PRODUCT NAME: ATR-101

STUDY NUMBER: ATR-101-301

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of ATR-101 for the Treatment of Cushing's Syndrome

Study Phase: 2
Product Name: ATR-101
IND Number: 129885
EudraCT Number: 2016-002240-17
NCT Number: NCT03053271

Indication: Endogenous Cushing's Syndrome

Sponsor: Millendo Therapeutics, Inc.

Sponsor Medical Contact: Vivian H. Lin, M.D.

Original Protocol: 24 May 2016
Global Protocol Amendment 1: 30 August 2016
Country-Specific Protocol Amendment 1/UK: 06 April 2017
Global Protocol Amendment 2: 14 March 2018

INVESTIGATOR'S AGREEMENT

Study Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of ATR-101 for the Treatment of Cushing's Syndrome

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STUDY INVESTIGATOR SIGNATURE

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 Millendo Therapeutics, Inc. or designee the subject's medical chart specifically for the purposes of this clinical study. I am fully conversant with Good Clinical Practices (GCP) 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: _____

_____

_____

SPONSOR SIGNATURE

Study Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of ATR-101 for the Treatment of Cushing's Syndrome

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 International Council on Harmonisation (ICH) Guidelines for GCP, the US Code of Federal Regulations (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: Mar 22, 2018

Address: 301 N. Main St.

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Ann Arbor, MI 48104

SYNOPSIS

Name of Sponsor/Company:
Millendo Therapeutics, Inc.

Name of Investigational Product:
ATR-101

Title of Study:
A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of ATR-101 for the Treatment of Cushing's Syndrome

Study Center(s): Approximately 14 sites in the United States and the United Kingdom

Studied Period:	**Phase of Development:**
Estimated date first subject enrolled: October 2016 Estimated date last subject completed: December 2021	2

Objectives:

Primary:

- To evaluate the efficacy and safety of orally-administered ATR-101 in adults with endogenous Cushing's syndrome

Secondary:

- To evaluate the changes in adrenal steroids and adrenal steroid intermediates
- To evaluate the change in adrenocorticotropic hormone (ACTH)
- To evaluate the change in metabolic syndrome-related parameters, including fasting glucose, insulin, lipid panel, blood pressure and body mass index (BMI)
- To assess the safety and tolerability of ATR-101
- To determine the pharmacokinetics (PK) of ATR-101 and its major metabolites
- To evaluate the PK/pharmacodynamic (PD) relationships of ATR-101

Methodology:

This Phase 2 multicenter study consists of two parts: an open-label intra-subject dose-escalation period of 8 weeks' duration, followed either by a double-blind randomized withdrawal period of 4 weeks' duration (if the subject meets randomization criteria) or by an additional open label dosing period of 4 weeks' duration (if the subject does not meet randomization criteria). A study schematic is shown in Figures 1, 2, and 3 below. A detailed schedule of study assessments is presented in Appendix 1.

Figure 1: Study Schematic, Screening and Open-Label Dose-Escalation Periods

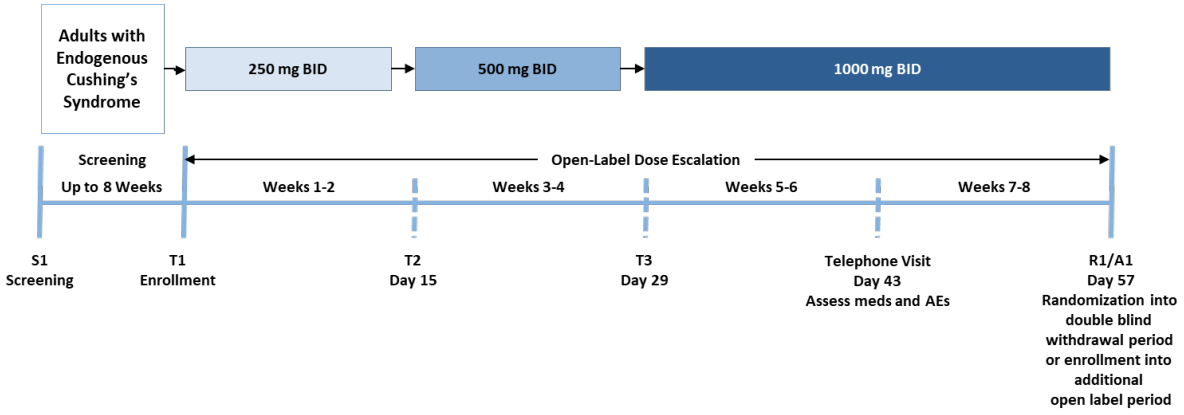


Figure 2: Study Schematic, Double-Blind Randomized Withdrawal Period

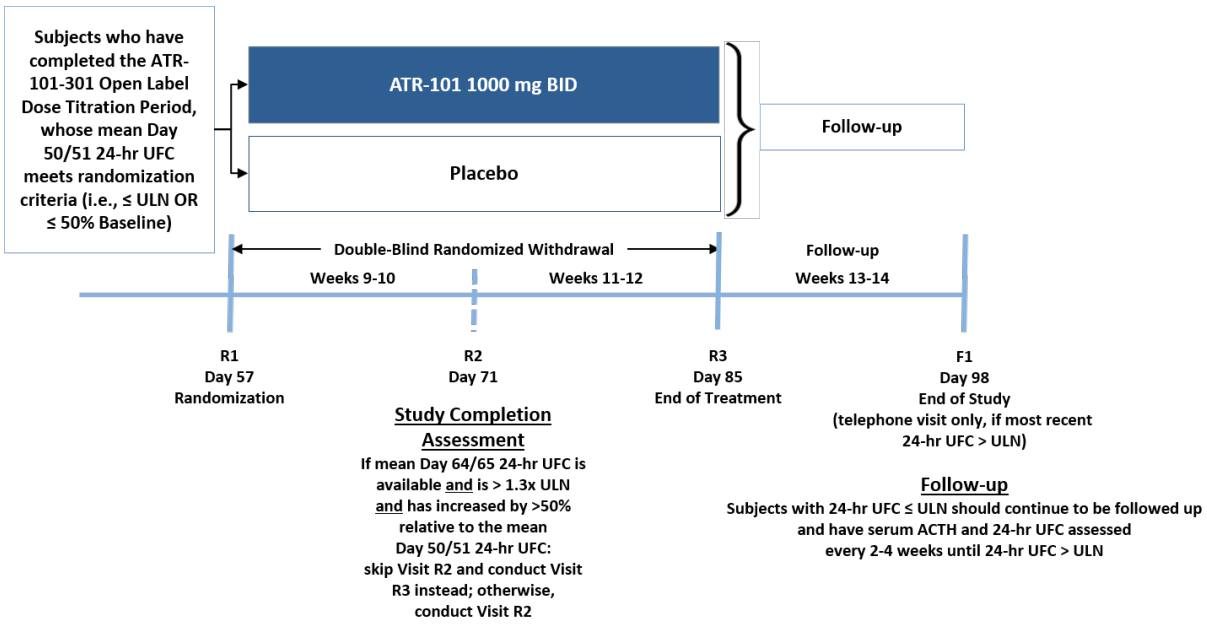
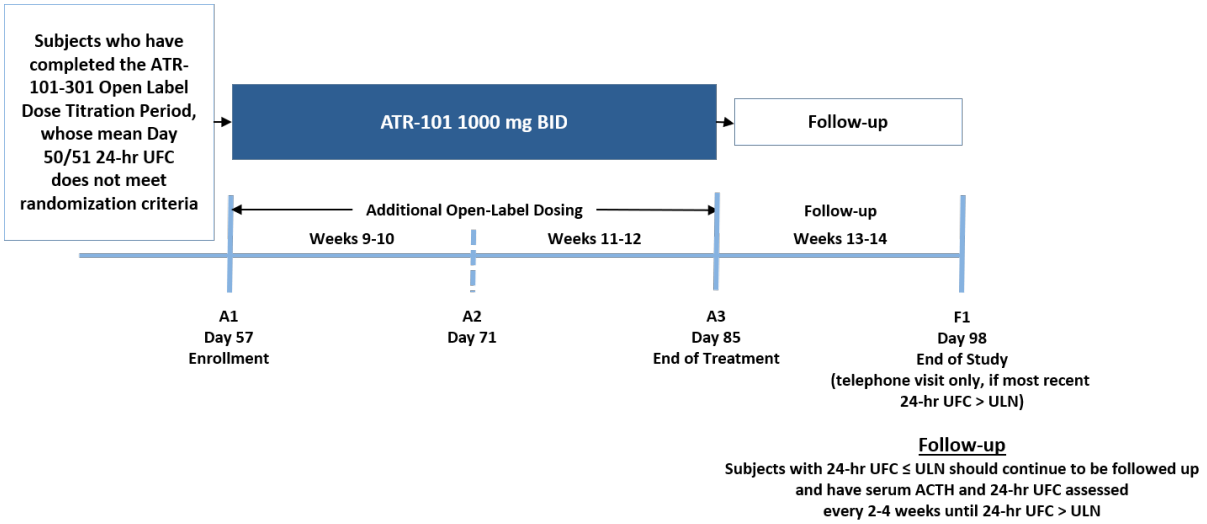


Figure 3: Study Schematic, Additional Open-Label Dosing Period



During a screening period of up to 8 weeks' duration, subjects will undergo a wash-out of medications used to treat Cushing's syndrome (if needed) and will then perform two 24-hour (hr) urine collections for baseline urinary free cortisol (UFC) assessment within 28 days prior to enrollment into the open-label dose-escalation period. At enrollment, all eligible subjects will be assigned to one of two 24-hr UFC strata. Strata will be assigned according to baseline 24-hr UFC values, calculated as the mean of all 24-hr UFC levels obtained within the 28 days prior to enrollment:

- Stratum I: 24-hr UFC 1.3 to < 4 × upper limit of normal (ULN)
- Stratum II: 24-hr UFC 4 to 10 × ULN

Enrollment into a particular stratum may be limited to ensure the inclusion of subjects in both strata.

Open-Label Dose-Escalation Period: The open-label dose-escalation period will be 8 weeks in duration and will allow each subject to receive three dose levels of ATR-101 (i.e., 250 mg twice daily (BID), 500 mg BID,

and 1000 mg BID). The 250 mg and 500 mg BID dose levels will each be used for 2 weeks, and the 1000 mg BID dose level will be used for 4 weeks.

- Study Days 1-14: At Visit T1, all subjects will be assigned to take the same starting dose of ATR-101, 250 mg BID, at the beginning of the open-label dose-escalation period. Twenty-four-hour UFCs will be assessed on Days 13 and 14 (collections start on Days 13 and 14, respectively, and finish on Days 14 and 15, respectively).
- Study Days 15-28: At Visit T2, all subjects will be assigned to take the next higher dose of ATR-101, 500 mg BID. Twenty-four-hour UFCs will be assessed on Days 27 and 28 (collections start on Days 27 and 28, respectively, and finish on Days 28 and 29, respectively).
- Study Days 29-56: At Visit T3, all subjects will be assigned to take the next higher dose of ATR-101, 1000 mg BID. Twenty-four-hour UFCs will be assessed on Days 41, 42, 50, 51, and 56 (collections start on Days 41, 42, 50, 51, and 56, respectively, and finish on Days 42, 43, 51, 52, and 57, respectively).

At any time, the ATR-101 dose may be down-titrated as needed for safety reasons at the discretion of the Investigator. There will be no wash-out period between the open-label dose-escalation period and either the double-blind randomized withdrawal period or the additional open-label dosing period.

Double-blind Randomized Withdrawal Period: The double-blind randomized withdrawal period will be up to 4 weeks in duration. A subject is eligible to enter the double-blind randomized withdrawal period if the mean of the Day 50 and Day 51 ("mean Day 50/51") 24-hr UFCs meets at least one of the following randomization criteria:

- 24-hr UFC ≤ ULN
- 24-hr UFC ≤ 50% relative to the baseline value

Eligible subjects will be randomized in a 1:1 ratio to receive either ATR-101 at the same dose level on which they achieved the mean Day 50/51 24-hr UFC ≤ ULN (or ≤ 50% of their baseline value) or matching placebo. Subjects will continue in the double-blind randomized withdrawal period for 4 weeks or until their mean Day 64/65 24-hr UFC is > 1.3 x ULN and has also increased by > 50% relative to their mean Day 50/51 24-hr UFC, whichever comes first. Subjects who are not eligible to be randomized will enter the Additional Open-Label Dosing Period instead of the Double Blind Randomized Withdrawal Period (see below).

- Study Days 57-70: Twenty-four-hour UFCs will be collected on Days 64 and 65 (collections start on Days 64 and 65, respectively, and finish on Days 65 and 66, respectively). At the time of Visit R2 (Day 71), if the mean Day 64/65 24-hr UFC result is available and is > 1.3 x ULN, and has also increased by > 50% relative to the mean Day 50/51 24-hr UFC, the subject will complete the End-of-Treatment (EoT) visit (Visit R3) instead of Visit R2 and may then be started on another agent at the discretion of his or her physician. Otherwise, the subject will continue in the double-blind, randomized withdrawal period.
- Study Days 71-85: Twenty-four-hour UFCs will be collected on Days 79 and 84 (collections start on Days 79 and 84, respectively, and finish on Days 80 and 85, respectively). The EoT visit (Visit R3) will be completed on Day 85. Note: if the mean Day 64/65 24-hr UFC was not available at the time of Visit R2, but subsequently is found to meet criteria for study completion, the EoT visit should be performed as soon as practicable, rather than on Day 85. Additionally, if the Day 79 or Day 84 24-hr UFC is > ULN, after completion of the EoT visit (Visit R3) the subject may begin treatment with another agent at the discretion of his or her physician.

Additional Open-Label Dosing Period: The additional open-label dosing period will be 4 weeks in duration. A subject is eligible to enter the additional open-label dosing period if they do not meet any of the randomization criteria described in the above section.

Eligible subjects will be assigned to take ATR-101 1000 mg BID (or a lower dose if needed for safety, at the discretion of the Investigator). Subjects will continue in the additional open-label dosing period for 4 weeks.

- Study Days 57-70: Twenty-four-hour UFCs will be collected on Days 69 and 70 (collections start on Days 69 and 70, and finish on Days 70 and 71, respectively).

- Study Days 71-85: Twenty-four-hour UFCs will be collected on Days 79 and 84 (collections start on Days 79 and 84, respectively, and finish on Days 80 and 85, respectively). The EoT visit (Visit A3) will be completed on Day 85. Note: if the Day 79 or Day 84 24-hr UFC is > ULN, after completion of the EoT visit (Visit A3) the subject may begin treatment with another agent at the discretion of his or her physician.

Follow-up Period: During the follow-up period, subjects will continue to be monitored for safety. Subjects whose most recent 24-hr UFC is ≤ ULN will have a follow-up visit (Visit F1) at the study site 2 weeks after their ET/EoT visit. Subjects whose most recent 24-hr UFC is > ULN will have a follow-up telephone visit instead of a study site visit.

- Study Days 86-98: If the Day 79 24-hr UFC is ≤ ULN, a follow-up visit (Visit F1) at the study site will be scheduled for Day 98, 2 weeks after the EoT visit. This visit will consist largely of safety assessments. Subjects whose Day 84 24-hr UFC is also ≤ ULN will begin a 24-hr urine collection on Day 92 and finish on Day 93. If the Day 79, Day 84 or Day 92 24-hr UFC is > ULN, a telephone visit will be conducted on Day 98 instead of a study site visit (in case of discrepant results, the latest result should be used). If the Day 92 24-hr UFC result is unknown at the time the Day 98 visit is due, the subject will proceed with having the Day 98 visit at the study site.
- Subjects whose Day 92 24-hr UFC is ≤ ULN should continue to be followed up and have morning serum ACTH and 24-hr UFC assessed every 2-4 weeks until their 24-hr UFC is > ULN or until the Investigator and the Medical Monitor agree that the subject is stable.

