subjects will be informed in detail about the study product to be administered, and the nature of the clinical investigation with its risks and discomforts to be expected. The subjects will also be instructed that they are free to withdraw their consent and discontinue participation in the clinical trial at any time. The PI/SI will verify that the subject has granted consent. Each subject will be given a copy of the signed ICF. Certified translated ICFs will be provided by the Sponsor in those languages required or requested by investigational sites.

6.3 Eligibility

Review of study inclusion/exclusion criteria will be done at the Screening visit, at the start of the Baseline Lead-in Period and reconfirmed prior to receiving the first dose of IMP (Dose Level 1). Noncompliance with IMP (i.e., not meeting 80-120%) during the Baseline Lead-in Period will result in Early Termination from the Study.

6.4 Medical History

A complete medical history will be obtained at the Screening visit. The following systems will be reviewed: head, eyes, ears, nose, and throat (HEENT), respiratory, cardiovascular, gastrointestinal/hepatobiliary (specifically, a history of liver dysfunction or the presence of hepatomegaly or splenomegaly), genitourinary/ reproductive, musculoskeletal, neurological, psychiatric, endocrine/metabolic, blood/lymphatic, dermatologic, and immunologic. Past surgeries will also be recorded.

6.5 Physical Examination

A complete physical examination will be obtained at Screening and the Final Study visit or Early Termination Visit.

An abbreviated (brief) physical exam will be completed as follows:

- Prior to the start of the Baseline Lead-in Period
- Prior to dosing on the first day of every Dose Level (active treatment)
- Prior to starting the placebo Washout Period at each Dose Level

The following systems will be examined for a complete physical examination: HEENT, respiratory, cardiovascular, gastrointestinal/hepatobiliary (specifically the presence of hepatomegaly or splenomegaly will be assessed), genitourinary/ reproductive, musculoskeletal, neurological, psychiatric, endocrine/metabolic, blood/lymphatic, dermatologic, and immunologic. On a brief physical examination, the following systems will be examined: respiratory, cardiovascular, gastrointestinal/hepatobiliary and any areas pertinent to any adverse events.

6.6 Vital Signs

Vital signs, including oral or tympanic temperature, systolic and diastolic blood pressure, pulse, respiratory rate, and body weight will be measured at Screening, at the start of the Baseline Lead-in Period, at Day 1 pre-dose and at 1, 2 and 4 hours post-dose for each dose level, at Day 15 pre-dose for each dose level and at the Final Study Visit or Early Termination Visit. Height will be measured at Screening.

6.7 Electrocardiography and Determination of QTc

All subjects will have 12-lead ECG assessments at Screening, Day 1 pre-dose and 2 hours post-dose for each dose level, Day 15 pre-dose for each dose level, and at the completion of the Placebo Washout Period on Day 29 (this ECG could serve as the pre-dose ECG, Day 1, if the subject is moving to the next dose level or as the ECG for the Final Study Visit or Early Termination Visit). ECGs will be stored for later analysis if needed.

If the QTc is greater than 470 msec on the Screening ECG, three consecutive ECGs will be obtained and the QTc values corrected by the Fridericia method will be averaged. If the average is greater than 470 msec, the subject will be ineligible for the study. In the event of an abnormal ECG (especially in the setting of an intraventricular conduction delay) that makes QTc determination unreliable by standard means, the QT interval will be corrected by the method of Rautaharju et al.[15]

6.8 Prior and/or Concomitant Medication Assessments

Prior and concomitant therapies will be documented throughout the study and include any treatments that have been taken within 30 days prior to the first placebo dose in the Baseline Lead-in Period until the Follow-up Visit. Any treatments given during the clinical trial other than IMP, including blood transfusions, parental fluids, herbal preparations, and all pre-medications are considered concomitant therapy and must be recorded on the eCRF. Following completion of the Final Study Visit, only concomitant medications related to follow-up of an AE should be recorded on the eCRF. All prior and concomitant medications will be coded to the latest version of the World Health Organization (WHO) Drug Dictionary.

6.9 Pharmacokinetic Assessments

Blood samples will be collected to profile the levels of ATR-101 and its metabolites at multiple days and times throughout the study. Assessment of ATR-101 levels may help to determine or establish pharmacokinetic and pharmacodynamic relationships. ATR-101 exposure levels may also help in the assessment of safety events. Sampling time points are presented for each of the applicable study days in Table 4. Samples for PK analysis will be taken prior to the first dose of ATR-101 (for each dose level) and up to 4 hours, post-dose. This time period is designed to capture the C_{max} (T_{max} is approximately 2 hours) and a few additional time points. Following the completion of the 14 day ATR-101 dosing period a single PK sample will be collected to assess trough levels of ATR-101 (morning of day 15). Subjects will then enter the 14 day placebo Washout Period. After completion of the placebo Washout period, subjects will either proceed to the next Dose Level and perform the same PK sampling as Day 1, or subjects will complete the Final Study Visit and do the same PK sampling as Day 15.

PK results will not be used to determine dose escalation. Approximately 4 mL of blood will be drawn at each sampling time point.

Table 4 Pharmacokinetic Sampling Time Points.

Visit	Sampling Time Point
Dose Level N, Day 1	Pre-dose, post-dose at 1, 2, 3, and 4 hours
Dose Level N, Day 15	Pre-dose, single blood draw

N=Dose Levels 1-5

6.10 Pharmacodynamic Assessments

The effects of ATR-101 on adrenal steroid synthesis will be assessed at each study visit by measuring steroids and steroid intermediates across the mineralocorticoid, glucocorticoid and androgen pathways. Plasma renin activity (PRA) is not an adrenal steroid, but it will be measured as an assessment of mineralocorticoid activity. In addition, ACTH levels will be assessed to determine the potential impact on the HPA-axis.

Pharmacodynamic measures:

- Glucocorticoid pathway: 17-OHP, progesterone
- Mineralocorticoid pathway: 11-deoxycorticosterone (11-DOC); PRA; aldosterone
- Androgens: androstenedione, total testosterone, free testosterone, DHEA, DHEA-S
- HPA-axis: ACTH

6.11 Timing of Pharmacodynamic Blood Samples and Dosing of Replacement Steroids

Adrenal steroids and steroid intermediates have a diurnal rhythmicity with peak 17-OHP occurring at around 8:00 AM. Thus, it is extremely critical that the timing of sample collection for efficacy endpoints and dosing of replacement steroids be precise and consistent. Every attempt should be made to collect the sample between 8:00-9:00 AM, but no later than 10:00AM. Study visits that require blood sample collection for steroid hormones, must adhere to the following:

- Morning dose of replacement GC and MC must not be given until after the blood sample is collected
- Blood sample collection must be done prior to **10:00 AM**

If both of these conditions are not met, the blood sample for steroid hormones must not be collected; the visit procedures should not be performed and the study visit must be rescheduled for the next day or as soon as feasible. The subject should continue taking study drug with the last dose occurring the evening prior to the rescheduled visit.

Dosing of GC and MC may take place after collection of blood samples for adrenal steroids and steroid intermediates.

Approximately 20 mL of blood will be collected for steroid hormone testing and approximately 10 mL of blood will be collected for testing synthetic glucocorticoid levels. If exogenous GC levels are suspected of confounding the efficacy outcome measures, additional testing may be performed. Further details on sample collection and handling are provided in the Laboratory Manual.

6.12 Adverse Events, Serious Adverse Events, and Reporting

6.12.1 Adverse Events, Severity, and Relationship

Adverse Event (AE): Any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with IMP.