Throughout the course of the study, safety evaluations will include assessment of AEs, concomitant medications, clinical laboratory tests, vital signs, physical examinations (PEs) and 12-lead electrocardiograms (ECGs).

It is anticipated that the overall duration of the study per subject will range from approximately 16-22 weeks, depending upon the duration (if any) required for wash-out and the duration of follow-up.

Number of Subjects (planned): Approximately 16 adults with endogenous Cushing's syndrome

Diagnosis and Criteria for Inclusion:

Inclusion Criteria:

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

1. Provision of signed and dated informed consent prior to any study-specific procedures
2. Men and women 18-80 years of age (inclusive) at screening
3. Subjects must have a confirmed diagnosis of endogenous Cushing's syndrome as evidenced by baseline UFC 1.3 to 10 × ULN (mean of all 24-hr UFC levels obtained during the screening period within 28 days of enrollment into the open-label dose-escalation period) AND documentation at any time of ONE of the following three criteria:
   - For subjects with a diagnosis of pituitary Cushing's syndrome, either:
     - Magnetic resonance imaging (MRI) confirmation of pituitary adenoma (greater than or equal to 0.6 cm), OR
     - For subjects with a pituitary microadenoma less than 0.6 cm, bilateral inferior petrosal sinus sampling (BIPSS) showing an ACTH gradient > 2 before or > 3 after corticotropin-releasing hormone (CRH) or desmopressin (DDAVP) stimulation, OR
     - For subjects who have had prior pituitary surgery: histopathology confirming an ACTH-staining adenoma
   - For subjects with a diagnosis of adrenal Cushing's syndrome: MRI or computed tomography (CT) of the adrenal glands showing an adrenal tumor
   - For subjects with a diagnosis of ectopic ACTH as the cause of their Cushing's syndrome: ACTH-dependent Cushing's syndrome and either:
     - MRI showing no pituitary adenoma, OR
     - MRI showing only a small pituitary adenoma (< 0.6 cm) AND a negative BIPSS, OR
     - For subjects who have had prior pituitary surgery: histopathology that is negative for an ACTH-staining adenoma

4. Subjects with a history of prior pituitary surgery must be at least 3 months post-surgery at the time of the screening visit
5. Body mass index (BMI) between 18 and 60 kg/m^2, inclusive, at screening
6. Female subjects must be postmenopausal > 2 years OR must have been permanently surgically sterilized (bilateral salpingectomy or tubal occlusion) > 2 years OR male partner(s) has had a vasectomy > 2 years OR must consent to use two permitted medically-acceptable methods of contraception throughout the study during any sexual intercourse with a male partner. Permitted medically-acceptable methods of birth control for this study include oral contraceptives, contraceptive implants, Depo-Provera®, contraceptive patch, vaginal ring, male condom, female condom, spermicide, diaphragm with spermicide, cervical cap with spermicide, contraceptive sponge, or an intrauterine device (IUD); IUDs must have been in place for at least 28 days prior to first dose of study drug.

Exclusion Criteria:

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

1. Pseudo-Cushing's syndrome, cyclic Cushing's syndrome or current iatrogenic Cushing's syndrome
2. Subjects who are considered candidates for surgical treatment of Cushing's syndrome, unless it is clearly documented that the subject has refused such surgery or that surgery cannot be scheduled for at least the anticipated duration of the study
3. Normal late night salivary cortisol value during screening, unless the subject's history clearly demonstrates that he or she does not have pseudo-Cushing's or cyclic Cushing's. If the subject has a normal late night salivary cortisol, and the PI feels the subject does not have pseudo-Cushing's or cyclic Cushing's, the subject may be enrolled with approval of the medical monitor
4. Normal 24-hr UFC during screening (this would be suggestive of cyclic Cushing's)
5. Radiotherapy of the pituitary within 6 months prior to or during screening
6. For subjects with pituitary Cushing's syndrome, any compression of the optic chiasm or the presence of a tumor within 2 mm of the optic chiasm on the most recent pituitary MRI prior to or during screening
7. Use of or medical requirement for any of the following medications within the timeframes specified below prior to collection of the first 24-hr UFC during Screening and throughout study participation (see Section 5.11 for additional prohibited and restricted medications):
   - Inhibitors of steroidogenesis (ketoconazole, metyrapone): 1 week
   - Pituitary-directed agents: Dopamine agonists (bromocriptine, cabergoline) and PPARγ agonists (rosiglitazone or pioglitazone): 4 weeks
   - Octreotide LAR, Lanreotide SR and Lanreotide autogel: 14 weeks
   - Octreotide (immediate release formulation): 1 week
   - Pasireotide: 4 weeks
   - Mitotane: 26 weeks
   - Mifepristone: 3 weeks
8. Uncontrolled diabetes mellitus, as evidenced by HbA1c > 9.0% at screening
9. Uncontrolled hypertension, defined as systolic blood pressure > 160 mmHg or diastolic blood pressure > 90 mmHg during screening. Note: if appropriate, subjects may have blood pressure medications adjusted and blood pressure reassessed at an unscheduled visit prior to Visit T1.
10. Any history of gastric or small intestinal surgery or any current disease that causes malabsorption. Note: irritable bowel syndrome is acceptable for inclusion
11. Alcohol or substance abuse (cocaine, amphetamines and/or opioids) within the year prior to screening
12. Abnormal laboratory values as per the guidelines listed below or any other clinically significant, unexplained laboratory abnormality according to the Investigator:
    - Serum ALT or AST > 3 × ULN
    - Serum total bilirubin > 1.5 × ULN
    - Serum creatinine > 1.5 × ULN
    - Glomerular filtration rate < 60 mL/min/1.73 m^2
13. Pregnant, breast-feeding, having conceived within the 6 months prior to screening, or having an intent to become pregnant during the study period
14. QTc > 470 msec on electrocardiogram at screening (subjects with a single QTc > 470 msec may have 2 additional ECGs taken during screening and the QTcs averaged; if the average QTc is > 470 msec then the subject is excluded)
15. Known history of Gilbert's syndrome

16. HIV, hepatitis B, or hepatitis C positivity at screening
17. Any malignancy within the previous 5 years, other than curatively treated basal or squamous cell skin cancer or cervical carcinoma *in situ*
18. Previous exposure to any amount of ATR-101
19. Participation in any study of an investigational drug within 30 days prior to screening
20. Significant psychiatric disease, recent severe physical stress, malnutrition, chronic excessive exercise, or any other medical or psychiatric condition that, in the opinion of the Investigator, is likely to confound the interpretation of the study results or prevent the subject from understanding the requirements of or successfully completing the study

Investigational Product, Dosage and Mode of Administration:

ATR-101 250-mg and 500-mg tablets for oral administration, one tablet twice per day for the 250 mg and 500 mg BID doses, respectively; and two 500-mg tablets twice per day for the 1000 mg BID dose

Duration of Treatment:

8 weeks in the open-label dose-escalation period and up to 4 weeks in the double-blind randomized withdrawal period or the additional open-label period

Reference Therapy, Dosage and Mode of Administration:

Placebo matching tablets for the ATR-101 500-mg tablets during the double-blind randomized withdrawal period

Study Endpoints:

Primary Efficacy Endpoint:

- The proportion of subjects with either a normal 24-hr UFC or a reduction in 24-hr UFC of ≥ 50% relative to their baseline value at the end of the double-blind randomized withdrawal period

Secondary Efficacy Endpoints: The secondary efficacy endpoints will include the following. Unless otherwise specified in the Statistical Analysis Plan, the endpoints will be evaluated for each post-baseline visit, at the end of the open-label dose-escalation period and at the end of the double-blind randomized withdrawal period, for the ITT population as a whole and for each baseline UFC stratum.

- The proportion of subjects with a normal 24-hr UFC at the end of the double-blind randomized withdrawal period
- The proportion of subjects with a reduction in 24-hr UFC of ≥ 50% relative to their baseline value at the end of the double-blind randomized withdrawal period
- The proportion of subjects with a normal 24-hr UFC at the end of the open-label dose-escalation period and at the end of the additional open-label dosing period
- The proportion of subjects with a reduction in 24-hr UFC of ≥ 50% relative to their baseline value at the end of the open-label dose-escalation period and at the end of the additional open-label dosing period
- The change and percentage change in the 24-hr UFC from randomization at the end of the double-blind randomized withdrawal period
- The change and percentage change in the 24-hr UFC from baseline at the end of the open-label dose-escalation period and at the end of the additional open-label dosing period
- The proportion of subjects with a normal late night salivary cortisol at the end of the double-blind randomized withdrawal period
- The proportion of subjects with a normal late night salivary cortisol at the end of the open-label dose-escalation period and at the end of the additional open-label dosing period
- The change and percentage change in the late night salivary cortisol from randomization at the end of the double-blind randomized withdrawal period
- The change and percentage change in the late night salivary cortisol from baseline at the end of the open-label dose-escalation period and at the end of the additional open-label dosing period
- The change and percentage change from baseline in blood hormone levels, including 11-DOC, 17-OHP, A, A4, ACTH, cortisol, DHEA, DHEAS, free T, P, renin, SHBG and total T

- The change from baseline in fasting glucose, insulin, lipid panel, systolic blood pressure, diastolic blood pressure and BMI

Pharmacokinetic Endpoints:

- The C_{max}, T_{max}, AUC, $t_{1/2}$ and other PK parameters of ATR-101 and its major metabolites (as appropriate and as the data allow)
- The relationship between C_{max} and AUC vs. the percentage change in 24-hr UFC; other PK/PD relationships may be explored as appropriate and as data allow

Safety Endpoints: Safety endpoints will include the incidence of treatment-emergent adverse events and serious adverse events, as well as changes from baseline in PEs, safety laboratory tests and ECG parameters.

Statistical Methods:

A Statistical Analysis Plan that includes a more technical and detailed description of the planned statistical analyses will be prepared prior to unblinding of the double-blind randomized withdrawal period of the study.

Analysis Populations:

Efficacy – The primary efficacy analysis population will be the Intent-to-Treat (ITT) population, based on all subjects who are randomized into the double-blind randomized withdrawal period and take at least one dose of double-blind study drug. The modified ITT (mITT) population, based on all subjects who complete at least 2 weeks in the double-blind randomized withdrawal period of the study, will be used for additional analyses. For efficacy analyses, subjects will be included in the treatment group to which they were randomized.

Safety – The safety population will include all treated subjects. Safety analyses will be based on the safety population. For the safety analyses for the double-blind randomized withdrawal period, subjects randomized to the placebo group who receive ATR-101 will be included in the treatment group of the active study drug that they received.

Pharmacokinetic – The PK population will include all subjects with measurable drug concentrations. PK analyses will be based on the PK population.

Sample Size:

A sample size of 16 enrolled patients is sufficient per clinical considerations. No formal sample size calculation was performed.

Analysis Methodology:

Primary endpoint – The primary efficacy endpoint, the proportion of subjects with either a normal 24-hr UFC or a reduction in UFC of ≥ 50% relative to their baseline value at the end of the double-blind randomized withdrawal period, will be evaluated using the Cochran-Mantel-Haenszel (CMH) test, controlling for baseline 24-hr UFC stratum.

Secondary endpoints – No further adjustments for multiple group comparisons, multiple additional endpoints or multiple subgroups of interest are planned.

Responder analyses and other categorical analyses will be based on the CMH test or Fisher's exact test, as appropriate and if the data allow. Continuous endpoints will be evaluated using ANCOVA or ANOVA model methodology, as appropriate and if the data allow.

Exploratory endpoints – Additional efficacy endpoints may be pre-specified in the Statistical Analysis Plan, including sensitivity analyses associated with drug compliance and missing data issues.

Safety endpoints – Adverse events counts (overall, as well as by severity, causality and seriousness) will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Descriptive statistics and shift tables will be used to summarize continuous laboratory, blood pressure and ECG parameters. Counts and shift tables will be used for categorical lab parameters.

Pharmacokinetic endpoints – 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}, AUC_{0-4} and trough levels.

Individual subject PK data will be analyzed along with pooling of subjects' data at each dose level. Individual PK parameters will be derived using the WinNonlin software, and table summaries will be provided using descriptive summary statistics.

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LIST OF ABBREVIATIONS

Table 1: Abbreviations

Abbreviation	Explanation
11-DOC	11-deoxycorticosterone
17-OHP	17-hydroxyprogesterone
A	aldosterone
A4	androstenedione
ACAT1	acyl-CoA:cholesterol acyltransferase 1
ACC	adrenocortical carcinoma
ACTH	adrenocorticotropic hormone
AE	adverse event
ALB	albumin
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
aPTT	activated partial thromboplastin time
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration-time curve
AUC_{0-4}	area under the concentration-time curve from time zero to 4 hrs post-dose
AUC_{0-4}/D	dose-normalized AUC_{0-4}
AUC_{0-24}	area under the concentration-time curve from time zero to 24 hrs post-dose
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
AUC_{0-t}	area under the concentration-time curve up to the last quantifiable concentration time point (t)
$AUC_{\%extrap}$	the percentage of $AUC_{0-\infty}$ extrapolated
BID	twice daily
BIPSS	bilateral inferior petrosal sinus sampling
BMI	body mass index
BUN	blood urea nitrogen
Ca	calcium
CE	cholesteryl ester
CFR	Code of Federal Regulations
CL	clearance
CL/F	oral clearance calculated as dose/$AUC_{0-\infty}$
C_{last}	last quantifiable concentration
C_{max}	maximum observed concentration
C_{max}/D	dose-normalized C_{max}
CMH	Cochran-Mantel-Haenszel
CQA	clinical quality assurance
CRA	clinical research associate

Abbreviation	Explanation
CRH	corticotrophin-releasing hormone
CSR	clinical study report
CT	computed tomography
CYP	cytochrome P450
DDAVP	desmopressin
demog	demographics
DHEA	dehydroepiandrosterone
DHEA-S	dehydroepiandrosterone sulfate
DSMB	Data Safety Monitoring Board
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EoS	end-of-study
EoT	end-of-treatment
ET	early termination
excl	exclusion
EudraCT	European Clinical Trials Database
DHEA-S	dehydroepiandrosterone sulfate
FC	free cholesterol
GC	glucocorticoid
GCP	Good Clinical Practice(s)
GFR	Glomerular filtration rate
GLP	Good Laboratory Practices
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
Hct	hematocrit
HCV	hepatitis C virus
HDL	high density lipoprotein
HEENT	head, eyes, ears, nose and throat
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council on Harmonisation
ID	identification number
IMP	investigational medicinal product
incl	inclusion
IND	Investigational new drug
INR	international normalized ratio
IRB	institutional review board
ITT	intent-to-treat
IUD	intrauterine device

Abbreviation	Explanation
IVRS/IWRS	interactive voice/web response system
λz	terminal phase rate constant
LDL	low density lipoprotein
MC	mineralocorticoid
MDR1	multidrug resistance protein 1
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
P	progesterone
P-gp	permeability glycoprotein
PD	pharmacodynamic
PE	physical examination
PK	pharmacokinetic(s)
PO	per os (by mouth)
PPARγ	peroxisome proliferator-activated receptor gamma
PT	prothrombin time
QT interval	the time from the start of the Q wave and the end of the T wave
QTc	corrected QT interval
QTcF	QT interval corrected using the Fridericia method
RBC	red blood cell
RECIST	response evaluation criteria in solid tumors
SAE	serious adverse event
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvate transaminase
SHBG	sex hormone binding globulin
T	testosterone
$t_{1/2}$	terminal phase half-life
TBD	to be determined
TdP	torsades des pointes
T_{max}	time of maximum concentration
TMF	trial master file
UFC	urinary free cortisol
ULN	upper limit of normal
US/USA	United States/United States of America
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