- All AEs reported for enrolled subjects during the clinical study will be recorded on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study consent. AEs in clinical investigation subjects include any change in the subject's condition. This includes symptoms, physical findings, or clinical syndromes.
- An abnormal laboratory value may be considered an AE if the identified laboratory abnormality leads to any type of intervention whether prescribed in the protocol or not. It is up to the PI/SI to determine whether an abnormal laboratory value constitutes an AE. If an abnormal laboratory value is caused by a disease process, the disease process and not the laboratory abnormality should be listed as the AE (e.g., if new onset viral hepatitis is causing elevated alanine aminotransferase (ALT), hepatitis and not the elevated ALT should be listed as the AE).
- Examples of laboratory abnormalities that should be considered AEs include those that result in withdrawal of the study treatment, withholding study treatment pending some investigational outcome, or additional concomitant treatment. All laboratory abnormalities considered to constitute an AE should be recorded on the appropriate AE page of the eCRF. Laboratory abnormalities do not need to be listed as separate AEs if they are considered to be part of a clinical syndrome that is being reported as an AE. It is the responsibility of the Investigator to review all laboratory findings in all subjects. Abnormal values should be commented upon as to clinical relevance or importance on the eCRF or the laboratory report as appropriate. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.
- AEs will be collected from the time the subject signs informed consent until 30 days after last dose of IMP.
- Every effort must be made by the PI/SI to categorize each AE according to its severity and its relationship to IMP.
- Subjects who develop toxicity on study will be followed until the event resolves, stabilizes or returns to baseline.

6.12.2 Assessing Severity of Adverse Events

The assessment of severity must be based on the Investigator's clinical judgement. Maximum severity should be assigned to one of the following categories:

- **Mild**: An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An AE which is sufficiently discomforting to interfere with normal everyday activities.
- **Severe**: An AE which prevents normal everyday activities.

An AE which is assessed as severe should not be confused with a serious AE. Refer to Section 6.12.5 for the definition of a serious AE.

6.12.3 Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are as follows:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, considering especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of non-study treatment related factors which are known to be associated with the occurrence of the event

Only AEs thought to be caused by IMP should be recorded as "related to IMP".

6.12.4 Classification of Causality

The relationship of an adverse event to the administration of the study drug is to be assessed according to the following definitions:

- No (unrelated, not related, no relation) – The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

- Yes (related) – The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified. The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

Not Related: A causal relationship between the study treatment and the AE is not a reasonable possibility.

Related: A causal relationship between the study treatment and the AE is a reasonable possibility. The Investigator must further qualify the degree of certainty as "**possible,**" "**probable**", or "**definite**."

6.12.5 Serious Adverse Events

6.12.5..1 Definition of Serious Adverse Events

A serious adverse event (experience; SAE) or reaction is any untoward medical occurrence which:

- Results in death
- Is life-threatening (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization

  NOTE: Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as a serious adverse event (SAE) under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness.

- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect.
- Is determined to be an important medical event (at the discretion of the Investigator)

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

The following hospitalizations are not considered to be SAEs because there is no "AE" (i.e., no untoward medical occurrence) associated with the hospitalization:

- Planned hospitalizations required by the protocol
- Hospitalization planned prior to informed consent (where the condition requiring the hospitalization has not changed post study drug administration)

6.12.5..2 Reporting Serious Adverse Events (SAEs)

Initial Reports

All SAEs occurring from the time of informed consent through the early termination/final visit and for 30 days following study drug discontinuation, whichever is longer, must be reported to Medpace Clinical Safety **within 24 hours** of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). All serious adverse events that the investigator considers related to study drug occurring after the 30-day follow-up period must be reported to the Sponsor.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at medpace-safetynotification@medpace.com or call the Medpace SAE hotline (phone number listed below), and fax the completed paper SAE form to Medpace (fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information:

Medpace Clinical Safety
Medpace SAE hotline – USA:
Telephone: +1-800-730-5779, ext. 2999 **or** +1-513-579-9911, ext. 2999
Facsimile: +1-866-336-5320 **or** +1-513-579-0444
e-mail: medpace-safetynotification@medpace.com

Follow-Up Reports

The investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment) or the subject dies.

Within 24 hours of receipt of follow-up information, the investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., subject discharge summary or autopsy reports) to Medpace Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

The Investigator should notify the IRB/ IEC of the occurrence of the SAE, in writing, in accordance with local requirements. A copy of this communication must be forwarded to the clinical research associate (CRA) and filed in the trial master file (TMF).

6.12.5..3 Pregnancy Reporting

Any pregnancy where the estimated date of conception occurred either prior to the study termination visit or within 30 days of last study treatment must be reported. The pregnancy must be reported to Medpace Clinical Safety within 24 hours (from the time the pregnancy is detected). Medpace Clinical Safety will then forward the Exposure In Utero form to the PI or SI for completion.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported, regardless of the length of time that has passed since the exposure to study treatment.

A subject becoming pregnant while on study drug will immediately be withdrawn from the study and early termination study procedures will be performed.

The subject should be followed by the PI or SI until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the PI or SI should notify Medpace Clinical Safety. At the completion of the pregnancy, the PI or SI will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the PU or SI should follow the procedures for reporting an SAE.

6.12.6 Regulatory Reporting of Adverse Events

AEs will be reported to the regulatory authorities in compliance with local and regional law and established guidance by the Sponsor or by a third party acting on behalf of the Sponsor. The format of these reports will be dictated by the local and regional requirements.

6.13 Clinical Laboratory Tests

Blood samples for steroids and steroid intermediate testing, synthetic glucocorticoid levels, hematology, serum chemistry, coagulation and urinalysis will be obtained at Screening, at the start of the Baseline Lead-in Period, at the start of every dose level (Day 1), at the start of every placebo Washout Period (Day 15) and at the Final Study Visit or the Early Termination Visit (Day 29).

Study visits that require blood sample collection for steroid hormones, must adhere to the following:

- Morning dose of replacement GC and MC must <u>not</u> be given until <u>after</u> the blood sample is collected
- Blood sample collection must be done prior to **10:00AM**

If both of these conditions are not met, the blood sample for efficacy endpoints must not be collected and another study visit must be scheduled for the next day or as soon as feasible.

Approximately 7 mL of blood will be collected for serum chemistry, 3 mL of blood for hematology and 3 mL of blood for PT/aPTT/INR. Approximately 20 mL of blood will be collected for steroid hormone testing and approximately 10 mL of blood will be collected for synthetic glucocorticoid testing. (See Table 5). Testing will be carried out by a central laboratory per the laboratory manual.

Subjects do not need to fast before the blood tests and will be in a seated or supine position during blood collection. Sampling time will be recorded on the eCRF.

For female subjects who are not surgically sterile or who have not been naturally post-menopausal for at least 12 consecutive months (i.e., who has had menses any time in the

preceding 12 consecutive months), serum pregnancy tests (ß-hCG) will be performed at Screening. A urine pregnancy test (UPT) will be obtained prior to the first dose at each dose level on Day 1. A UPT will also be obtained at the Final Study Visit or Early Termination Visit. Sampling time will be recorded on the eCRF.

Blood samples for serology (HBsAg, Hepatitis C antibody and HIV) will be obtained at Screening. Approximately 4 mL of blood will be collected for serology.

Abnormal, clinically significant results may be verified to rule out laboratory error. Persistent relevant abnormal values must be followed up until the cause is determined or until they return to the previous values. Abnormal laboratory findings that are considered clinically significant by the PI/SI should be recorded as AEs (see Section 6.12.1).