Cushing's syndrome is a condition that results from the chronic effects of excessive glucocorticoids. Exogenous Cushing's syndrome, the most common form, is due to treatment with glucocorticoid medications. Endogenous Cushing's syndrome is rare, with an incidence of 2-3 cases per million per year, and is usually divided into adrenocorticotropic hormone (ACTH)-dependent causes and ACTH-independent causes.[1] Cushing's disease, the most common cause (~70-80%) of endogenous Cushing's syndrome, is due to an ACTH-secreting pituitary tumor.[2] Cushing's disease is further classified as being due to micro- or macroadenomas based on the size of the pituitary tumor.[2] Other causes of endogenous Cushing's syndrome include primary adrenal gland tumors and ectopic (non-pituitary) ACTH-secreting tumors.[1]

Cushing's syndrome of any cause results in the clinical manifestations of weight gain, hypertension, diabetes, decreased short-term memory, depression, hirsutism, recurrent infection, weak bones and other adverse effects.[3,4,5] If left untreated, Cushing's syndrome can be life-threatening. Mortality rates for untreated, uncontrolled Cushing's syndrome are high with cardiovascular causes being most common.[3,4]

Treatment of endogenous Cushing's syndrome depends upon the etiology. For Cushing's disease, surgical intervention via transsphenoidal resection of the pituitary tumor serves as first line therapy. The success rate depends largely upon the size of the tumor (micro- vs. macro-adenoma) and the expertise of the surgeon. Overall, ~65-90% of Cushing's disease patients with microadenomas are cured with transsphenoidal surgery.[6] Success rates fall significantly for subsequent surgeries and recurrence rates are as high as 20%.[6] External beam radiation also serves a role in the management of Cushing's disease, usually in the setting of failed transsphenoidal surgery. Success rates with radiation therapy are highly variable and results can take years.[7] For Cushing's syndrome due to non-pituitary causes, including ectopic ACTH-secreting tumors and adrenocortical tumors or bilateral adrenal hyperplasia, surgical intervention serves as the primary treatment modality. Medical therapies for Cushing's disease are generally used immediately prior to transsphenoidal surgery or following surgery if there is disease recurrence. Medical therapies can be broadly categorized as steroidogenesis inhibitors (ketoconazole, metyrapone), cortisol receptor blockers (mifepristone) or centrally-acting agents (somatostatin analogues, dopamine agonists).[7] In the United States (US), only mifepristone and pasireotide (a somatostatin analogue) are labeled for the treatment of Cushing's syndrome and Cushing's disease, respectively. Consequently, there is a need for additional therapies for Cushing's syndrome.

1.2. Rationale for the Use of ATR-101 in Cushing's Syndrome

ATR-101, an acyl-CoA:cholesterol acyltransferase 1 (ACAT1) inhibitor, may provide an extremely valuable tool for the clinician managing Cushing's syndrome. ACAT1 is a membrane-bound enzyme that catalyzes the esterification of free cholesterol (FC) to cholesteryl ester (CE). ACAT1 is highly expressed in the adrenal glands compared with other tissues[8] and ATR-101 is found at higher levels in the adrenal glands compared to other sites in the body.[9] Both of these factors are likely to contribute to the selectivity of ATR-101's effects. In the adrenal glands, CE serves as a substrate reservoir for steroid biosynthesis. At low doses/exposures, ATR-101 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. Dose-dependent inhibition of adrenal steroidogenesis across the entire steroidogenic pathway may result in dose-dependent decreases in all steroids including cortisol and may provide an opportunity to normalize these cortisol levels in Cushing's syndrome patients. Use of ATR-101 in the treatment of Cushing's syndrome 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.

1.2.1. Preclinical Studies

ATR-101 has been studied extensively *in vitro* and *in vivo*. Two proof-of-concept dog studies have been conducted, which validate the mechanism-of-action studies.[9] In the first study, 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 Cushing's syndrome. Ten dogs with confirmed Cushing's syndrome (three of adrenal and seven of 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. Plasma baseline cortisol concentrations at initial and final evaluations were not significantly different, although baseline cortisol concentrations did decrease in 4 of 10 dogs. 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 mg/kg BID and three of eight animals (one male, two females) at 10 mg/kg BID exhibited clinical signs consistent with adrenal insufficiency (subsequently resulting in a change from 30 to 20 mg/kg BID and from 10 to 7.5 mg/kg BID). 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 post-treatment observation period following the 13-week study was 4 weeks, with mean effects demonstrating signs of recovery in both male (2/2) and female (1/2) dogs. The decreases in adrenal function (decreases in basal and ACTH-stimulated cortisol measurements), decreased adrenal weights and histologic changes, were all anticipated effects based upon published studies.[10,11]

1.2.2. Clinical Studies

Two clinical studies (ATR-101-001 and ATR-101-101) have been initiated with ATR-101. Study ATR-101-001 is a Phase 1, first-in-human, maximum tolerated dose (MTD) study to determine the safety of ATR-101 in subjects with ACC, a rare but highly malignant and aggressive cancer. ATR-101 doses for this indication are markedly higher than those proposed for the treatment of Cushing's syndrome and are targeted for apoptotic effects. Mean area under the curve (AUC_{0-24}) values as high as ~45,000 ng·hr/mL have been observed with acceptable toxicity and the MTD has yet to be defined. Antitumor activity in this study is being evaluated by objective measures of tumor size (RECIST criteria) and assessment of adrenal cortical steroid production. As of March 1, 2016, 54 ACC subjects have been exposed to ATR-101 at doses ranging from 1.6 to 102.4 mg/kg/day. The most commonly observed reactions have been mild or moderate nausea, vomiting and diarrhea at the higher doses of ATR-101. There has been one serious adverse event (SAE) of vomiting and diarrhea that was considered to be related to ATR-101 by the Investigator. One subject with baseline liver dysfunction had a reversible non-serious grade 3 increase of alanine aminotransferase (ALT). Hypersensitivity rashes have been observed as has self-limiting dysuria.

Study ATR-101-101, a randomized, 3-way crossover food effect study, was performed in 14 healthy human volunteers. Subjects took a 500-mg tablet of ATR-101 under three different administration conditions: in the fasted state with water, in the fasted state with cola (an acidic beverage), or after a standard high-fat meal. ATR-101 exposure was approximately 1.9-fold higher when taken after a meal than when taken in the fasted state with water. Administration with cola resulted in exposure to ATR-101 that was approximately 1.2 times the exposure when taken fasted with water. ATR-101 was very well tolerated in the food effect study with no SAEs and few adverse events (AEs), none of which changed the safety profile of ATR-101.

Additional information may be found in the current version of the Investigator's Brochure.[9]

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. There have been no previous studies of ATR-101 in subjects with Cushing's syndrome. The use of ATR-101 for the treatment of Cushing's syndrome presents a novel therapeutic approach.

1.3. Research Hypothesis

The study will evaluate the hypothesis that treatment of adult subjects with endogenous Cushing's syndrome with ATR-101 will result in decreases in cortisol production and that subsequent randomized withdrawal from ATR-101 or continued treatment will demonstrate a return towards baseline levels or maintenance of effect, respectively.

1.4. Rationale for Conducting This Study

This Phase 2 study of ATR-101 will be used to establish the proof-of-concept for the use of ATR-101 in adult subjects with endogenous Cushing's syndrome.

2. STUDY OBJECTIVES

2.1. Primary Objective

- To evaluate the efficacy and safety of orally-administered ATR-101 in adults with endogenous Cushing's syndrome

2.2. Secondary Objectives

- To evaluate the changes in adrenal steroids and adrenal steroid intermediates
- To evaluate the change in ACTH
- To evaluate the change in metabolic syndrome-related parameters, including fasting glucose, insulin, lipid panel, blood pressure and body mass index (BMI)
- To assess the safety and tolerability of ATR-101
- To determine the pharmacokinetics (PK) of ATR-101 and its major metabolites
- To evaluate the PK/pharmacodynamic (PD) relationships of ATR-101

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This Phase 2 multicenter study consists of two parts: an open-label intra-subject dose-escalation period of 8 weeks' duration, followed either by a double-blind randomized withdrawal period of 4 weeks' duration (if the subject meets randomization criteria) or by an additional open label dosing period of 4 weeks' duration (if the subject does not meet randomization criteria). A study schematic is shown in Figures 1, 2, and 3 below.

Figure 1: Study Schematic, Screening and Open-Label Dose-Escalation Periods

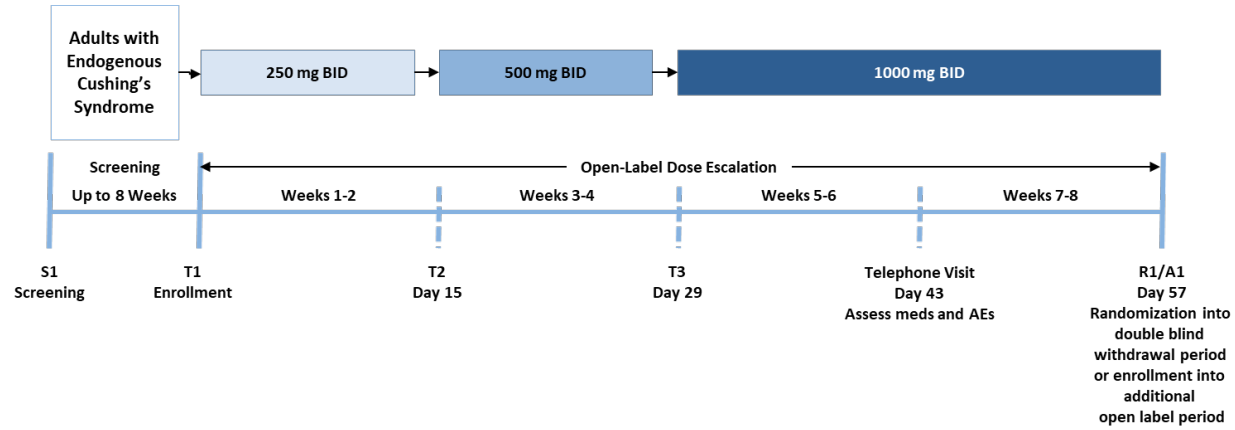


Figure 2: Study Schematic, Double-Blind Randomized Withdrawal Period

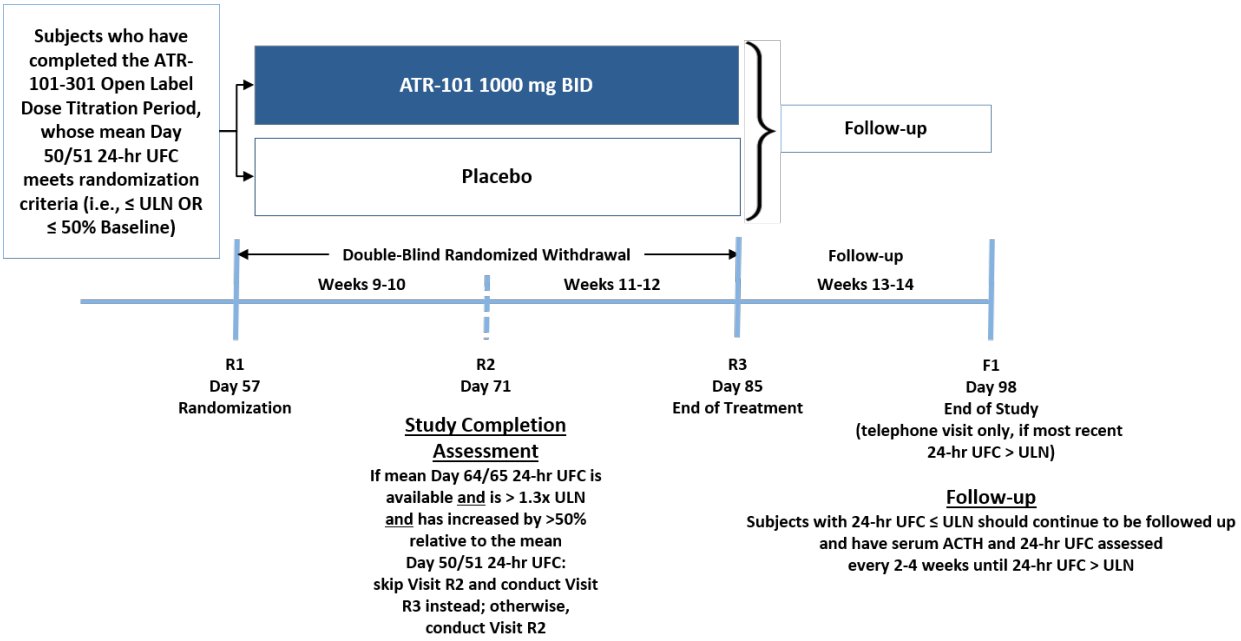
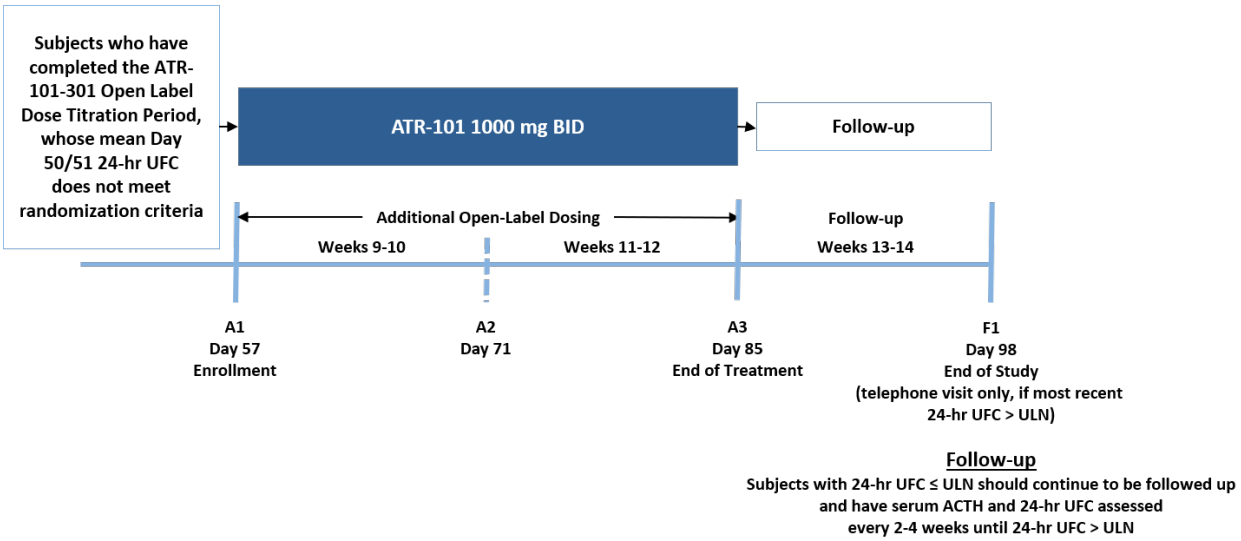


Figure 3: Study Schematic, Additional Open-Label Dosing Period



3.1.1. Screening Period

During a screening period of up to 8 weeks' duration, subjects will undergo a wash-out of medications used to treat Cushing's syndrome (if needed) and will then perform two 24-hour (hr) urine collections for baseline urinary free cortisol (UFC) assessment within 28 days prior to enrollment into the open-label dose-escalation period. At enrollment, all eligible subjects will be assigned to one of two 24-hr UFC strata. Strata will be assigned according to baseline 24-hr UFC values, calculated as the mean of all 24-hr UFC levels obtained within the 28 days prior to enrollment:

- Stratum I: 24-hr UFC 1.3 to < 4 × upper limit of normal (ULN)
- Stratum II: 24-hr UFC 4 to 10 × ULN

Enrollment into a particular stratum may be limited to ensure the inclusion of subjects in both strata.