Table 5 List of Clinical Laboratory Tests.

Hematology	Hematocrit (Hct), Hemoglobin (Hgb), Platelet count, Red blood cell (RBC) count, White blood cell (WBC) count with differential, Hemoglobin A1c
Serum Chemistry	Albumin (ALB), Alkaline phosphatase (ALK-P), Alanine aminotransferase (ALT; SGPT), Aspartate aminotransferase (AST; SGOT), Blood urea nitrogen (BUN), Calcium (Ca), Creatinine, Glucose, Total bilirubin, Total protein, Serum electrolytes (magnesium, sodium, potassium, chloride, bicarbonate),
Coagulation	PT/aPTT, INR
Urinalysis	Appearance, Bilirubin, Color, Glucose, Ketones, Microscopic examination of sediment, Nitrite, Occult blood, pH, Protein, Specific gravity, Urobilinogen
Steroid Hormones and intermediates	Glucocorticoid pathway: 17-OHP, progesterone, cortisol Mineralocorticoid pathway: 11-DOC; PRA; aldosterone Androgens: androstenedione, total testosterone, free testosterone, SHBG, DHEA, DHEAS Adrenocorticotropic hormone (ACTH)
Synthetic Glucocorticoid Screen	Betamethasone, Budesonide, Dexamethasone, Fludrocortisone, Flunisolide, Fluorometholone, Hydrocortisone, Megestrol acetate, Methylprednisolone, Prednisolone, Prednisone, Triamcinolone, Triamcinolone acetonide
Pregnancy Testing	Serum and Urine Pregnancy Tests (ß-hCG)
Serology	Hepatitis B surface antigen (HBsAg), Hepatitis C antibody, Human immunodeficiency virus (HIV)

6.13.1 Sample Collection, Storage, and Shipping

Sample collection, storage and shipment procedures for clinical laboratory samples will be provided in the laboratory manual.

6.14 Blood Sample Collection

In total, approximately 687 mL of blood will be collected during the study from each subject enrolled that continues through all five dose levels. This consists of approximately 173 mL for safety, 124 mL for PK, 390 mL for pharmacodynamic sampling.

6.15 Removal of Subjects from the Study or Study Drug

In accordance with the Declaration of Helsinki and subsequent conferences, subjects have the right to withdraw from the study at any time for any reason. The PI/SI and the Sponsor also have the right to withdraw subjects from the study. Subjects may be removed from the study for the following reasons:

1. In the PI or SI's judgment, administration of study drug would be detrimental to the subject's health.
2. The subject withdraws consent for continued participation or refuses further treatment with the investigational product.
3. The subject is noncompliant with the protocol.
4. The subject becomes pregnant.
5. The subject dies.
6. The subjects experiences an SAE or medically important event that would preclude further treatment with study drug
7. Need to initiate therapy with an excluded medication

Subjects should return to the investigational site for a Final Study Visit or Early Termination Visit after withdrawal/removal from the clinical trial. The reason for and date of withdrawal/removal from the clinical trial will be documented in the subject's medical records. Investigational site personnel must attempt to determine whether the reason for withdrawal was an AE, and if so, this must be reported in accordance with the procedures provided in Section 6.12. For all subjects who do not complete the clinical trial, regardless of the duration of treatment, all relevant information related to the withdrawal/removal will be entered into the eCRF.

Subjects who withdraw or are removed from the clinical trial may be replaced at the discretion of the Sponsor. All enrolled subjects will be fully accounted for and documented in the final clinical study report (CSR).

7 STUDY ACTIVITIES

Visit time points are intended as targets, and variations may be made to allow for logistical considerations and to accommodate scheduling conflicts. Refer to Section 6.1.

7.1 Screening Visit (Day -21 to Day -1)

Prior to any screening evaluations, written informed consent must be obtained. All Screening procedures are to be completed within a 21 day window.

The following procedures are to be performed at the Screening Visit:

- Review and signature of the ICF
- Review of inclusion/exclusion criteria
- Recording of medical history, demographics data, prior and concomitant medication history
- Complete physical examination
- Vital signs (including blood pressure, pulse, respiration, height, body weight and temperature)
- 12-lead ECG
- Blood sampling for hematology, serum chemistry, PT/aPTT/INR
- Urinalysis
- Blood sampling for serology
- **Blood sampling for steroids/steroid intermediates (before 10 AM) only if the replacement steroids (GC/MC) have not been dosed that morning**
  Note: The test may be repeated one time at the Investigator's discretion if there is reason to suspect the results are inaccurate.
- Blood sampling for exogenous glucocorticoid levels.
- Serum pregnancy testing (β-hCG) for females who are not surgically sterile or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who have had menses any time in the preceding 12 consecutive months)
- AE reporting, if applicable
- Scheduling of next visit (Baseline Lead-in Period)
- Provide instructions to hold GC and MC morning dose prior to the next visit.

7.2 Baseline Lead-in Period

The following procedures are to be performed on Day 1 of the Baseline Lead-In Period:

- Vital signs (including blood pressure, pulse, respiration, body weight and temperature)
- Brief physical examination
- Review concomitant medications
- Review inclusion/exclusion criteria to confirm eligibility
- Blood sampling for hematology, serum chemistry, PT/aPTT/INR (subjects do not need to fast)
- AE reporting, if applicable

- **Blood sampling for steroids/steroid intermediates (before 10 AM) only if the replacement steroids (GC/MC) have not been dosed that morning**
- Blood sampling for exogenous glucocorticoid levels.
- Dispense IMP (Important Reminder: Subject is to remain blinded as to whether treatment is ATR-101 or placebo)
- Provide instructions to hold GC and MC morning dose prior to the next visit.

7.3 Dose Level 1, Days 1-28

ATR-101 Treatment Period, Days 1-14

The following procedures are to be performed on Day 1 of the ATR-101 dosing period:

Prior to dosing on Day 1

- Re-confirm eligibility based on inclusion/exclusion criteria (Note: Screening and Baseline visit 17-OHP level must be > 4x ULN)
- Confirm that the morning dose of replacement steroids (GC/MC) was not taken
  Note: If the morning dose of replacement GC and MC was taken the visit cannot be performed. The visit must be rescheduled for the next day or as soon as possible. Instruct the subject to continue taking their study drug with the last dose occurring the evening prior to the rescheduled visit.

- Confirm the day and time of the last dose of IMP
- Perform drug accountability and confirm compliance with IMP
- Review of concomitant medication
- Assess AEs
- Abbreviated physical examination
- Vital signs (including blood pressure, pulse, respiration, body weight and temperature)
- 12-lead ECG
- Urine pregnancy testing (β-hCG) for females who are not surgically sterile or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who have had menses any time in the preceding 12 consecutive months)
- Blood sampling for hematology, serum chemistry, PT/aPTT/INR (subjects do not need to be fasting)
- **Blood sampling for steroids/steroid intermediates (before 10 AM)**
- Blood sampling for exogenous glucocorticoid levels.
- Blood sampling for ATR-101 PK assessment (pre-dose)

Administer first dose ATR-101 125 mg (after consumption of food)

- Blood sampling for PK assessment at 1, 2, 3, and 4 hours post-dose
- 12-lead ECG 2 hours post-dose
- Dispense IMP for Days 1-14
- Recheck vital signs at 1, 2 and 4 hours post-dose
- Scheduling of next visit (Dose Level 1, Day 15)

- Provide instructions to hold GC and MC morning dose prior to the next visit.

Placebo Washout Period, Days 15-28

The following procedures are to be performed on Day 15 after the completion of the 14 day ATR-101 dosing period.

Prior to dosing on Day 15

- Confirm that the morning dose of replacement steroids (GC/MC) was not taken
  Note: If the morning dose of replacement GC and MC was taken the visit cannot be performed. The visit must be rescheduled for the next day or as soon as possible. Instruct the subject to continue taking their study drug with the last dose occurring the evening prior to the rescheduled visit.

- Confirm the day and time of the last dose of IMP
- Perform drug accountability and confirm compliance with IMP from Days 1-14
- Review of concomitant medication
- Assess AEs
- Abbreviated physical examination
- Vital signs (including blood pressure, pulse, respiration, body weight and temperature)
- 12-lead ECG
- Blood sampling for hematology, serum chemistry, PT/aPTT/INR (subjects do not need to be fasting)
- **Blood sampling for steroids/steroid intermediates (before 10 AM)**
- Blood sampling for exogenous glucocorticoid levels.
- Blood sampling for ATR-101 PK assessment (trough levels)

Administer first dose of placebo (after consumption of food)

- Dispense IMP for Days 15-28
- Scheduling of next visit (Day 29)
- Provide instructions to hold GC and MC morning dose prior to the next visit.

7.4 Final Study Visit or Next Dose Level, Day 1

Subjects will return to the clinic immediately after the completion of the 14 day Placebo Washout Period (i.e. 29 days after starting the Dose Level). The PI or SI will review the 17-OHP results obtained on Day 15 and determine whether this visit will be conducted as the Final Study Visit or Dose Level 2, Day 1 Visit:

- If 17-OHP $\leq$2 x ULN, complete the Final Study Visit (see Section 7.6), or
- If 17-OHP >2 x ULN, proceed to Dose Level 2, Day 1

The PI or SI must assess overall safety (i.e. brief physical exam, laboratory test results and AE reporting) prior to proceeding to Dose Level 2, Day 1.

7.5 Dose Levels 2, 3, 4 and 5

Dose Levels 2, 3, 4, and 5 will follow the same visit schedule and procedures as Dose Level 1 (Section 7.3 and 7.4). However, Dose Level 5 is the final dose level and the visit immediately following completion of the Level 5 Placebo Washout Period will be the Final Study Visit regardless of the Day 15 laboratory results.

7.6 Final Study Visit

The Final Study Visit will take place if the primary outcome measure is met (17-OHP $\leq$2 x ULN) or at the completion of Dose Level 5. The following procedures will be performed.

- Confirm that the morning dose of replacement steroids (GC/MC) was not taken or if taken confirm the day and time of the last dose
  Note: If the morning dose of replacement steroids (GC/MC) was taken, it is acceptable to complete the Final Study Visit
- Confirm the day and time of the last dose of IMP
- Perform drug accountability and confirm compliance with IMP
- Review of concomitant medication
- Assess AEs
- Complete physical examination
- Vital signs (including blood pressure, pulse, respiration, body weight and temperature)
- 12-lead ECG
- Blood sampling for hematology, serum chemistry, PT/aPTT/INR
- Urinalysis
- Urine pregnancy testing (β-hCG) for females who are not surgically sterile or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who have had menses any time in the preceding 12 consecutive months)
- **Blood sampling for steroids/steroid intermediates (before 10 AM)**
- Blood sampling for exogenous glucocorticoid levels
- Blood sampling for ATR-101 PK assessment (trough levels)

7.7 Early Termination Visit

The Early Termination Visit will occur if a subject is not able to complete the study procedures as detailed in the protocol for any reason. The schedule of events for the Early Termination Visit is identical to the Final Study Visit (See Section 7.6).

- Confirm that the morning dose of replacement steroids (GC/MC) was not taken or if taken confirm the day and time of the last dose
  Note: If the morning dose of replacement steroids (GC/MC) was taken, it is acceptable to complete the Final Study Visit
- Confirm the day and time of the last dose of IMP
- Perform drug accountability and confirm compliance with IMP
- Review of concomitant medication

- Assess AEs
- Complete physical examination
- Vital signs (including blood pressure, pulse, respiration, body weight and temperature)
- 12-lead ECG
- Blood sampling for hematology, serum chemistry, PT/aPTT/INR
- Urinalysis
- Urine pregnancy testing (β-hCG) for females who are not surgically sterile or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who have had menses any time in the preceding 12 consecutive months)
- **Blood sampling for steroids/steroid intermediates (before 10 AM)**
- Blood sampling for exogenous glucocorticoid levels
- Blood sampling for ATR-101 PK assessment (trough levels)

7.8 Follow-up Visit

Two weeks after completion of the Final Study Visit or Early Termination Visit, the PI, SI or other qualified medical personnel from the study center will contact the subject. A telephone interview will take place to confirm the status of the subject. Any safety events will be reported and concomitant medications, including replacement steroids will be recorded. This telephone interview will conclude the subject's study participation.

8 QUALITY CONTROL AND ASSURANCE

Before any subjects can be enrolled at an investigational site and prior to the conduct of any protocol-specific procedures, formal training of investigational site personnel will be conducted. The PI/SI and all relevant investigational site staff are to be trained on all aspects of the trial for which they are responsible. Site personnel may be trained at a formal initiation visit, at an Investigator's Meeting, or by another means as necessary. Monitoring and auditing procedures will be conducted in compliance with the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP). Onsite verification of the eCRFs for completeness and clarity, crosschecking with source documents, and clarification of administrative matters will be performed on a regular basis. The investigational site will be monitored immediately following enrollment of the first subject at the site (i.e., within approximately 2 weeks) to verify that inclusion/exclusion criteria have been fulfilled. Subsequent monitoring visits will occur at regular intervals as noted in the monitoring plan. Through frequent communications with the investigational site, the CRA will ensure that the investigation is conducted according to protocol design and all applicable regulatory requirements. Additional details on the monitoring of this clinical trial are provided in Section 10.5. During the course of the clinical trial, investigational sites, the clinical trial database, and all associated clinical trial documentation may be subject to quality assurance audits by the Sponsor, or their appointed representatives, on a planned or as-needed basis. In addition, representatives of associated regulatory bodies may conduct inspections at their discretion. The Investigator is responsible for ensuring direct access to all protocol-specific materials for the purpose of these activities.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

Sample size considerations are based on a Simon 2-stage Minimax design with 1-sided alpha of 5% and 80% power.

Stage 1 consists of 9 completed subjects. The study will stop at Stage 1 if either of the following conditions are met:

- Futility criteria: defined as $\leq$2 of 9 (22%) subjects meeting the primary outcome measure (17-OHP $\leq$2 x ULN)
- Success criteria: defined as $\geq$7 of 9 (78%) subjects meeting the primary outcome measure (17-OHP $\leq$2 x ULN)

Stage 2 will commence if 3, 4, 5 or 6 of the 9 subjects meet the primary outcome measure. In this scenario, accrual will continue with up to 8 additional subjects for a total of no more than 17 subjects. Accrual may stop earlier with sufficient evidence for further development if a total of 7 or more subjects respond (minimum observed response rate of 7/17, 41%).

The study medical monitor along with the Sponsor may determine if a subject will be replaced in order to have a minimum of 9 evaluable subjects for Stage 1. Possible reasons for replacement may be due to extreme noncompliance with IMP not related to an adverse event, noncompliance with the protocol such as the use of prohibited medications that could confound results.

9.2 Analysis Populations

An intent to treat population is not deemed necessary for this study given the relatively small number of subjects.