3.1.2. Open-Label Dose-Escalation Period

The open-label dose-escalation period will be 8 weeks in duration and will allow each subject to receive three dose levels of ATR-101 (i.e., **250 mg BID**, **500 mg BID,** and **1000 mg BID**). The 250 mg and 500 mg BID dose levels will each be used for 2 weeks, and the 1000 mg BID dose level will be used for 4 weeks.

- Study Days 1-14: At Visit T1, all subjects will be assigned to take the same starting dose of ATR-101, 250 mg BID, at the beginning of the open-label dose-escalation period. Twenty-four-hour UFCs will be assessed on Days 13 and 14 (collections start on Days 13 and 14, respectively, and finish on Days 14 and 15, respectively).
- Study Days 15-28: At Visit T2, all subjects will be assigned to take the next higher dose of ATR-101, 500 mg BID. Twenty-four-hour UFCs will be assessed on Days 27 and 28

(collections start on Days 27 and 28, respectively, and finish on Days 28 and 29, respectively).

- Study Days 29-56: At Visit T3, all subjects will be assigned to take the next higher dose of ATR-101, 1000 mg BID. Twenty-four-hour UFCs will be assessed on Days 41, 42, 50, 51, and 56 (collections start on Days 41, 42, 50, 51, and 56, respectively, and finish on Days 42, 43, 51, 52, and 57, respectively).

At any time, the ATR-101 dose may be down-titrated as needed for safety reasons at the discretion of the Investigator. There will be no wash-out period between the open-label dose-escalation period and either the double-blind randomized withdrawal period or the additional open-label dosing period.

3.1.3. Double-blind Randomized Withdrawal Period

The double-blind randomized withdrawal period will be up to 4 weeks in duration. A subject is eligible to enter the double-blind randomized withdrawal period if the mean of the Day 50 and Day 51 ("mean Day 50/51") 24-hr UFCs meets at least one of the following randomization criteria:

- 24-hr UFC ≤ ULN
- 24-hr UFC ≤ 50% relative to the baseline value

Eligible subjects will be randomized in a 1:1 ratio to receive either ATR-101 at the same dose level being used at the completion of the open-label dose-escalation period (expected to be 1000 mg BID) or matching placebo. Subjects will continue in the double-blind randomized withdrawal period for 4 weeks or until their mean Day 64/65 24-hr UFC is > 1.3 x ULN and has also increased by > 50% relative to their mean Day 50/51 24-hr UFC, whichever comes first. Subjects who are not eligible to be randomized will enter the Additional Open-Label Dosing Period instead of the Double Blind Randomized Withdrawal Period (see below).

- Study Days 57-70: Twenty-four-hour UFCs will be collected on Days 64 and 65 (collections start on Days 64 and 65, respectively, and finish on Days 65 and 66, respectively). At the time of Visit R2 (Day 71), if the mean Day 64/65 24-hr UFC result is available and is > 1.3 x ULN, and has also increased by > 50% relative to the mean Day 50/51 24-hr UFC, the subject will complete the End-of-Treatment (EoT) visit (Visit R3) instead of Visit R2 and may then be started on another agent at the discretion of his or her physician. Otherwise, the subject will continue in the double-blind, randomized withdrawal period.
- Study Days 71-85: Twenty-four-hour UFCs will be collected on Days 79 and 84 (collections start on Days 79 and 84, respectively, and finish on Days 80 and 85, respectively). The EoT visit (Visit R3) will be completed on Day 85. Note: if the mean Day 64/65 24-hr UFC was not available at the time of Visit R2, but subsequently is found to meet criteria for study completion, the EoT visit should be performed as soon as practicable, rather than on Day 85. Additionally, if the Day 79 or Day 84 24-hr UFC is > ULN, after completion of the EoT visit (Visit R3) the subject may begin treatment with another agent at the discretion of his or her physician.

3.1.4. Additional Open-Label Dosing Period

The additional open-label dosing period will be 4 weeks in duration. A subject is eligible to enter the additional open-label dosing period if they do not meet any of the randomization criteria described in the above section.

Eligible subjects will be assigned to take ATR-101 1000 mg BID (or a lower dose if needed for safety, at the discretion of the Investigator). Subjects will continue in the additional open-label dosing period for 4 weeks.

- Study Days 57-70: Twenty-four-hour UFCs will be collected on Days 69 and 70 (collections start on Days 69 and 70, and finish on Days 70 and 71, respectively).
- Study Days 71-85: Twenty-four-hour UFCs will be collected on Days 79 and 84 (collections start on Days 79 and 84, respectively, and finish on Days 80 and 85, respectively). The EoT visit (Visit A3) will be completed on Day 85. Note: if the Day 79 or Day 84 24-hr UFC is > ULN, after completion of the EoT visit (Visit A3) the subject may begin treatment with another agent at the discretion of his or her physician.

3.1.5. Follow-up Period

During the follow-up period, subjects will continue to be monitored for safety. Subjects whose most recent 24-hr UFC is ≤ ULN will have a follow-up visit (Visit F1/End-of-Study, EoS; this is the same as the end of trial) at the study site 2 weeks after their ET/EoT visit. Subjects whose most recent 24-hr UFC is > ULN will have a follow-up telephone visit instead of a study site visit.

- Study Days 86-98: If the Day 79 24-hr UFC is ≤ ULN, a follow-up visit (Visit F1) at the study site will be scheduled for Day 98, 2 weeks after the EoT visit. This visit will consist largely of safety assessments. Subjects whose Day 84 24-hr UFC is also ≤ ULN will begin a 24-hr urine collection on Day 92 and finish on Day 93. If the Day 79, Day 84 or Day 92 24-hr UFC is > ULN, a telephone visit will be conducted on Day 98 instead of a study site visit (in case of discrepant results, the latest result should be used). If the Day 92 24-hr UFC result is unknown at the time the Day 98 visit is due, the subject will proceed with having the Day 98 visit at the study site.
- Subjects whose Day 92 24-hr UFC is ≤ ULN should continue to be followed up and have morning serum ACTH and 24-hr UFC assessed every 2-4 weeks until their 24-hr UFC is > ULN or until the Investigator and the Medical Monitor agree that the subject is stable.

Throughout the course of the study, safety evaluations will include assessment of AEs, concomitant medications, clinical laboratory tests, vital signs, physical examinations (PEs) and 12-lead electrocardiograms (ECGs).

A detailed schedule of study assessments is presented in Appendix 1.

3.2. Rationale for Study Design

This Phase 2 study will assess the ability of ATR-101 at various dose levels to suppress cortisol production in subjects with endogenous Cushing's syndrome. For subjects who meet randomization criteria, this study consists of an open-label dose-escalation period followed by a relatively brief (up to 4 weeks) placebo-controlled double-blind randomized withdrawal period

(where subjects are randomized in a 1:1 ratio either to continue to receive ATR-101 or matching placebo). This study design permits a placebo comparison with ATR-101 while minimizing the time during which subjects may experience elevated cortisol levels. Subjects who do not meet randomization criteria at the end of the open-label dose-escalation period will continue into an additional 4-week open-label dosing period, which permits assessment of efficacy following a longer duration of dosing with ATR-101.

The double-blinded withdrawal period of the study is randomized in order to minimize any bias in determining which subject receives ATR-101 or placebo. The study is double blinded so there is no bias introduced by knowledge of the treatment identity received by a subject in reporting the clinical findings. Double blinding also minimizes the bias in assessing treatment response measures that could be introduced by the Investigators had they known the treatment identity. The study is placebo-controlled in order to have a comparison group to help determine whether safety findings during the study are related to the study drug and also to provide a control rate for the assessment of efficacy. Stratification by baseline cortisol level allows for a balance of subjects with higher and lower levels in the treatment groups.

Based on toxicity investigations in preclinical species, previous clinical observations in PK and PD responses, expected bioavailability and safety demonstrated in a previous ATR-101 study in subjects with ACC, the doses of 250 mg BID, 500 mg BID and 1000 mg BID have been selected to evaluate the clinical effects of ATR-101 in subjects with Cushing's syndrome.

3.3. Study Duration

It is anticipated that the overall duration of the study per subject will range from approximately 16-22 weeks, depending upon the duration (if any) required for wash-out and the duration of follow-up.

3.4. Number of Subjects

Approximately 16 subjects are planned to be enrolled in this study. At enrollment, all eligible subjects will be assigned to one of two 24-hr UFC strata. Strata will be assigned according to baseline 24-hr UFC level: 1.3 to < 4 × ULN (Stratum I) and 4 to 10 × ULN (Stratum II). Enrollment into a particular stratum may be limited to ensure the inclusion of subjects in both strata. The subject population will consist of adults with endogenous Cushing's syndrome with 24-hr UFC 1.3 to 10 × ULN.

The study will be conducted at approximately 14 sites in North America and the United Kingdom.

3.5. Treatment Assignment

There are a total of 3 dose levels for ATR-101 during the open-label dose-escalation period:

- 250 mg BID
- 500 mg BID
- 1000 mg BID

All enrolled subjects will be assigned to take the same starting dose of ATR-101, 250 mg BID. Dose escalation to the next higher dose of ATR-101, 500 mg BID, will occur at Visit T2. Further dose escalation to the next higher dose of ATR-101, 1000 mg BID, will occur at Visit T3.

A subject may enter the double-blind randomized withdrawal period if the mean Day 50/51 24-hr UFC is ≤ ULN or ≤ 50% relative to the baseline value. Such subjects will be randomized 1:1 to receive either ATR-101 at the same dose level on which they achieved the mean Day 50/51 24-hr UFC ≤ ULN (or ≤ 50% of their baseline value) (expected to be 1000 mg BID) or matching placebo in a double-blinded manner.

Subjects who do not meet any of the randomization criteria will enter the additional open-label dosing period and receive ATR-101 1000 mg BID.

3.6. Special Safety Topics

Preclinical studies at exposure levels much higher than those anticipated for this study have identified adrenal suppression with apoptotic histologic changes. The predicted exposures in this study are much lower; 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.[9]

Adrenal suppression may present as adrenal insufficiency or as hypoaldosteronism. Subjects presenting with unexplained symptoms suggestive of adrenal insufficiency, such as fatigue, nausea, low blood pressure, characteristic electrolyte abnormalities (hyponatremia and hyperkalemia), etc., should be promptly evaluated for adrenal insufficiency and given replacement corticosteroids and/or mineralocorticoids as clinically indicated.

Subjects who develop unexplained persistent hyperkalemia and/or hyperchloremic metabolic acidosis should be evaluated for hypoaldosteronism. Subjects with confirmed hypoaldosteronism should receive mineralocorticoid replacement (e.g., fludrocortisone at a starting dose of 50-100 µg/day) and should not be on any salt restrictions. Guidelines for the diagnosis and treatment of adrenal insufficiency and hypoaldosteronism may be found in Appendix 6.[12]

3.7. Lowering the Dose for Safety Purposes

Study drug doses may be decreased in the open-label period if a subject develops adrenal insufficiency or hypoaldosteronism, or if required for another safety-related reason in the opinion of the Investigator. Any adjustments to the study drug dose should be discussed with the Medical Monitor. If subjects cannot tolerate the lowest dose of study drug (i.e., 250 mg BID), they should be discontinued from the study and undergo an ET visit.

3.8. Criteria for Study Termination

Specific stopping criteria will not be defined due to the relatively small sample size. However, the frequency of study visits and safety laboratory tests will enable the early detection of any suspected adverse drug reactions. Due to the mechanism of action of ATR-101, Investigators should be alert to the potential for relative and absolute adrenal insufficiency. In addition, a single occurrence of the following safety events will trigger an expedited safety meeting, consisting of at least the Medical Monitor and the Sponsor Chief Medical Officer, to review the case.

- Hepatic toxicity such as marked elevations in transaminases (> 5x ULN) or simultaneous elevations in hepatic transaminases > 3x ULN and bilirubin > 2x ULN (i.e., Hy's Law)
- Severe renal impairment (e.g., creatinine clearance < 30 mL/min or glomerular filtration rate < 30 mL/min/1.73 m^2)
- Severe cardiovascular dysfunction such as new arrhythmia, valvular dysfunction, or NYHA Class III or IV heart failure

If it is determined that the event is drug-related and a clear safety signal has been identified, early termination of the study may occur.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

4.1. Inclusion Criteria

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

1. Provision of signed and dated informed consent prior to any study-specific procedures
2. Men and women 18-80 years of age (inclusive) at screening
3. Subjects must have a confirmed diagnosis of endogenous Cushing's syndrome as evidenced by baseline UFC 1.3 to 10 × ULN (mean of all 24-hr UFC levels obtained during the screening period within 28 days of enrollment into the open-label dose-escalation period) AND documentation at any time of ONE of the following three criteria:
   - For subjects with a diagnosis of pituitary Cushing's syndrome, either:
     - Magnetic resonance imaging (MRI) confirmation of pituitary adenoma (greater than or equal to 0.6 cm), OR
     - For subjects with a pituitary microadenoma less than 0.6 cm, bilateral inferior petrosal sinus sampling (BIPSS) showing an ACTH gradient > 2 before or > 3 after corticotropin-releasing hormone (CRH) or desmopressin (DDAVP) stimulation, OR
     - For subjects who have had prior pituitary surgery: histopathology confirming an ACTH-staining adenoma
   - For subjects with a diagnosis of adrenal Cushing's syndrome: MRI or computed tomography (CT) of the adrenal glands showing an adrenal tumor
   - For subjects with a diagnosis of ectopic ACTH as the cause of their Cushing's syndrome: ACTH-dependent Cushing's syndrome and either:
     - MRI showing no pituitary adenoma, OR
     - MRI showing only a small pituitary adenoma (< 0.6 cm) AND a negative BIPSS, OR
     - For subjects who have had prior pituitary surgery: histopathology that is negative for an ACTH-staining adenoma
4. Subjects with a history of prior pituitary surgery must be at least 3 months post-surgery at the time of the screening visit
5. Body mass index (BMI) between 18 and 60 kg/m^2, inclusive, at screening
6. Female subjects must be postmenopausal > 2 years OR must have been permanently surgically sterilized (bilateral salpingectomy or tubal occlusion) > 2 years OR male partner(s) has had a vasectomy > 2 years OR must consent to use two permitted medically-acceptable methods of contraception throughout the study during any sexual intercourse with a male partner. Permitted medically-acceptable methods of birth control for this study include oral contraceptives, contraceptive implants, Depo-Provera®, contraceptive patch, vaginal ring, male condom, female condom, spermicide, diaphragm with spermicide, cedrvical cap with spermicide, contraceptive sponge, or an intrauterine device (IUD); IUDs must have been in place for at least 28 days prior to first dose of study drug.