The per protocol population will include all subjects that have taken at least 11 days of ATR-101 treatment at Dose Level 1 (the lowest dose level) and have at least one post-baseline efficacy assessment (i.e.17-OHP) without having a significant protocol deviation.

The safety population will include all subjects that received at least one dose of IMP.

9.3 Patient Demographics and Baseline Characteristics

Demographic and clinical characteristics of subjects enrolled onto this study will be summarized. For categorical variables, frequencies and percentages will be provided. Means with standard deviations or medians/percentiles will summarize non-categorical variables.

9.4 Treatment

A frequency distribution will be generated for the dose levels administered. Any deviations to the dose escalation criteria will also be noted.

9.5 Primary Efficacy Endpoint

The primary efficacy endpoint will be the percentage of responders. **A responder is defined as a subject that meets the primary outcome measure of 17-OHP $\leq$2 x ULN at any dose level.** Subjects will enter the study with 17-OHP $\geq$ 4 x ULN. The 17-OHP level associated with the primary outcome measure is aligned to clinical management practices for classic CAH.

9.6 Secondary Endpoints

Descriptive statistics and graphical summaries within each cohort, and for each dose as appropriate, will be utilized to present the pharmacokinetic and pharmacodynamics parameters assessed.

9.7 Safety

Safety parameters, including adverse events, treatment discontinuations, laboratory changes and abnormalities, and changes in ECG parameters will be tabulated and each dose, as appropriate.

9.8 Pharmacokinetic and Pharmacodynamic Analyses

Pharmacokinetic (PK) assessments will be performed at each dose level to determine ATR-101 exposures and to profile PK/PD relationships. PK assessments will include C_{max}, Area Under the Curve ($AUC_{0\text{-}4\ hr}$), and trough levels.

Individual subject PK data will be analyzed along with pooling of subjects' data at each dose level.

PK/PD analyses will be detailed in the Statistical Analysis Plan.

9.9 Interim Analysis

No interim analysis is planned for this study as neither the efficacy nor the safety results will be blinded to the PI/SI, study medical monitor or the Sponsor.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

Prior to initiation of the study at each investigational site, the protocol, the informed consent form(s), the subject information sheet(s), details of the subject recruitment procedures, and any other relevant study documentation will be submitted to the responsible local and/or national IRB/IEC. A letter from the IRB/IEC indicating approval of the Investigator and study site must be submitted to the study Sponsor. All reviews and approval by the IRB/IEC will be in accordance with Title 21 of the Code of Federal Regulations (CFR), Part 56.

The PI/SI will promptly report any new information that may adversely affect the safety of subjects or the conduct of the study to the IRB/IEC. Similarly, the PI/SI will submit written summaries of the study status to the IRB/IEC annually, or more frequently if requested. Upon completion of the study, the Investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

10.2 Ethical Conduct of the Study

The guidelines of the World Medical Association Declaration of Helsinki in its revised edition (48th General Assembly, Somerset West, Republic of South Africa, October 1996), the guidelines of ICH GCP (CPMP/ICH/135/95), as well as the demands of national drug and data protection laws and other applicable regulatory requirements, will be strictly followed.

10.3 Subject Information and Consent

The PI/SI is responsible for ensuring that subjects do not undergo any study-related examination or activity before giving informed consent. The subject must give written consent after the receipt of detailed information regarding the study. The verbal explanation will cover all the elements specified in the written information provided to the subject. If the written informed consent is provided by the legal guardian because the subject is unable to do so, a written or verbal assent from the subject must also be obtained.

The PI/SI will inform the subject of the aims, methods, anticipated benefits, and potential hazards of the study, including any discomfort it may entail. The subject must be given every opportunity to clarify any points he/she does not understand and must be provided with more information if requested. At the end of the interview, the subject may be given time to reflect and can request more time if needed. The subject and/or legal guardian will be required to sign and date the informed consent form. After completion, informed consent forms will be kept and archived by the PI in the PI study file.

It should be emphasized to the subject that he or she is at liberty to either discontinue IMP and/or withdraw consent to participate at any time, without penalty or loss of benefits to which he or she is otherwise entitled. Subjects who refuse to give or withdraw written informed consent may not be included or continued in this study, but this will not affect their subsequent care.

Please refer to Title 21 of the CFR, Part 50 – Protection of Human Subjects for specific details on this regulation.

10.4 Subject Confidentiality

Personal and sensitive data will be treated as confidential. The results of the clinical trial will be made available for review by authorized representatives of the Sponsor and/or submitted to the IRB/IEC, and regulatory authorities.

Prior to the subject's enrollment in the clinical trial, the subject's consent is required for the data to be used for these purposes and to gain direct access to their medical records for data verification purposes. The subject must be assured that their identity will be protected. To facilitate this, a unique identification number will be assigned and it will be used when reporting study-related data.

Additionally, in the US, the Health Insurance Portability and Accountability Act of 1996 ("HIPAA") requires that all subjects grant permission to use their personal health information. Therefore, in addition to the protocol-specific ICF, each subject located in the United States (US) will be asked to provide authorization to use his/her personal health information by signing a separate HIPAA Authorization Form.

10.5 Study Monitoring

It is understood that the Sponsor or its designee (e.g., the CRA) will contact and visit the PI/SI regularly for monitoring purposes. The CRA will be allowed, on request, to inspect the various records of the clinical trial (i.e., eCRFs, source documents, and any other pertinent data), provided that subject confidentiality is maintained in accordance with local requirements. It will be the CRA's responsibility to inspect the eCRFs at regular intervals throughout the clinical trial, to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data entered. The CRA must have access to all subject records needed to verify the entries on the eCRF. The PI/SI (or a designee) agrees to cooperate with the CRA to ensure that problems detected during these monitoring visits are resolved.

In addition, the Sponsor may perform a Clinical Quality Assurance (CQA) audit randomly at a sample of clinical sites, or for cause as warranted. The CQA audit will examine the accuracy of source documentation, record retention, data management, and compliance. These audits will be independent of routine monitoring by the CRA with prior written notification provided to the site.

10.6 Case Report Forms and Study Records

This clinical trial will utilize an electronic data capture system for the management of clinical data. The data will be collected in electronic form (i.e., via an eCRF) to allow for data entry at the site from source documentation directly into the electronic database. Access to the electronic system will be restricted, and users will only be able to access the system via authorized individual accounts. All changes to data in the database will be tracked and time

stamped automatically, including updates to data entries and resolution of data queries generated by the CRA or data reviewer.

Training will be provided to all system users based on their individual access and use requirements initially and ongoing throughout the course of the clinical trial as needed. Documentation of training will be kept in the site regulatory file and in Sponsor's TMF.

A comprehensive Data Management Plan will be written outlining the standard operating procedures, internal/external security safeguards, system and change controls, and training procedures and will be filed in the Sponsor's TMF. A cumulative record will also be kept of the user and access privileges for all authorized users across the clinical trial.

The system and procedures for electronic database set-up, entry, review, access, security, and auditing are designed in specific compliance with 21 CFR 11 and the Food and Drug Administration's (FDA's) Part 11 Guidance for Industry supplement "Computerized Systems Used in Clinical Investigations" dated May 2007. Any additional electronic systems that may be used by vendors (e.g., PK) or clinical sites (e.g., electronic medical records used as source documents) should comply with these same regulatory standards.

As a final step in the data management process, a 100% quality control review will be performed on the key efficacy and safety parameters. In addition, a random subject sample (approximately 10%) will be selected to perform a database audit. The purpose of this audit is to detect systematic and random errors.