4.2. Exclusion Criteria

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

1. Pseudo-Cushing's syndrome, cyclic Cushing's syndrome or current iatrogenic Cushing's syndrome

2. Subjects who are considered candidates for surgical treatment of Cushing's syndrome, unless it is clearly documented that the subject has refused such surgery or that surgery cannot be scheduled for at least the anticipated duration of the study
3. Normal late night salivary cortisol value during screening unless the subject's history clearly demonstrates that he or she does not have pseudo-Cushing's or cyclic Cushing's. If the subject has a normal late night salivary cortisol, and the PI feels the subject does not have pseudo-Cushing's or cyclic Cushing's, the subject may be enrolled with approval of the medical monitor
4. Normal 24-hr UFC during screening (this would be suggestive of cyclic Cushing's)
5. Radiotherapy of the pituitary within 6 months prior to or during screening
6. For subjects with pituitary Cushing's syndrome, any compression of the optic chiasm or the presence of a tumor within 2 mm of the optic chiasm on the most recent pituitary MRI prior to or during screening
7. Use of or medical requirement for any of the following medications within the timeframes specified below prior to collection of the first 24-hr UFC during Screening and throughout study participation (see Section 5.11 for additional prohibited and restricted medications):
   - Inhibitors of steroidogenesis (ketoconazole, metyrapone): 1 week
   - Pituitary-directed agents: Dopamine agonists (bromocriptine, cabergoline) and PPARγ agonists (rosiglitazone or pioglitazone): 4 weeks
   - Octreotide LAR, Lanreotide SR and Lanreotide autogel: 14 weeks
   - Octreotide (immediate release formulation): 1 week
   - Pasireotide: 4 weeks
   - Mitotane: 26 weeks
   - Mifepristone: 3 weeks
8. Uncontrolled diabetes mellitus, as evidenced by HbA1c > 9.0% at screening
9. Uncontrolled hypertension, defined as systolic blood pressure > 160 mmHg or diastolic blood pressure > 90 mmHg during screening. Note: if appropriate, subjects may have blood pressure medications adjusted and blood pressure reassessed at an unscheduled visit prior to Visit T1.
10. Any history of gastric or small intestinal surgery or any current disease that causes malabsorption. Note: irritable bowel syndrome is acceptable for inclusion
11. Alcohol or substance abuse (cocaine, amphetamines and/or opioids) within the year prior to screening
12. Abnormal laboratory values as per the guidelines listed below or any other clinically significant, unexplained laboratory abnormality according to the Investigator:
    - Serum ALT or AST > 3 × ULN
    - Serum total bilirubin > 1.5 × ULN
    - Serum creatinine > 1.5 × ULN
    - Glomerular filtration rate < 60 mL/min/1.73 m^2
13. Pregnant, breast-feeding, having conceived within the 6 months prior to screening, or having an intent to become pregnant during the study period
14. QTc > 470 msec on electrocardiogram at screening (subjects with a single QTc > 470 msec may have 2 additional ECGs taken during screening and the QTcs averaged; if the average QTc is > 470 msec then the subject is excluded)
15. Known history of Gilbert's syndrome
16. HIV, hepatitis B, or hepatitis C positivity at screening

17. Any malignancy within the previous 5 years, other than curatively treated basal or squamous cell skin cancer or cervical carcinoma *in situ*
18. Previous exposure to any amount of ATR-101
19. Participation in any study of an investigational drug within 30 days prior to screening
20. Significant psychiatric disease, recent severe physical stress, malnutrition, chronic excessive exercise, or any other medical or psychiatric condition that, in the opinion of the Investigator, is likely to confound the interpretation of the study results or prevent the subject from understanding the requirements of or successfully completing the study

4.3. Subject Withdrawal Criteria

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 Investigator 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 Investigator's judgment, it is in the best interest of the subject to discontinue study participation.
2. The subject experiences an adverse event that would preclude further treatment with the study drug.
3. The subject withdraws consent for continued participation or refuses further treatment with the investigational product.
4. The subject is noncompliant with the protocol.
5. The subject becomes pregnant.
6. The subject cannot tolerate the lowest dose of study drug.

Subjects should return to the study site for an ET visit (which consists of the same procedures as at Visit R3) after withdrawal/removal from the clinical study. The reason for and date of withdrawal/removal from the study must 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 6.9. For all subjects who do not complete the study, regardless of the duration of treatment, all relevant information related to the withdrawal/removal will be entered into the electronic case report form (eCRF).

Subjects who withdraw or are removed from the clinical study after enrollment into the open-label dose-escalation period will not be replaced. All enrolled subjects will be fully accounted for and documented in the final clinical study reports (CSRs).

5. TREATMENT OF SUBJECTS

5.1. Assignment of Subject Identification Numbers

Once the subject has signed the informed consent form (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 will be utilized to identify the subject throughout the study. Once the subject ID has been assigned, the site will contact the interactive voice/web response system (IVRS/IWRS) to register the subject ID. Each subject ID will only be assigned to one subject, e.g., if a subject is withdrawn from the study early, their subject ID will not be used for a new subject.

5.2. Description of Study Drug

The ATR-101 Drug Product consists of a white, round, immediate release tablet of strengths 250 mg or 500 mg of ATR-101 for oral administration. The 250-mg and 500-mg tablets are similar in appearance to each other. A placebo tablet (ATR-101 Drug Product Placebo) has been developed to match the appearance of the active 250-mg and 500-mg tablets in size, shape, color and weight. The tablet formulations are described in Table 2.

Table 2: Investigational Product

	Investigational Product	
Product Name:	ATR-101	Placebo
Dosage Form:	tablet	tablet
Unit Dose	250 mg or 500 mg or 2 x 500 mg	0 mg
Route of Administration	Oral	Oral
Physical Description	Plain, round, biconvex, white film-coated tablets	Plain, round, biconvex, white film-coated tablets that appear similar to ATR-101 500-mg tablets
Inactive Ingredients	Mannitol, microcrystalline cellulose, croscarmellose sodium, pregelatinized starch, hypromellose, magnesium stearate and Opadry II white	Microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate and Opadry II white
Manufacturer	Corealis Pharma, Inc.	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 Investigator's Brochure.[9]

5.3. Study Drug Packaging and Labeling

The formulation and bulk packaging of ATR-101 Drug Product and Drug Product Placebo tablets will be conducted according to standard procedures. Study drug will be packaged and labeled by the Sponsor's designated contract packager and labelled according to regulatory requirements. Study drug will be provided to sites as blinded clinical supplies. Additional details will be provided in the Pharmacy Manual.

5.4. Study Drug 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 Investigator 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 Investigator 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 Investigator 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.

5.5. Study Drug Administration

Study drug doses should be taken approximately 12 hrs 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 8 AM (08:00) and every evening at 8 PM (20:00)).

Study drug 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 study drug.

On the morning of study visits, subjects should not take their study drug (if applicable) until directed by study site personnel. At each study visit from T1 to R2/A2, a trough PK level will be collected within 30 minutes prior to dosing and subjects will eat a breakfast prior to dose administration. See the Pharmacy Manual for more details.

5.6. Dose Escalation

During the 8-week open-label dose-escalation period, all subjects will initially be assigned to take ATR-101 250 mg BID. At Visits T2 and T3, dose escalation to the next higher dose level (500 mg and 1000 mg BID, respectively) will occur.

5.7. Study Drug Compliance

The investigational product is to be dispensed by qualified personnel at the study site and only to subjects enrolled in the study. Subject compliance with therapy will be assessed by reviewing the collected study drug at scheduled study visits and documenting the review on the eCRF. If subject compliance with study drug administration is outside of the range of 80-120%, then the subject will receive additional instruction on compliance.

5.8. Randomization and Blinding

After the open-label dose-escalation period, subjects whose mean Day 50/51 24-hr UFC level is ≤ ULN or ≤ 50% relative to their baseline value will undergo a placebo-controlled, double-blind randomized withdrawal from ATR-101 in which they will be randomized either to continue ATR-101 or placebo. Randomization will be stratified by baseline 24-hr UFC level (calculated as the mean of all 24-hr UFC levels obtained within the 28 days prior to enrollment into the open-label dose-escalation period).

Subjects will continue on the dose of ATR-101 on which they achieved the mean Day 50/51 24-hr UFC ≤ ULN (or ≤ 50% of their baseline value) or a matching placebo. The matching placebo tablets for the ATR-101 500-mg tablets will maintain double-blind status. Subjects will be administered ATR-101 and/or placebo tablets BID as described in Section 5.5.

The following personnel will be unblinded as to the exact content of investigational treatments (i.e., the randomization code) during the double-blind randomized withdrawal period:

- Personnel analyzing the PK samples

The randomization list will be kept in a secure location until after database lock at the end of the study. However, the study drug assignment will be available if unblinding is required for an SAE. The procedures for emergency unblinding are provided in Appendix 5.

Subjects will be assigned to one of two 24-hr UFC strata. Strata will be assigned by the IVRS/IWRS system according to the baseline 24-hr UFC value, calculated as the mean of all 24-hr UFC levels obtained within the 28 days prior to enrollment into the open-label dose-escalation period:

- Stratum I: 1.3 to < 4 × ULN
- Stratum II: 4 to 10 × ULN

Enrollment into a particular stratum may be limited to ensure the inclusion of subjects in both strata.

5.9. Additional Open-Label Dosing

Subjects who do not meet any of the randomization criteria, i.e., those whose mean Day 50/51 24-hr UFC is not sufficiently low, will enter an additional open-label dosing period rather than the randomized withdrawal period and be assigned to take ATR-101 1000 mg BID (or a lower dose if needed for safety, at the discretion of the Investigator).

5.10. Study Drug Handling and Disposal

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

5.11. Concomitant Medications

Use of concomitant medications should be kept to a minimum during the study. However, if concomitant medications are considered necessary for the subject's welfare and are unlikely to interfere with the investigational product, they may be given at the discretion of the Investigator. During the study (i.e., from screening (Visit S1) until the end of the study/end of trial (Visit F1)), any medication given other than the study drug (including blood transfusions and parenteral fluids) is to be considered a concomitant medication and must be documented on the eCRF. See Section 6.5 for additional details regarding documentation of prior and concomitant medications.

5.12. Prohibited and Restricted Medications

The following medications are prohibited from within the timeframes specified below prior to Day -14 through the end of the study and should be washed out for at least the timeframes indicated prior to the collection of blood and salivary hormone levels and 24-hr UFCs during the screening period:

- Inhibitors of steroidogenesis (ketoconazole, metyrapone): 1 week
- Pituitary-directed agents: Dopamine agonists (bromocriptine, cabergoline) and PPARγ agonists (rosiglitazone or pioglitazone): 4 weeks
- Octreotide LAR, Lanreotide SR and Lanreotide autogel: 14 weeks
- Octreotide (immediate release formulation): 1 week
- Pasireotide: 4 weeks
- Mitotane: 26 weeks
- Mifepristone: 3 weeks
- Fenofibrate: 5 days
- Carbenoxolone: 4 days

The use of the following medications is restricted as follows:

- Anti-lipid medications should remain at the same dose and frequency of use as at screening during the study
- Changes in antidiabetic medications should be limited to those that are medically necessary

Drugs and foods (such as black licorice) that inhibit 11-HSD2 can increase UFC levels and are prohibited during the study.

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

Medications that are known to prolong the QT/QTc interval at therapeutic exposures (Appendix 2, List A) and those that only cause prolonged QT intervals in unusual circumstances (e.g., overdosage; Appendix 2, Lists B and C) should be used with caution.

ATR-101 is metabolized by CYP enzymes and is a moderate inhibitor of CYP3A4. As a consequence, ATR-101 may interfere with the metabolism of other medicines that are metabolized by CYP3A4. In addition, the metabolism of ATR-101 may be affected by other medicines or foods such as grapefruit products that inhibit CYP3A4; thus, grapefruit products should be avoided. Drugs known to be metabolized by CYP3A4 are shown in Appendix 3 and should be used with caution if they are known to interact with weak or moderate CYP3A4 inhibitors.

Preclinical data indicate that ATR-101 may compete with certain drugs for P-glycoprotein (P-gp) in the intestinal lumen. Consequently, the drugs listed in Appendix 4 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 2 or 3, and may be contraindicated by those properties.

5.13. Prohibited Procedures

The following procedures are prohibited during the study:

- Elective pituitary or adrenal surgery
- Bariatric surgery or other elective gastrointestinal surgeries that may affect absorption

6. STUDY PROCEDURES

Subjects need to be fasting after 10 PM (22:00; water and maintenance medications allowed) the evening prior to Visits S1, R1/A1, and R3/A3/ET to allow for collection of the fasting lipid panel, glucose and insulin (if the subject is not fasting, proceed with the visit but mark the sample collection as being non-fasting). All blood hormone collections should be performed between 6-10 AM (06:00-10:00), as close to 8 AM (08:00) as practicable. All early morning saliva collections should be performed 30-45 minutes after awakening for the day. All late night saliva collections should be performed between 10 PM-12 AM (22:00-00:00).

If applicable (i.e., Visits T2 to R3/A3/ET), subjects should take their evening dose of study drug the evening prior to study visits (and also note the approximate time of the dose). On the morning of Visits T1 to R2/A2, subjects should wait to take their morning dose of study drug until directed by site personnel at the study site.

6.1. Allowable Variation in Time of Procedures

The indicated study days for assessments are intended as targets and variations may be made to allow for logistical considerations and to accommodate scheduling conflicts. Unless otherwise specified in this protocol, assessments from Visit T1 to Visit R3/A3 are to be completed within + 2 days of the planned date. All other assessments may be completed within ± 7 days of the planned date. If a positive window is used, the timing of subsequent assessments may be re-anchored. The Medical Monitor or designee should be contacted to discuss any assessments that will occur outside of these windows.

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 or Ethics Committee (IRB/EC)-approved ICF. Potential subjects will be informed in detail about the study drug and the nature of the clinical investigation with the risks and discomforts to be expected. The subjects will also be instructed that they are free to withdraw their consent and discontinue their participation in the clinical study at any time. The Investigator or qualified designee 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/after the screening visit (Visit S1), before enrolling the subject into the open-label dose-escalation period at Visit T1 and before either randomizing the subject or enrolling the subject into the additional open-label dosing period at Visit R1/A1. Please note that prior to enrolling the subject into the open-label dose-escalation period, regarding the laboratory values, only the Visit T1 pregnancy test (if applicable and if performed at the site), and the Visit S1 hematology, chemistry, PT, PTT, INR, HbA1c, lipid panel, serology, pregnancy test (if applicable), urinalysis, urine drug screen, 24-hr UFC, and salivary cortisol levels need to be reviewed. The screening blood hormone levels are for baselining purposes and the results do not need to be available prior to enrolling the subject.

6.4. Medical History

A complete medical history will be obtained at the screening visit (Visit S1). 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. Prior and/or Concomitant Medication Assessments

Prior and concomitant medications that should be recorded include any treatments taken from screening (Visit S1) until the end of the study/end of trial (Visit F1), as well as any radiotherapy for Cushing's syndrome performed at any time prior to screening and any treatments for Cushing's syndrome taken within the year prior to screening. Any treatments given during the study other than ATR-101, including blood transfusions, parenteral fluids and herbal preparations, are considered to be concomitant therapies and must be recorded on the eCRF.

6.6. Vital Signs, Height, Weight and Body Mass Index

Vital signs (temperature, systolic and diastolic blood pressure, pulse and respiratory rate) and weight will be measured at each study visit.

Systolic and diastolic blood pressure should be taken in the same arm per subject at each study visit after the subject has been sitting for at least 5 minutes. Any clinically necessary deviations to this will be documented but do not need to be confirmed with the Medical Monitor prior to occurrence or documented as a protocol deviation.

Body weight will be obtained at each study visit, using a calibrated scale, after voiding and without shoes or outerwear (i.e., coats). Height will be assessed only at screening. Body mass index will be calculated based on body weight and screening height.

6.7. Physical Examination

A complete PE will be obtained at Visits S1, T1, R1/A1, and R3/A3/ET. A brief PE will be performed at Visits T2, T3, R2/A2, and F1 (if the subject has their follow-up visit at the study site), with particular attention to assessing the subjects for adrenal insufficiency. At all other visits, targeted PEs may be performed if needed based on adverse events and positives from review of systems.

The following systems will be examined for a complete PE: HEENT, respiratory, cardiovascular, gastrointestinal/hepatobiliary (specifically the presence of hepatomegaly or splenomegaly will be assessed), musculoskeletal, neurological and dermatologic. On a brief PE, the following systems will be examined: respiratory, cardiovascular, gastrointestinal/hepatobiliary and any areas pertinent to any adverse events and positives from review of systems.