10.7 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) is not planned for this study since treatment is unblinded to study personnel and the overall small size of the study generally limits the value of pooling data across the study population. All study PI/SI will have the ability to assess benefit:risk for each subject in almost real time. The study medical monitor and Sponsor will have access to safety and efficacy data from across the entire study population. The study design limits the duration of ATR-101 treatment duration and assesses safety every 2 weeks.

10.8 Protocol Deviations

Protocol deviations from inclusion/exclusion criteria, concomitant medication restrictions, and from any other protocol requirements that could, at least hypothetically, result in significant risk to the subject and/or affect the outcome of the study will be collected. Additionally, nonadherence to the study procedures or schedule as defined by the protocol such as a missed procedure or an out-of-window study visit will be documented as protocol deviations.

10.9 Access to Source Documentation

The PI/SI must permit the authorized Sponsor, agents of the Sponsor, and regulatory agency employees to enter and inspect any site where the drug or records pertaining to the drug are held and to inspect and copy all records relating to an investigation including subject records. To ensure the accuracy of data submitted, it is mandatory that representatives of the Sponsor and of the regulatory agencies have direct access to source documents (e.g., subject medical records,

charts, laboratory reports) for the purpose of quality assurance audits either by Millendo or their appointed representatives. Subject confidentiality will be protected at all times.

10.10 Data Generation and Analysis

Data processing and management will be performed by the Sponsor or its designee. Data will be promptly entered into the study database and reviewed and issues resolved prior to database closure.

Personal and sensitive personal data will be treated as confidential. The results of the study will be made available for review by authorized representatives of the Sponsor and/or submitted to the IRB/IEC, and regulatory authorities. Prior to the subject's enrollment in the study, the subject's consent is required for the data to be used for these purposes and to gain direct access to their medical records for data verification purposes. The subject must be assured that their identity will be protected. To facilitate this, a unique identification number will be assigned and it will be used when reporting study-related data.

10.11 Retention of Data

Copies of all study documents should be retained by the PI for 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 at least two years have elapsed since the formal discontinuation of clinical development of the investigational product, in accordance with 21 CFR 312.62. These documents should be retained for a longer period, however, if required by regulatory requirements or by 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. The final database will be archived by the Sponsor according to the regulatory requirements.

10.12 Financial Disclosure

PI and SI are required to provide full disclosure of any financial relationship to the Sponsor or its designee(s) prior to participation in any trial-related activities. Additionally, PI/SI are required to promptly provide updated information to the Sponsor or its designee(s) regarding any relevant changes in financial interests that occur during the course of the clinical trial and for 1 year after completion of the clinical trial. For additional guidance, refer to 21 CFR 312.53(c) (4), 312.64(d), 812.43(c) (5), 812.110(d).

10.13 Premature Termination of the Study

If the study is prematurely terminated or suspended, the Sponsor will promptly inform the PI/SI /institutions and the regulatory authority(s) of the termination or suspension and the reason(s) for the termination or suspension.

10.14 Clinical Study Report

A CSR will be written for this study with a structure and content that will conform to the ICH guidance, "Structure and Content of Clinical Study Reports, ICH Topic E3, July 1996".

10.15 Subject Insurance and Indemnity

The Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the subjects' participating in this study. The terms of insurance will be kept in the Sponsor's regulatory files.

10.16 Amendments to the Protocol

Modifications of the signed protocol are only possible by approved protocol amendments and with the agreement of all responsible persons. The procedure for approval of a protocol amendment is identical to that for approval of the protocol. The IRB/IEC must be informed of all protocol amendments and should be asked for its opinion as to whether a full re-evaluation of the ethical aspects of the study is necessary by the committee. This should be fully documented.

The PI/SI must not implement any deviation from or change to the protocol without discussion and agreement by the Sponsor in writing and prior review and documented approval/favorable opinion of the amendment from the relevant IRB or IEC, except where it is necessary to eliminate an immediate hazard to study subjects or where the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor or change of telephone number).

Protocol amendments will be submitted to the appropriate authority(s) as required by the applicable regulatory requirement(s).

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Appendix 1 Sponsor Signature

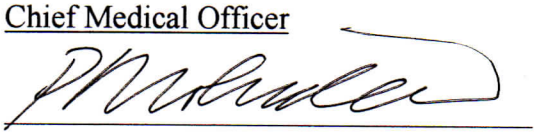
Study Title: A Phase 2, Multicenter, Study of ATR-101 for the Treatment of Congenital Adrenal Hyperplasia.

SPONSOR SIGNATURE

I have read and approve the protocol and appendices. My signature, in conjunction with the signature of the Investigator, confirms the agreement of both parties that the clinical trial will be conducted in accordance with the protocol and all applicable laws and regulations, including, but not limited to, the ICH Guidelines for GCP, the US CFR, and the ethical principles that have their origins in the Declaration of Helsinki, as well as all applicable privacy laws.

Name: Pharis Mohideen, MD
Please print

Title: Chief Medical Officer

Signature 

Date: JAN 14, 2016

Address: 301 N. Main St.
Suite 100
Ann Arbor, MI 48104

Appendix 2 Investigator's Signature

Study Title: A Phase 2, Multicenter, Study of ATR-101 for the Treatment of Congenital Adrenal Hyperplasia

STUDY INVESTIGATOR SIGNATURE

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

This protocol is provided for use by you, your staff, and the Institutional Review Board or Ethics Committee. The information contained in this document is confidential and belongs to the Sponsor. Except as may be otherwise agreed to in writing, by accepting or reviewing these materials, you agree to hold such information in confidence and not to disclose it to others (except where required by applicable law) nor use it for unauthorized purposes. In the event of actual or suspected breach of this obligation, the Sponsor must be promptly notified.

By my signature below, I agree to conduct this clinical study in accordance with applicable government regulations or laws, and institutional/ethical review and informed consent practices. I have read the Investigator's Brochure and protocol. I agree to ensure the confidentiality of my subjects; however, I agree to make available to The Sponsor or designee the subject's medical chart specifically for the purposes of this clinical study. I am fully conversant with Good Clinical Practices and agree to conduct the clinical study in accordance with these principles and the procedures described in this protocol. I am aware of my responsibilities as an Investigator.

Name: _____
Please print

Title: _____

Signature _____

Date: _____

Address: _____

_____

_____

Appendix 3 Drugs that Prolong the QT/QTc interval

List A. Drugs that prolong the QT Interval that are prohibited.