6.8. Electrocardiography and Determination of QTc

All subjects will have 12-lead ECGs performed at Visits S1, R1/A1, and R3/A3/ET prior to study drug dosing (if applicable). The ECG test tracings will be interpreted by usual clinic

procedures and ECG findings will be recorded on the eCRF. ECGs will be stored for later analysis if needed.

If the QTc is greater than 470 msec on the screening (Visit S1) 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.

For all ECGs, the QT interval will be corrected using the Fridericia method ($QTcF = QT/RR^{0.33}$). During the study, if the QTcF is greater than 470 msec, a repeat 12-lead ECG will be obtained as soon as practicable.

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.[13]

6.9. Adverse Events, Serious Adverse Events and Reporting

6.9.1. Definition of Adverse Event, Adverse Drug Reaction and Unexpected Adverse Drug Reaction

Adverse Event (AE): Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

- All AEs, regardless of relationship to study drug, should be collected beginning from the time the subject signs the study consent until the last study visit or 30 days after the last dose of study drug, whichever is later. (Any SAE judged by the Investigator to be related to the study treatment should be reported to the Sponsor regardless of the length of time that has passed since study completion.) AEs in study subjects include any change in the subject's condition. This includes symptoms, physical findings, or clinical syndromes.
- Wherever possible, a specific disease or syndrome, rather than individual associated signs and symptoms should be identified by the Investigator and recorded. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure. Any medical condition already present at screening should not be reported as an AE unless the medical condition or signs or symptoms present at baseline worsens in severity or seriousness at any time during the study. Clinically significant examination (e.g. electrocardiogram) findings that are detected during the study or are present at screening and worsen during the study should be reported as an AE.
- 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 Investigator 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 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 safety 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.
- Every effort must be made by the Investigator to categorize each AE according to its severity and its relationship to study drug.
- Subjects who develop toxicity on study will be followed until the event resolves, stabilizes or returns to baseline.

Adverse Reaction: All noxious and unintended responses to study drug at any dose should be considered to be adverse reactions. “Responses to study drug” means that there is a causal relationship between the study drug and the responses. “Suspected adverse reaction” implies a lesser degree of certainty about causality than “adverse reaction.”

Unexpected Adverse Reaction: An unexpected adverse reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For the study drug, the reference safety information is included in the version of the Investigator's Brochure currently in force. The reference safety information will be reviewed yearly and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

6.9.2. Assessing Severity of Adverse Events

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

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

An AE that is assessed as severe should not be confused with a serious AE (SAE). Refer to Section 6.9.4.1 for the definition of an SAE.

6.9.3. Assessing Relationship to Study Treatment

The Investigator will categorize each AE as to its potential relationship to study drug: **unrelated**, **unlikely related**, **possibly related**, **probably related** and **definitely related**. 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 that are known to be associated with the occurrence of the event

The relationship categories of unrelated and unlikely related will be summarized for reporting purposes as **Not Related**. For Not Related events, the time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship with study drug, and another cause of the AE (concomitant drugs, therapies, complications, etc.) is suspected.

The relationship categories of possibly, probably and definitely related will be summarized for reporting purposes as **Related**. Only AEs thought to be caused by the study drug should be classified as "related to study drug." For Related events, 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.

6.9.4. Serious Adverse Events

6.9.4.1. Definition of Serious Adverse Event

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

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

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

  - Hospitalizations for respite/hospice care
  - Hospitalization planned prior to informed consent (where the condition requiring the hospitalization has not changed post study drug administration)

- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect, or
- Is determined to be an important medical event (at the discretion of the Investigator)

  Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the SAE definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

6.9.4.2. Reporting SAEs – Procedure for Investigators

Initial Reports

SAEs, regardless of causality assessment, must be collected beginning from the time the subject signs the study consent until the last study visit or 30 days after the last dose of study drug, whichever is longer. All SAEs must be reported to Medpace Clinical Safety **within 24 hrs** of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned seriousness criteria). Any SAE judged by the Investigator to be related to the study treatment should be reported to the Sponsor regardless of the length of time that has passed since study completion.

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 seriousness 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 or email the completed paper SAE form to Medpace (fax number/email address listed below) within 24 hrs of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hrs of the system becoming available.

It is very important that the SAE electronic case report form be filled out as completely as possible at the time of the initial report, including if possible the Investigator's assessment of causality. The minimum information needed for making a preliminary SAE report is the protocol number, the subject ID, an adverse event term and the name of the person reporting the information to the Sponsor. Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports and other documents requested by the Sponsor (see Follow-up Reports, below).

Medpace Clinical Safety Contact Information:

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

Medpace SAE hotline – Europe:
Telephone: +49 89 89 55 718 44
Fax: +49 89 89 55 718 104
e-mail: medpace-safetynotification@medpace.com

Follow-up Reports

All AEs and SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Within 24 hrs 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 the follow-up information changes the Investigator's assessment of causality, this should also be noted on the follow-up SAE form. 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/EC of the occurrence of the SAE, in writing, in accordance with local requirements.

6.9.5. Pregnancy Reporting

Any pregnancy following study drug dosing 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 Investigator should report the pregnancy to Medpace Clinical Safety within 24 hrs of being notified. Medpace Clinical Safety will then forward the Exposure *In Utero* form to the Investigator for completion. **The contact information for reporting pregnancies is the same as for reporting SAEs** (Section 6.9.4.2).

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 Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Medpace Clinical Safety. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the fetus has a congenital anomaly, the Investigator should follow the procedures for reporting an SAE.

6.9.6. 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.

6.10. Laboratory Tests

Blood, urine and saliva samples for assessments of efficacy, safety and PK will be obtained as shown in the study schedule in Appendix 1. Please see the Laboratory Manual for blood collection volumes. Testing of clinical laboratory samples will be carried out by the central clinical laboratory and will include the tests listed in Table 3. Testing of PK samples will be carried out by the central PK laboratory. Samples may also be assessed for other parameters relevant to steroid metabolism. Subjects need to fast from 10 PM (22:00; water and maintenance medications allowed) the evening prior to Visits S1, R1 and R3/ET. Subjects need to be in a seated position for at least 15 minutes prior to collection of blood hormone levels so that renin and aldosterone levels are stable. For other blood tests, subjects may be seated or supine.

For all female subjects of childbearing potential, a serum pregnancy test will be performed via the central laboratory at screening (Visit S1) and a urine pregnancy test will be performed at the study site (preferred; however, if required by the institution/IRB/EC, a serum or urine sample may be submitted to a laboratory for pregnancy testing instead) at all subsequent study visits.

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 baseline value. Abnormal laboratory findings that are considered clinically significant by the Investigator should be recorded as AEs as appropriate (Section 6.9).

Table 3: List of Clinical Laboratory Tests

Hematology	hematocrit (Hct), hemoglobin (Hgb), platelet count, red blood cell (RBC) count, white blood cell (WBC) count with differential
Chemistry	albumin (ALB), alkaline phosphatase (ALK-P), alanine aminotransferase (ALT; SGPT), aspartate aminotransferase (AST; SGOT), blood urea nitrogen (BUN), calcium (Ca), creatinine (including calculated glomerular filtration rate), glucose, total bilirubin, total protein, electrolytes (magnesium, sodium, potassium, chloride, bicarbonate)
Coagulation	PT, aPTT, INR
Metabolic	insulin, HbA1c, lipid panel (total cholesterol, LDL, HDL, triglycerides)
Hormones	11-DOC, 17-OHP, A, A4, ACTH, cortisol, DHEA, DHEAS, free T, P, renin, SHBG, total T
Urinalysis	appearance, bilirubin, color, glucose, ketones, microscopic examination of sediment, nitrite, occult blood, pH, protein, specific gravity, urobilinogen
Other	HBsAg, HCV, HIV, serum and urine pregnancy tests, urine drug screen, UFC (including total volume and total creatinine), salivary cortisol

11-DOC, 11-deoxycorticosterone; 17-OHP, 17-hydroxyprogesterone; A, aldosterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; aPTT, activated partial thromboplastic time; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; HbA1c, hemoglobin A1c; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; INR, international normalized ratio; LDL-C, low-density lipoprotein cholesterol; P, progesterone; PT, prothrombin time; SHBG, sex hormone binding globulin; T, testosterone; UFC, urinary free cortisol

6.10.1. Efficacy Assessments

6.10.1.1. 24-Hour Urinary Free Cortisol

24-hr urine collections for assessment of UFC will be performed using the standard procedure (see Laboratory Manual). If a urine collection is suspected to be incomplete, a repeat 24-hr UFC may be performed with approval of the Medical Monitor.

Two collections will be done during the screening period, within 28 days prior to enrollment into the open-label dose-escalation period (Visit T1), and results reviewed for eligibility prior to enrollment. Subjects who require wash-out of medications should perform these collections AFTER wash-out.

During the Open-Label Dose-Escalation Period of the study, subjects will begin a 24-hr urine collection on Days 13, 14, 27, 28, 41, 42, 50, 51, and 56. In addition, subjects in the Double-Blind Randomized Withdrawal Period of the study will begin a 24-hr urine collection on Days 64, 65, 79, and 84; and subjects in the Additional Open-Label Dosing Period of the study will begin a 24-hr urine collection on Days 69, 70, 79, and 84. The collections that occur within 2 days before study visits should be brought to the corresponding study visit (along with any other samples that had not been previously submitted). For all other collections, when completed, a visiting nurse may assist with processing and shipping these 24-hr collections to the central laboratory, or the subject may submit them to the study site, per subject preference.

The mean of the Day 50 and the Day 51 ("mean Day 50/51") 24-hr UFC results will be used by the Investigator to determine whether the subject meets criteria for randomization. For subjects in the Double-Blind Randomized Withdrawal Period of the study, the mean of the Day 64 and the Day 65 ("mean Day 64/65") 24-hr UFC results, if available at the time of Visit R2, will be used by the Investigator to determine whether the subject should undergo Visit R3 rather than Visit R2. The Day 79 result and the Day 84 result will be used to make the initial determinations of whether the subject's follow-up visit should be conducted at the study site or via telephone.

In addition, subjects whose Day 84 24-hr UFC is ≤ ULN will collect an additional 24-hr urine sample for UFC on Day 92. This result, if available at the time the Day 98 visit is due, will also be used to determine whether the subject's follow-up visit should be conducted at the study site or via telephone.

Subjects whose Day 92 24-hr UFC is ≤ ULN should continue to be followed up and have morning serum ACTH and 24-hr UFC assessed every 2-4 weeks until their 24-hr UFC is > ULN or until the Investigator and the Medical Monitor agree that the subject is stable.

Further details on sample collection and handling are provided in the Laboratory Manual.

6.10.1.2. Salivary Cortisol

Two early morning (30-45 minutes after awakening for the day) and two late night (10 PM – 12 AM; 22:00-00:00) saliva collections for salivary cortisol should be performed during the screening period within 28 days of enrollment into the open-label dose-escalation period and results reviewed for eligibility prior to enrollment. The two early morning collections should be done on different days from each other, as should the two late night collections. Subjects who require wash-out of medications should perform these collections AFTER wash-out.

During the Open-Label Dose-Escalation Period of the study, subjects will perform an early morning saliva collection and a late night saliva collection at home on Days 13, 14, 27, 28, 41, 42, 50, 51, and 56. In addition, subjects in the Double-Blind Randomized Withdrawal Period of the study will perform an early morning saliva collection and a late night saliva collection at home on Days 64, 65, 79, and 84; and subjects in the Additional Open-Label Dosing Period of the study will perform an early morning saliva collection and a late night saliva collection at home on Days 69, 70, 79, and 84. The collections that occur within 2 days before study visits should be brought to the corresponding study visit. For all other collections, when completed, a visiting nurse may assist with processing and shipping these collections to the central laboratory, or the subject may submit them to the study site, per subject preference. All saliva samples will be submitted to the central laboratory for processing.

Further details on sample collection and handling are provided in the Laboratory Manual.

6.10.1.3. Blood Hormone Levels

Levels of 11-DOC, 17-OHP, A, A4, ACTH, cortisol, DHEA, DHEAS, free T, P, renin, SHBG and total T will be measured at the central laboratory using validated methods at all study visits. Changes in hormone levels during the study will be used to assess the efficacy of ATR-101.

Further details on sample collection and handling are provided in the Laboratory Manual.

6.10.1.4. Glucose, Insulin and HbA1c

Subjects need to be fasting after 10 PM (22:00; water and maintenance medications allowed) the evening prior to Visits S1, R1/A1, and R3/A3/ET to allow for determination of fasting glucose and fasting insulin levels. Fasting glucose, insulin and HbA1c will be measured at the central laboratory using validated methods for these visits and used for calculations of insulin sensitivity. Further details on sample collection and handling are provided in the Laboratory Manual.

6.10.1.5. Lipid Panel

Subjects need to be fasting after 10 PM (22:00; water and maintenance medications allowed) the evening prior to Visits S1, R1/A1, and R3/A3/ET to allow for collection of the fasting lipid panel. Fasting lipids (total cholesterol, LDL, HDL and triglycerides) will be measured at the central laboratory using validated methods for these study visits. Further details on sample collection and handling are provided in the Laboratory Manual.

6.10.2. Pharmacokinetic Assessments

Approximately 4 mL of blood will be drawn at each sampling time point:

Table 4: Pharmacokinetic Sampling Time Points

Visit	Sampling Time Points (Morning Dose Only)
T1, T2, T3	0 (within 30 min predose), 1 (± 5 min), 2 (± 10 min), 3 (± 10 min) and 4 hr (± 10 min)
R1, R2	0 hr (trough, within 30 min predose)
R3/ET	0 hr

Logistic considerations may dictate a deviation from the specified time point; therefore, a window is permitted around each sampling time point, as shown in Table 4: sampling times up to and including 1 hr post-dose have a window of ± 5 min and subsequent time points have a window of ± 10 min. Actual times of sampling and actual dosing times of ATR-101 must be recorded on the eCRF. Specific collection and shipment procedures for PK samples are provided in the Laboratory Manual. All samples will be analyzed using a validated assay at a central laboratory.

PK parameters will be derived using non-compartmental methods employing WinNonlin® Phoenix version 6.3 or later (Pharsight Corp., Mountain View, CA). The following PK parameters will be estimated for ATR-101 and its major metabolites as data permit and as appropriate:

Table 5: Pharmacokinetic Parameters

C_{last}	The last quantifiable drug concentration determined directly from individual concentration-time data
C_{max}	The maximum drug concentration determined directly from individual concentration-time data
C_{max}/D	Dose-normalized C_{max}, calculated as the ratio of C_{max} to dose
T_{max}	The observed time to reach maximum concentration
AUC_{0-t}	The area under the concentration-time curve from time zero to the time of the last quantified concentration, calculated using the linear-up/log-down trapezoidal rule
AUC_{0-4}	The area under the concentration-time curve from time zero to 4 h after dosing, calculated using the linear-up/log-down trapezoidal rule
AUC_{0-4}/D	Dose-normalized AUC_{0-4}, calculated as the ratio of AUC_{0-4} to dose
λz	The terminal phase rate constant, estimated by linear regression through the terminal phase of the log concentration-time profile
$t_{½}$	The terminal phase half-life, calculated as: $t_{½} = \frac{\ln(2)}{\lambda z}$
$AUC_{0-\infty}$	The area under the concentration versus time curve from time 0 to infinity (first dose only), calculated as $AUC_{0-4} + C_{last}/\lambda_z$
$AUC_{\%extrap}$	Percentage of $AUC_{0-\infty}$ extrapolated, represented as $(1 - AUC_{0-t}/AUC_{0-\infty})*100$
CL/F	Oral clearance calculated as: $Dose/AUC_{0-\infty}$ (Day 1 only)

6.10.3. Pharmacodynamic Assessments

The relationship between C_{max}, AUC and other PK parameters with efficacy assessments (Section 6.10.1) will be explored as appropriate.

6.10.4. Blood Sample Collection, Storage and Shipping

Sample collection, storage and shipment procedures for clinical laboratory samples are provided in the Laboratory Manual.

7. STUDY ACTIVITIES

During the study, blood samples for hormones should be collected between 6-10 AM (06:00-10:00), as close to 8 AM (08:00) as practicable. Early morning saliva samples should be collected 30-45 minutes after awakening for the day. Late night saliva samples should be collected between 10 PM and 12 AM (22:00-00:00). Within this protocol, references to the study day of a 24-hr UFC collection mean that the collection was to have begun on that study day (e.g., a "Day 14" 24-hr UFC is one that was to have begun on Day 14 and completed on Day 15). All sample collections and study visits and procedures from Visit T1 to Visit R3/A3/ET have a window of + 2 days. All other sample collections, study visits, and procedures have a window of ± 7 days.

Study visit designations (S1, T1, etc.) are shown in the detailed schedule of study assessments presented in Appendix 1.

7.1. Screening Visit, Visit S1

The screening visit should be conducted within 56 days (8 weeks) prior to enrollment into the open-label dose-escalation period. The date of screening is considered to be the date that the first study-related screening assessment is performed. At screening, appropriate study site personnel should:

- Obtain and document informed consent from the subject prior to any study procedures being performed.
- Assign a study-specific subject number.
- Contact the IVRS/IWRS to register the subject in the study
- Obtain and record medical history, demographic data and prior and current medications.
- Record vital signs, height and weight.
- Perform a complete PE.
- Obtain a 12-lead ECG.
- Collect fasting blood samples for hematology, chemistry, PT, aPTT, INR, insulin, HbA1c, lipid panel, HBsAg, HCV, HIV, hormones (11-DOC, 17-OHP, A, A4, ACTH, cortisol, DHEA, DHEAS, free T, P, renin, SHBG and total T) and serum pregnancy test.
  - Note: Subjects who require wash-out of medications that affect cortisol levels should NOT have their hormone levels drawn at S1. Instead, they should complete the required wash-out and return to the site for hormone levels later during the screening period.
  - All blood hormone collections should be performed between 6-10 AM (06:00-10:00), as close to 8 AM (08:00) as practicable.
  - Subjects need to be in a seated position for at least 15 minutes prior to collection of blood hormone levels so that renin and aldosterone levels are stable.
  - If the subject is not fasting, proceed with the visit but mark the sample collection as being non-fasting.

- Collect a urine sample for urinalysis and urine drug screen.
- Review all assessable inclusion and exclusion criteria.
- Provide instructions to the subject regarding 24-hr urine samples and early morning (30-45 minutes after awakening for the day) and late night (10 PM-12 AM; 22:00-00:00) saliva samples to be collected at home prior to the next visit.
  - During the screening period, subjects must perform two 24-hr urine collections, two early morning saliva collections and two late night saliva collections within 28 days prior to enrollment into the open-label dose-escalation period (Visit T1). The two early morning collections should be done on different days from each other, as should the two late night collections. These samples need to be submitted to the central laboratory for processing in time for results to be reviewed for eligibility prior to enrollment.
  - Per subject preference, these samples may be brought to the study site, or a visiting nurse may assist with processing the samples and shipping them to the central laboratory.
  - Subjects who require wash-out of medications should perform these collections AFTER wash-out.
- Schedule the next study visit (Visit T1) so that the blood hormone sample collections for that visit will occur as close to 8 AM (08:00) as practicable and between 6-10 AM (06:00-10:00).

7.2. Open-label Dose-escalation Period

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria should be enrolled and enter the 8-week open-label dose-escalation period. During the open-label dose-escalation period, subjects will take their assigned study drug and undergo assessments to evaluate efficacy, safety, tolerability and PK of study drug. At Visit T1, all subjects will initially be assigned to take ATR-101 250 mg BID. After 2 weeks, at Visit T2, all subjects will be assigned to take the next higher dose of ATR-101, 500 mg BID. After 2 additional weeks, at Visit T3, all subjects will be assigned to take the next higher dose of ATR-101, 1000 mg BID. At any time, the ATR-101 dose may be down-titrated as needed for safety reasons at the discretion of the Investigator.

7.2.1. Visit T1 (Day 1)

At Visit T1, appropriate study site personnel should:

- Record adverse events and update medications.
- Record vital signs and weight.
- Perform a complete PE.
- Collect a urine sample for urinalysis and, if the subject is a woman of childbearing potential, perform a urine pregnancy test (preferred; or submit a serum or urine sample to a laboratory for pregnancy testing if required by your institution/IRB/EC).
- Review all inclusion and exclusion criteria to confirm that the subject is eligible for the study, including all 24-hr UFC and late night salivary cortisol levels collected within the past 28 days.

- Review the mean of all 24-hr UFC levels obtained within the past 28 days to determine the subject's 24-hr UFC stratum (1.3 to < 4 × ULN (Stratum I) or 4 to 10 × ULN (Stratum II)).
- Please note that prior to enrolling the subject, regarding the laboratory values, only the Visit T1 pregnancy test (if applicable and if performed at the site), and the Visit S1 hematology, chemistry, PT, PTT, INR, HbA1c, lipid panel, serology, pregnancy test (if applicable), urinalysis, urine drug screen, 24-hr UFC, and salivary cortisol levels, need to be reviewed. The screening blood hormone levels are for baselining purposes and the results do not need to be available prior to the enrolling the subject.
- Contact the IVRS/IWRS to confirm enrollment of the subject into the open-label dose-escalation period and obtain study drug assignment.
- Collect blood samples for hematology, chemistry, hormones (11-DOC, 17-OHP, A, A4, ACTH, cortisol, DHEA, DHEAS, free T, P, renin, SHBG and total T) and PK within 30 minutes prior to administration of study drug.
  - All blood hormone collections should be performed between 6-10 AM (06:00-10:00), as close to 8 AM (08:00) as practicable.
  - Subjects need to be in a seated position for at least 15 minutes prior to collection of blood hormone levels so that renin and aldosterone levels are stable.
- Dispense open-label study drug (ATR-101 250-mg tablets) and instruct the subject on self-administration of study drug orally with food BID.
- Have the subject eat breakfast.
- Ask the subject to self-administer study drug with a nonalcoholic beverage (except grapefruit juice) while at the study site. Record the exact time of study drug administration.
- Collect plasma PK samples 1, 2, 3 and 4 hrs after administration of study drug. Record the exact time of each PK sample collection.
- Provide instructions to the subject regarding 24-hr urine samples and saliva samples to be collected at home prior to the next visit (Section 7.2.2).
- Schedule the next study visit (Visit T2) so that the blood hormone sample collections for that visit will occur as close to 8 AM (08:00) as practicable and between 6-10 AM (06:00-10:00).
- Remind the subjects that they will need to record the approximate time of their evening study drug dose prior to their next visit.
- Remind the subjects that on the morning of their next visit, they should wait to take their morning dose of study drug until directed by site personnel at the study site, and they will need to bring the 24-hr urine and saliva samples collected on or prior to Day 14 to the study site.

7.2.2. Between Visits T1 and T2, Between Visits T2 and T3 and Between Visits T3 and R1/A1

On Days 13, 14, 27, 28, 41, 42, 50, 51, and 56 during the open-label dose-escalation period, subjects should:

- Collect an early morning saliva sample.
- Collect a late night saliva sample.
- Begin a 24-hr urine collection.

In addition, at the indicated study days during the open-label dose-escalation period, subjects should:

- Days 14, 28 and 56 (the day prior to Visits T2, T3 and R1/A1, respectively): Record the approximate time of the evening study drug dose.
- Days 15, 29, and 57 (the day of Visits T2, T3, and R1/A1, respectively): Take any collected saliva samples and 24-hr urine samples (i.e., the Day 13/14, 27/28, and 56 saliva samples and 24-hr urine samples, respectively; and any other saliva samples and urine samples that were not previously submitted) to the study site.
- Days 43 and 52: Take the 24-hr urine collection and any collected saliva samples to the study site, or a visiting nurse will assist with processing the samples and shipping them to the central laboratory, per subject preference.
- Day 56 (the evening prior to Visit R1): Fast after 10 PM (22:00; water and maintenance medications allowed).

7.2.3. Visit T2 (Day 15)

At Visit T2, appropriate study site personnel should:

- Receive the Day 13 and Day 14 saliva collections and 24-hr urine collections from the subject and submit these to the central laboratory for analysis.
- Record adverse events and update medications.
- Record vital signs and weight.
- Perform a brief PE, with particular attention to assessing the subject for possible adrenal insufficiency.
- Collect blood samples for hematology, chemistry, hormones (11-DOC, 17-OHP, A, A4, ACTH, cortisol, DHEA, DHEAS, free T, P, renin, SHBG and total T) and PK within 30 minutes prior to administration of study drug.
  - All blood hormone collections should be performed between 6-10 AM (06:00-10:00), as close to 8 AM (08:00) as practicable.
  - Subjects need to be in a seated position for at least 15 minutes prior to collection of blood hormone levels so that renin and aldosterone levels are stable.
- If the subject is a woman of childbearing potential, collect a urine sample and perform a urine pregnancy test (preferred; or submit a serum or urine sample to a laboratory for pregnancy testing if required by your institution/IRB/EC).
- Record the date and time of the subject's last previous study drug dose (expected to have occurred the evening prior to the visit).

- Collect study drug and assess compliance.
- Contact IVRS/IWRS to obtain study drug assignment.
- Dispense open-label study drug (ATR-101 500-mg tablets) and instruct the subject on self-administration of study drug orally with food BID.
- Have the subject eat breakfast.
- Ask the subject to self-administer study drug with a nonalcoholic beverage (except grapefruit juice) while at the study site. Record the exact time of study drug administration.
- Collect plasma PK samples 1, 2, 3 and 4 hrs after administration of study drug. Record the exact time of each PK sample collection.
- Provide instructions to the subject regarding 24-hr urine samples and saliva samples to be collected at home prior to the next visit (Section 7.2.2).
- Schedule the next study visit (Visit T3) so that the blood hormone sample collections for that visit will occur as close to 8 AM (08:00) as practicable and between 6-10 AM (06:00-10:00).
- Remind the subjects that they will need to record the approximate time of their evening study drug dose prior to their next visit.
- Remind the subjects that on the morning of their next visit, they should wait to take their morning dose of study drug until directed by site personnel at the study site, and that they will need to bring the 24-hr urine and saliva samples collected on or prior to Day 28 to the study site.

7.2.4. Visit T3 (Day 29)

At Visit T3, appropriate study site personnel should:

- Receive the Day 27 and Day 28 saliva collections and 24-hr urine collections (and any other collections that were not previously submitted) from the subject and submit these to the central laboratory for analysis.
- Record adverse events and update medications.
- Record vital signs and weight.
- Perform a brief PE, with particular attention to assessing the subject for possible adrenal insufficiency.
- Collect blood samples for hematology, chemistry, hormones (11-DOC, 17-OHP, A, A4, ACTH, cortisol, DHEA, DHEAS, free T, P, renin, SHBG and total T) and PK within 30 minutes prior to administration of study drug.
  - All blood hormone collections should be performed between 6-10 AM (06:00-10:00), as close to 8 AM (08:00) as practicable.
  - Subjects need to be in a seated position for at least 15 minutes prior to collection of blood hormone levels so that renin and aldosterone levels are stable.

- If the subject is a woman of childbearing potential, collect a urine sample and perform a urine pregnancy test (preferred; or submit a serum or urine sample to a laboratory for pregnancy testing if required by your institution/IRB/EC).
- Record the date and time of the subject's last previous study drug dose (expected to have occurred the evening prior to the visit).
- Collect study drug and assess compliance.
- Contact IVRS/IWRS to obtain study drug assignment.
- Dispense open-label study drug and instruct the subject on self-administration of study drug orally with food BID.
- Have the subject eat breakfast.
- Ask the subject to self-administer study drug with a nonalcoholic beverage (except grapefruit juice) while at the study site. Record the exact time of study drug administration.
- Collect plasma PK samples 1, 2, 3 and 4 hrs after administration of study drug. Record the exact time of each PK sample collection.
- Provide instructions to the subject regarding 24-hr urine samples and saliva samples to be collected at home prior to the next visit (Section 7.2.2).
- Schedule the next study visit (Visit R1/A1) so that the blood hormone sample collections for that visit will occur as close to 8 AM (08:00) as practicable and between 6-10 AM (06:00-10:00).
- Remind the subjects that the evening prior to their next visit, they need to be fasting after 10 PM (22:00; water and maintenance medications allowed) and they will need to record the approximate time of their evening study drug dose.
- Remind the subjects that on the morning of their next visit, they should wait to take their morning dose of study drug until directed by site personnel at the study site, and that they will need to bring the 24-hr urine and saliva samples collected on or prior to Day 56 to the study site (if not previously submitted).

7.2.5. Telephone Visit Between Visits T3 and R1/A1 (Day 43)

At the Day 43 telephone visit, appropriate study site personnel should:

- Contact the subject by telephone.
- Record adverse events, with particular attention to assessing the subject for possible adrenal insufficiency, and update medications.
- Remind the subjects that on the morning of their next visit, they should wait to take their morning dose of study drug until directed by site personnel at the study site, and that they will need to bring the 24-hr urine and saliva samples collected on or prior to Day 56 to the study site (if not previously submitted).

7.3. Double-blind Randomized Withdrawal Period

Subjects whose mean Day 50/51 24-hr UFC level is ≤ ULN or ≤ 50% of their baseline value are eligible to enter the 4-week double-blind randomized withdrawal period. (Subjects who do not meet either of these randomization criteria will instead enter an additional 4-week open-label dosing period, described in Section 7.4.) Subjects entering the randomized withdrawal period will be randomized in a 1:1 ratio either to continue to receive ATR-101 at the dose at which they achieved mean Day 50/51 24-hr UFC ≤ ULN or ≤ 50% of their baseline value (expected to be 1000 mg BID), or matching placebo. Randomization will be stratified by baseline 24-hr UFC level (calculated as the mean of all 24-hr UFC levels obtained within the 28 days prior to enrollment into the open-label dose-escalation period). Subjects' 24-hr UFC levels will be followed during this period to determine the efficacy of ATR-101 in maintaining lowered levels compared to placebo.

During the double-blind randomized withdrawal period, the Investigator should assess the mean Day 64/65 24-hr UFC result as soon as possible to determine whether the subject meets criteria for study completion. Subjects are considered to have completed the study during the double-blind randomized withdrawal period when their mean Day 64/65 24-hr UFC level is > 1.3 x ULN and has also increased by > 50% relative to their mean Day 50/51 24-hr UFC level, or if they reach Visit R3 without meeting these criteria. When subjects are found to have completed the study, they should return to the study site immediately for Visit R3.

7.3.1. Visit R1 (Day 57)

Prior to Visit R1, the Investigator should review the baseline 24-hr UFC level (calculated as the mean of all 24-hr UFC levels obtained within the 28 days prior to enrollment into the open-label dose-escalation period) and compare it to the mean Day 50/51 24-hr UFC result to determine whether the subject meets criteria to enter the double-blind randomized withdrawal period of the study (the subject is eligible if the mean Day 50/51 24-hr UFC is ≤ ULN or ≤ 50% of the baseline value). If the subject does not meet criteria to enter the double-blind randomized withdrawal period, the subject should instead enter an additional 4-week open-label dosing period, described in Section 7.4.