Generic Name	Brand Name	Class/Clinical Use	Comments
Amiodarone	Pacerone®	Anti-arrhythmic/abnormal heart rhythm	Females>Males,TdP risk regarded as low
Arsenic trioxide	Trisenox®	Anti-cancer/Leukemia	
Astemizole	Hismanal®	Antihistamine/Allergic rhinitis	No Longer available in U.S.
Azithromycin	Zithromax®	Antibiotic/bacterial infection	
Bepridil	Vascor®	Anti-anginal/heart pain	Females>Males
Chloroquine	Aralen®	Anti-malarial/malaria infection	
Chlorpromazine	Thorazine®	Anti-psychotic/Anti-emetic/schizophrenia/nausea	
Cisapride	Propulsid®	GI stimulant/heartburn	No longer available in U.S.
Citalopram	Celexa®	Anti-depressant/depression	
Clarithromycin	Biaxin®	Antibiotic/bacterialinfection	
Disopyramide	Norpace®	Anti-arrhythmic/abnormal heart rhythm	Females>Males
Dofetilide	Tikosyn®	Anti-arrhythmic/abnormal heart rhythm	Females > Males
Domperidone	Motilium®	Anti-nausea/nausea	Not available in U.S.
Droperidol	Inapsine®	Sedative; Anti-nausea/ anesthesia adjunct, nausea	
Erythromycin	E.E.S.®	Antibiotic; GI stimulant/bacterial infection; increase GI motility	Females>Males
Erythromycin	Erythrocin®	Antibiotic; GI stimulant/bacterial infection; increase GI motility	Females>Males
Escitalopram	Cipralex®	Anti-depressant/Major depression/Anxiety disorders	
Escitalopram	Lexapro®	Anti-depressant/Major depression/Anxiety disorders	
Flecainide	Tambocor®	Anti-arrhythmic/abnormal heart rhythm	
Halofantrine	Halfan®	Anti-malarial/malaria infection	Females>Males
Haloperidol	Haldol®	Anti-psychotic/schizophrenia, agitation	TdP risk with I.V. or excess dosage
Ibutilide	Corvert®	Anti-arrhythmic/abnormal heart rhythm	Females>Males
Levomethadyl	Orlaam®	Opiate agonist/pain control, narcotic dependence	Not available in U.S.
Mesoridazine	Serentil®	Anti-psychotic/schizophrenia	
Methadone	Dolophine®	Opiate agonist/pain control, narcotic dependence	Females>Males
Methadone	Methadose®	Opiate agonist/pain control, narcotic dependence	Females>Males
Moxifloxacin	Avelox®	Antibiotic/bacterial infection	
Pentamidine	NebuPent®	Anti-infective/pneumocystis pneumonia	Females>Males
Pentamidine	Pentam®	Anti-infective/pneumocystis pneumonia	Females>Males
Pimozide	Orap®	Anti-psychotic/Tourette's tics	Females>Males
Probucol	Lorelco®	Antilipemic/Hypercholesterolemia	No longer available in U.S.
Procainamide	Pronestyl®	Anti-arrhythmic/abnormal heart rhythm	
Procainamide	Procan®	Anti-arrhythmic/abnormal heart rhythm	
Quinidine	Quinaglute®	Anti-arrhythmic/abnormal heart rhythm	Females>Males
Quinidine	Cardioquin®	Anti-arrhythmic/abnormal heart rhythm	Females>Males
Sevoflurane	Ulane®	Anesthetic, general/anesthesia	Label warning for patients with congenital long QT or patients taking QT prolonging drugs
Sevoflurane	Sojourn®	Anesthetic, general/anesthesia	Label warning for patients with congenital long QT or patients taking QT prolonging drugs
Sotalol	Betapace®	Anti-arrhythmic/abnormal heart rhythm	Females>Males
Sparfloxacin	Zagam®	Antibiotic/bacterial infection	No longer available in U.S.
Terfenadine	Seldane®	Antihistamine/Allergic rhinitis	No longer available in U.S.
Thioridazine	Mellaril®	Anti-psychotic/schizophrenia	
Vandetanib	Caprelsa®	Anti-cancer/Thyroid cancer	

LIST B. Drugs with conditional risk of QT prolongation, to be used with caution

Generic Name	Brand Name	Class/Clinical Use	Comments
Amisulpride	Solian® and others	Antipsychotic, atypical	Risk of TdP with overdose - not available in US
Amitriptyline	Elavil®	Tricyclic Antidepressant /depression	Risk of TdP with overdosage
Ciprofloxacin	Cipro®	Antibiotic/bacterial infection	Drug interaction risk - metabolic inhibitor
Clomipramine	Anafranil®	Tricyclic Antidepressant /depression	
Desipramine	Pertofrane®	Tricyclic Antidepressant /depression	Risk of TdP with overdosage
Diphenhydramine	Benadryl®	Antihistamine/Allergic rhinitis, insomnia	Risk of QT increase/TdP in overdosages
Diphenhydramine	Nytol®	Antihistamine/Allergic rhinitis, insomnia	Risk of QT increase/TdP in overdosages
Doxepin	Sinequan®	Tricyclic Antidepressant /depression	
Fluconazole	Diflucan®	Anti-fungal/fungal infection	Drug interaction risk metabolic inhibitor. Can also increase QT at high doses - 800 mg/day
Fluoxetine	Sarafem®	Anti-depressant/ depression	
Fluoxetine	Prozac®	Anti-depressant/ depression	
Galantamine	Reminyl®	Cholinesterase inhibitor /Dementia, Alzheimer's	
Imipramine	Norfranil®	Tricyclic Antidepressant /depression	TdP risk with excess dosage
Itraconazole	Sporanox®	Anti-fungal/fungal infection	Drug interaction risk - metabolic inhibitor
Ketoconazole	Nizoral®	Anti-fungal/fungal infection	Prolongs QT & Drug interaction risk – metabolic inhibitor.
Nortriptyline	Pamelor®	Tricyclic Antidepressant /depression	
Paroxetine	Paxil®	Anti-depressant/ depression	
Protriptyline	Vivactil®	Tricyclic Antidepressant /depression	
Ritonavir	Norvir®	Protease inhibitor/HIV	
Sertraline	Zoloft®	Anti-depressant/ depression	
Solifenacin	VESIcare®	muscarinic receptor anatagonist/treatment of overactive bladder	
Trazodone	Desyrel®	Anti-depressant/ Depression, insomnia	
Trimethoprim-Sulfa	Septra® or Bactrim®	Antibiotic/bacterial infection	Also available in DS (double strength)
Trimipramine	Surmontil®	Tricyclic Antidepressant /depression	

LIST C. Drugs with possible risk of QT prolongation, to be used with caution

Generic Name	Brand Name	Class/Clinical Use	Comments
Alfuzosin	Uroxatral®	Alpha1-blocker/Benign prostatic hyperplasia	
Amantadine	Symmetrel®	Dopaminergic/Anti-viral/ Anti-infective/ Parkinson's Disease	
Artenimol+piperaquine	Eurartesim®	Anti-malarial	Not available in U.S.
Atazanavir	Reyataz®	Protease inhibitor/HIV	
Bedaquiline	Sirturo®	Anti-infective/Drug resistant Tuberculosis	Black Box for QT
Chloral hydrate	Noctec®	Sedative/sedation/insomnia	
Clozapine	Clozaril®	Anti-psychotic /schizophrenia	
Dolasetron	Anzemet®	Anti-nausea/nausea, vomiting	
Dronedarone	Multaq®	Anti-arrhythmic/Atrial Fibrillation	
Eribulin	Halaven®	Anti-cancer/metastatic breast neoplasias	
Famotidine	Pepcid®	H2-receptor antagonist/ Peptic ulcer/ GERD	
Felbamate	Felbatrol®	Anti-convulsant/seizure	
Fingolimod	Gilenya®	Immunosuppressant/Multiple Sclerosis	
Foscarnet	Foscavir®	Anti-viral/HIV infection	
Fosphenytoin	Cerebyx®	Anti-convulsant/seizure	
Gatifloxacin	Tequin®	Antibiotic/bacterial infection	Oral/I.V. forms no longer available in U.S. and Canada, only ophthalmic
Gemifloxacin	Factive®	Antibiotic/bacterial infection	
Granisetron	Kytril®	Anti-nausea/nausea and vomiting	
Iloperidone	Fanapt®	Antipsychotic, atypical/ Schizophrenia	
Indapamide	Lozol®	Diuretic/stimulate urine & salt loss	
Isradipine	Dynacirc®	Anti-hypertensive/high blood pressure	
Lapatinib	Tykerb®	Anti-cancer/breast cancer, metastatic	
Lapatinib	Tyverb®	Anti-cancer/breast cancer, metastatic	
Levofloxacin	Levaquin®	Antibiotic/bacterial infection	
Lithium	Lithobid®	Anti-mania/bipolar disorder	
Lithium	Eskalith®	Anti-mania/bipolar disorder	
Mirtazapine	Remeron	Anti-depressant	
Moexipril/HCTZ	Uniretic®	Anti-hypertensive/high blood pressure	
Nicardipine	Cardene®	Anti-hypertensive/high blood pressure	
Nilotinib	Tasigna®	Anti-cancer/Leukemia	
Octreotide	Sandostatin®	Endocrine/acromegaly, carcinoid diarrhea	
Ofloxacin	Floxin®	Antibiotic/bacterial infection	
Olanzapine	Zyprexa®	Antipsychotic, atypical/ Schizophrenia, bipolar	Combo c fluoxetine: Symbyax
Ondansetron	Zofran®	Anti-emetic/nausea and vomiting	
Oxytocin	Pitocin®	Oxytocic/Labor stimulation	
Paliperidone	Invega®	Antipsychotic, atypical/ Schizophrenia	
Perflutren lipid microspheres	Definity®	Imaging contrast agent/ Echocardiography	
Quetiapine	Seroquel®	Anti-psychotic/schizophrenia	
Ranolazine	Ranexa®	Anti-anginal/chronic angina	
Risperidone	Risperdal®	Anti-psychotic/schizophrenia	
Roxithromycin*	Rulide®	Antibiotic/bacterial infection	*Not available in U.S.
Sertindole	Serdolect®	Antipsychotic, atypical/ Anxiety, Schizophrenia	Not available in U.S.
Sertindole	Serlect®	Antipsychotic, atypical/ Anxiety, Schizophrenia	Not available in U.S.
Sunitinib	Sutent®	Anti-cancer/RCC, GIST	
Tacrolimus	Prograf®	Immunosuppressant/ Immune suppression	
Tamoxifen	Nolvadex®	Anti-cancer/breast cancer	
Telithromycin	Ketek®	Antibiotic/bacterial infection	
Tizanidine	Zanaflex®	Muscle relaxant	
Vardenafil	Levitra®	phosphodiesterase inhibitor/ vasodilator	
Venlafaxine	Effexor®	Anti-depressant/depression	
Voriconazole	VFend®	Anti-fungal/anti-fungal	
Ziprasidone	Geodon®	Anti-psychotic/schizophrenia	

Appendix 4 Drugs Known to Interact with CYP3A4

SUBSTRATES: 3A4,5,7

Macrolide antibiotics:
clarithromycin
erythromycin (not 3A5)
NOT azithromycin
telithromycin

Anti-arrhythmics:
quinidine-OH (not3A5)

Benzodiazepines:
alprazolam
diazepam-3OH
midazolam
triazolam

Immune Modulators:
cyclosporine
tacrolimus (FK506)

HIV Antivirals:
indinavir
nelfinavir
ritonavir
saquinavir

Prokinetic:
cisapride

Antihistamines:
astemizole
chlorpheniramine
terfenadine

Calcium Channel Blockers:
amlodipine
diltiazem
felodipine
lercanidipine
nifedipine2
nisoldipine
nitrendipine
verapamil

HMG CoA Reductase Inhibitors:
atorvastatin
cerivastatin
lovastatin
NOT pravastatin
NOT rosuvastatin
simvastatin

Steroid 6beta-OH:
estradiol
hydrocortisone
progesterone
testosterone

Miscellaneous:
alfentanyl
aprepitant
aripiprazole
buspirone
cafergot
caffeine_TMU
cilostazol
cocaine
codeine-Ndemethylation
dapsone
dexamethasone
dextromethorphan
docetaxel
domperidone
eplerenone
fentanyl
finasteride
gleevec
haloperidol
irinotecan
LAAM
lidocaine
methadone
nateglinide
ondansetron
pimozide
propranolol
quetiapine
quinine
risperidone
salmeterol
sildenafil
sirolimus
tamoxifen
taxol
terfenadine
trazodone
vincristine
zaleplon
ziprasidone
zolpidem

INHIBITORS 3A4,5,7

HIV Antivirals:
indinavir
nelfinavir
ritonavir

Antibiotics
clarithromycin
itraconazole
ketoconazole
nefazodone
saquinavir
telithromycin

aprepitant
erythromycin
fluconazole

Grapefruit juice

Miscellaneous
verapamil
diltiazem
cimetidine
amiodarone
NOT azithromycin
chloramphenicol
ciprofloxacin
delaviridine
diethyldithiocarbamate
fluvoxamine
gestodene
imatinib
mibefradil
mifepristone
norfloxacin
norfluoxetine
star fruit
voriconazole

INDUCERS 3A4,5,7
HIV Antivirals:
efavirenz
nevirapine

Miscellaneous
barbiturates
carbamazepine
glucocorticoids
modafinil
oxcarbazepine
phenobarbital
phenytoin
pioglitazone
rifabutin
rifampin
St. John's wort
troglitazone

Appendix 5 Drugs that may Interact with P-glycoprotein

Transporter	MDR1/PgP
Gene	*ABCB1*
Amiodarone	S/Inhib
Amitriptyline	Inhib
Amprenavir	Induc
Astemizole	Inhib
Atorvastatin	S/Inhib
Boceprevir	S/Inhib
Bromocriptine	Inhib
Carvedilol	Inhib
Chlorpromazine	Inhib
Clarithromycin	Inhib
Clotrimazole	Induc
Cyclosporine	S/Inhib
Desipramine	Inhib
Dexverapamil	Inhib
Diltiazem	S/Inhib
Dipyridamole	Inhib
Disulfiram	Inhib
Doxepin	Inhib
Erythromycin	S/Inhib
Fluphenazine	Inhib
Glibenclamide	Inhib
Haloperidol	Inhib
Imipramine	Inhib
Indinavir	S/Induc
Itraconazole	S/Inhib
Ketoconazole	Inhib
Lidocaine	S/Inhib
Lovastatin	S/Inhib
Maprotiline	Inhib
Mefloquine	Inhib
Meperidine	Inhib
Methadone	Inhib
Mibefradil	Inhib
Midazolam	Inhib
Mifepristone	Inhib
Nelfinavir	S/Induc
Nicardipine	S/Inhib
Nifedipine	Inhib
Ofloxacin	Inhib
Pentazocine	Inhib
Prazosin	Induc
Prochlorperazine	Inhib
Progesterone	Inhib/Induc
Propafenone	Inhib
Propranolol	S/Inhib
Quercetin	Induc
Quinidine	S/Inhib
Quinine	Inhib
Reserpine	inhib
Retinoic acid	Induc
Rifampin	S/Induc
Ritonavir	S/inhib
Saquinavir	S/Inhib
Simvastatin	S/Inhib
St. Johns Wort	Induc
Tacrolimus	S/Inhib
Tamoxifen	Inhib
Telaprevir	S/Inhib
Temsirolimus	S/Inhib
Testosterone	Inhib
Trimipramine	Inhib
Vaspodar	Inhib
Verapamil	S/Inhib

Inhib = Inhibition;
Induc = Induction;
S = Substrate;
MDR = multidrug resistance protein

Source: Pharmacology Weekly
http://www.pharmacologyweekly.com/content/pages/medications-drugs-substrates-inhibitors-inducers-efflux-transporters