At Visit R1, appropriate study site personnel should:

- Receive the Day 56 saliva collections and 24-hr urine collection (and any other collections that were not previously submitted) from the subject and submit these to the central laboratory for analysis.
- Record adverse events and update medications.
- Record vital signs and weight.
- Perform a complete PE.
- Obtain a 12-lead ECG.
- Collect fasting blood samples for hematology, chemistry, PT, aPTT, INR, insulin, HbA1c, lipid panel, hormones (11-DOC, 17-OHP, A, A4, ACTH, cortisol, DHEA, DHEAS, free T, P, renin, SHBG and total T) and PK within 30 minutes prior to administration of study drug.

  - All blood hormone collections should be performed between 6-10 AM (06:00-10:00), as close to 8 AM (08:00) as practicable.
  - Subjects need to be in a seated position for at least 15 minutes prior to collection of blood hormone levels so that renin and aldosterone levels are stable.
  - If the subject is not fasting, proceed with the visit but mark the sample collection as being non-fasting.

- Collect a urine sample for urinalysis and, if the subject is a woman of childbearing potential, perform a urine pregnancy test (preferred; or submit a serum or urine sample to a laboratory for pregnancy testing if required by your institution/IRB/EC).
- Record the date and time of the subject's last previous study drug dose (expected to have occurred the evening prior to the visit).
- Collect study drug and assess compliance.
- Confirm that the subject meets criteria for randomization into the double-blind randomized withdrawal period of the study. If not, enroll the subject into the additional open-label dosing period of the study, described in Section 7.4.
- Contact IVRS/IWRS to randomize the subject into the double-blind randomized withdrawal period and obtain study drug assignment.
- Dispense blinded study drug and instruct the subject on self-administration of study drug orally with food BID.
- Have the subject eat breakfast.
- Ask the subject to self-administer study drug with a nonalcoholic beverage (except grapefruit juice) while at the study site. Record the exact time of study drug administration.
- Provide instructions to the subject regarding 24-hr urine samples and saliva samples to be collected at home prior to the next visit (Section 7.3.2).
- Schedule the next study visit (Visit R2) so that the blood hormone sample collections for that visit will occur as close to 8 AM (08:00) as practicable and between 6-10 AM (06:00-10:00).
- Remind the subjects that they will need to record the approximate time of their evening study drug dose prior to their next visit.
- Remind the subjects that on the morning of their next visit, they should wait to take their morning dose of study drug until directed by site personnel at the study site.

7.3.2. Between Visits R1 and R2 and Between Visits R2 and R3/ET

On Days 64, 65, 79, and 84 during the double-blind randomized withdrawal period, subjects should:

- Collect an early morning saliva sample.
- Collect a late night saliva sample.
- Begin a 24-hr urine collection.

In addition, at the indicated study days during the double-blind randomized withdrawal period, subjects should:

- Days 66 and 80: Take the 24-hr urine collections and any collected saliva samples to the study site, or a visiting nurse will assist with processing the samples and shipping them to the central laboratory, per subject preference.
- Days 70 and 84 (the day prior to Visits R2 and R3/ET, respectively): Record the approximate time of the evening study drug dose.
- Day 85 (the day of Visit R3/ET): Take the Day 84 24-hr urine collection and any collected saliva samples (i.e., the Day 84 samples, and any other samples that were not previously submitted) to the study site.
- Day 84 (the evening prior to Visit R3/ET): Fast after 10 PM (22:00; water and maintenance medications allowed).

7.3.3. Visit R2 (Day 71)

At the time of Visit R2, if the Day 64 and Day 65 24-hr UFC results are available, the Investigator should assess the mean to determine whether the subject meets criteria for study completion. Subjects are considered to have met criteria for completing the study when their mean Day 64/65 24-hr UFC level is > 1.3 x ULN and has also increased by > 50% relative to their Day 50/51 24-hr UFC level, or if they reach Visit R3 without meeting these criteria. If subjects are found to have met criteria for completing the study, their next study visit should be Visit R3, rather than Visit R2.

At Visit R2, appropriate study site personnel should:

- Record adverse events and update medications.
- Record vital signs and weight.
- Perform a brief PE, with particular attention to assessing the subject for adrenal insufficiency.
- Collect blood samples for hematology, chemistry, hormones (11-DOC, 17-OHP, A, A4, ACTH, cortisol, DHEA, DHEAS, free T, P, renin, SHBG and total T) and PK within 30 minutes prior to administration of study drug.
  - All blood hormone collections should be performed between 6-10 AM (06:00-10:00), as close to 8 AM (08:00) as practicable.
  - Subjects need to be in a seated position for at least 15 minutes prior to collection of blood hormone levels so that renin and aldosterone levels are stable.
- If the subject is a woman of childbearing potential, collect a urine sample and perform a urine pregnancy test (preferred; or submit a serum or urine sample to a laboratory for pregnancy testing if required by your institution/IRB/EC).
- Record the date and time of the subject's last previous study drug dose (expected to have occurred the evening prior to the visit).
- Collect study drug and assess compliance.

- Contact IVRS/IWRS to obtain study drug assignment.
- Dispense blinded study drug and instruct the subject on self-administration of study drug orally with food BID.
- Have the subject eat breakfast.
- Ask the subject to self-administer study drug with a nonalcoholic beverage (except grapefruit juice) while at the study site. Record the exact time of study drug administration.
- Provide instructions regarding 24-hr urine samples and saliva samples to be collected at home prior to the next visit (Section 7.3.2).
- Schedule the next study visit (Visit R3) so that blood hormone sample collections for that visit will occur as close to 8 AM (08:00) as practicable and between 6-10 AM (06:00-10:00).
- Remind the subjects that the evening prior to their next visit, they need to be fasting after 10 PM (22:00; water and maintenance medications allowed) and they will need to record the approximate time of their evening study drug dose.
- Remind the subjects that on the morning of their next visit, they should not take any study drug, and that they will need to bring the 24-hr urine and saliva samples collected on or prior to Day 84 to the study site (if not previously submitted).

7.3.4. Visit R3 (Day 85; End-of-Treatment)/Early Termination

At Visit R3 (EoT)/ET, appropriate study site personnel should:

- Receive the Day 84 saliva collections and 24-hr urine collection (and any other collections that were not previously submitted) from the subject and submit these to the central laboratory for analysis.
- Record adverse events and update medications.
- Record vital signs and weight.
- Perform a complete PE.
- Obtain a 12-lead ECG.
- Collect fasting blood samples for hematology, chemistry, PT, aPTT, INR, insulin, HbA1c, lipid panel, hormones (11-DOC, 17-OHP, A, A4, ACTH, cortisol, DHEA, DHEAS, free T, P, renin, SHBG and total T) and PK.
  - All blood hormone collections should be performed between 6-10 AM (06:00-10:00), as close to 8 AM (08:00) as practicable.
  - Subjects need to be in a seated position for at least 15 minutes prior to collection of blood hormone levels so that renin and aldosterone levels are stable.
  - If the subject is not fasting, proceed with the visit but mark the sample collection as being non-fasting.

- Collect a urine sample for urinalysis and, if the subject is a woman of childbearing potential, perform a urine pregnancy test (preferred; or submit a serum or urine sample to a laboratory for pregnancy testing if required by your institution/IRB/EC).
- Record the date and time of the subject's last previous study drug dose (expected to have occurred the evening prior to the visit).
- Collect study drug and assess compliance.
- If the subject's most recent available 24-hr UFC result is ≤ ULN, then:
  - A Day 92 24-hr UFC may or may not be needed. Provide instructions regarding a 24-hr urine sample to be collected at home starting in 7 days (Day 92 or R3/ET+7) (Section 7.5.1). If the Day 84 24-hr UFC result is > ULN, inform the subject that they will not need to collect this sample.
  - Schedule the next study visit (Visit F1).
- If the subject's most recent 24-hr UFC is > ULN, follow up with the subject via telephone in 13 days to assess for new AEs. Subjects who have ongoing AEs should be followed up as appropriate. After completing Visit R3/ET, subjects whose most recent 24-hr UFC is > ULN may begin treatment with another agent for Cushing's syndrome at the discretion of their physicians.

7.4. Additional Open-Label Dosing Period

Subjects whose mean Day 50/51 24-hr UFC level does NOT meet randomization criteria (i.e., it is NOT either ≤ ULN or ≤ 50% of their baseline value) are eligible to enter the 4-week additional open-label dosing period. (Subjects who DO meet either of these randomization criteria will instead enter the 4-week double-blind randomized withdrawal period, described in Section 7.3.) Subjects entering the additional open-label dosing period will be assigned to take ATR-101 1000 mg BID. Subjects' 24-hr UFC levels will be followed during this period to determine the efficacy of a longer duration of dosing with ATR-101 in achieving lowered levels.

7.4.1. Visit A1 (Day 57)

At Visit A1, appropriate study site personnel should:

- Receive the Day 56 saliva collections and 24-hr urine collection (and any other collections that were not previously submitted) from the subject and submit these to the central laboratory for analysis.
- Record adverse events and update medications.
- Record vital signs and weight.
- Perform a complete PE.
- Obtain a 12-lead ECG.
- Collect fasting blood samples for hematology, chemistry, PT, aPTT, INR, insulin, HbA1c, lipid panel, hormones (11-DOC, 17-OHP, A, A4, ACTH, cortisol, DHEA, DHEAS, free T, P, renin, SHBG and total T) and PK within 30 minutes prior to administration of study drug.

  - All blood hormone collections should be performed between 6-10 AM (06:00-10:00), as close to 8 AM (08:00) as practicable.
  - Subjects need to be in a seated position for at least 15 minutes prior to collection of blood hormone levels so that renin and aldosterone levels are stable.
  - If the subject is not fasting, proceed with the visit but mark the sample collection as being non-fasting.

- Collect a urine sample for urinalysis and, if the subject is a woman of childbearing potential, perform a urine pregnancy test (preferred; or submit a serum or urine sample to a laboratory for pregnancy testing if required by your institution/IRB/EC).
- Record the date and time of the subject's last previous study drug dose (expected to have occurred the evening prior to the visit).
- Collect study drug and assess compliance.
- Confirm that the subject does NOT meet criteria for randomization into the double-blind randomized withdrawal period of the study.
- Contact IVRS/IWRS to enroll the subject in the additional open-label dosing period and obtain study drug assignment.
- Dispense open-label study drug and instruct the subject on self-administration of study drug orally with food BID.
- Have the subject eat breakfast.
- Ask the subject to self-administer study drug with a nonalcoholic beverage (except grapefruit juice) while at the study site. Record the exact time of study drug administration.
- Provide instructions to the subject regarding 24-hr urine samples and saliva samples to be collected at home prior to the next visit (Section 7.4.2).
- Schedule the next study visit (Visit A2) so that the blood hormone sample collections for that visit will occur as close to 8 AM (08:00) as practicable and between 6-10 AM (06:00-10:00).
- Remind the subjects that they will need to record the approximate time of their evening study drug dose prior to their next visit.
- Remind the subjects that on the morning of their next visit, they should wait to take their morning dose of study drug until directed by site personnel at the study site, and that they will need to bring the 24-hr urine and saliva samples collected on or prior to Day 70 to the study site (if not previously submitted).

7.4.2. Between Visits A1 and A2 and Between Visits A2 and A3/ET

On Days 69, 70, 79, and 84 during the additional open-label dosing period, subjects should:

- Collect an early morning saliva sample.
- Collect a late night saliva sample.
- Begin a 24-hr urine collection.

In addition, at the indicated study days during the open-label dose-escalation period, subjects should:

- Day 80: Take the 24-hr urine collection and any collected saliva samples to the study site, or a visiting nurse will assist with processing the samples and shipping them to the central laboratory, per subject preference.
- Days 70 and 84 (the day prior to Visits A2 and A3/ET, respectively): Record the approximate time of the evening study drug dose.
- Day 85 (the day of Visit A3/ET): Take the Day 84 24-hr urine collection and any collected saliva samples (i.e., the Day 84 samples, and any other samples that were not previously submitted) to the study site.
- Day 84 (the evening prior to Visit A3/ET): Fast after 10 PM (22:00; water and maintenance medications allowed).

7.4.3. Visit A2 (Day 71)

At Visit A2, appropriate study site personnel should:

- Receive the Day 69 and Day 70 saliva collections and 24-hr urine collections (and any other collections that were not previously submitted) from the subject and submit these to the central laboratory for analysis.
- Record adverse events and update medications.
- Record vital signs and weight.
- Perform a brief PE, with particular attention to assessing the subject for adrenal insufficiency.
- Collect blood samples for hematology, chemistry, hormones (11-DOC, 17-OHP, A, A4, ACTH, cortisol, DHEA, DHEAS, free T, P, renin, SHBG and total T) and PK within 30 minutes prior to administration of study drug.
  - All blood hormone collections should be performed between 6-10 AM (06:00-10:00), as close to 8 AM (08:00) as practicable.
  - Subjects need to be in a seated position for at least 15 minutes prior to collection of blood hormone levels so that renin and aldosterone levels are stable.
- If the subject is a woman of childbearing potential, collect a urine sample and perform a urine pregnancy test (preferred; or submit a serum or urine sample to a laboratory for pregnancy testing if required by your institution/IRB/EC).
- Record the date and time of the subject's last previous study drug dose (expected to have occurred the evening prior to the visit).
- Collect study drug and assess compliance.
- Contact IVRS/IWRS to obtain study drug assignment.
- Dispense open-label study drug and instruct the subject on self-administration of study drug orally with food BID.

- Have the subject eat breakfast.
- Ask the subject to self-administer study drug with a nonalcoholic beverage (except grapefruit juice) while at the study site. Record the exact time of study drug administration.
- Provide instructions regarding 24-hr urine samples and saliva samples to be collected at home prior to the next visit (Section 7.4.2).
- Schedule the next study visit (Visit A3) so that blood hormone sample collections for that visit will occur as close to 8 AM (08:00) as practicable and between 6-10 AM (06:00-10:00).
- Remind the subjects that the evening prior to their next visit, they need to be fasting after 10 PM (22:00; water and maintenance medications allowed) and they will need to record the approximate time of their evening study drug dose.
- Remind the subjects that on the morning of their next visit, they should not take any study drug, and that they will need to bring the 24-hr urine and saliva samples collected on or prior to Day 84 to the study site (if not previously submitted).

7.4.4. Visit A3 (Day 85; End-of-Treatment)/Early Termination

At Visit A3 (EoT)/ET, appropriate study site personnel should:

- Receive the Day 84 saliva collections and 24-hr urine collection (and any other collections that were not previously submitted) from the subject and submit these to the central laboratory for analysis.
- Record adverse events and update medications.
- Record vital signs and weight.
- Perform a complete PE.
- Obtain a 12-lead ECG.
- Collect fasting blood samples for hematology, chemistry, PT, aPTT, INR, insulin, HbA1c, lipid panel, hormones (11-DOC, 17-OHP, A, A4, ACTH, cortisol, DHEA, DHEAS, free T, P, renin, SHBG and total T) and PK.
  - All blood hormone collections should be performed between 6-10 AM (06:00-10:00), as close to 8 AM (08:00) as practicable.
  - Subjects need to be in a seated position for at least 15 minutes prior to collection of blood hormone levels so that renin and aldosterone levels are stable.
  - If the subject is not fasting, proceed with the visit but mark the sample collection as being non-fasting.
- Collect a urine sample for urinalysis and, if the subject is a woman of childbearing potential, perform a urine pregnancy test (preferred; or submit a serum or urine sample to a laboratory for pregnancy testing if required by your institution/IRB/EC).
- Record the date and time of the subject's last previous study drug dose (expected to have occurred the evening prior to the visit).

- Collect study drug and assess compliance.
- If the subject's most recent available 24-hr UFC result is ≤ ULN, then:
  - A Day 92 24-hr UFC may or may not be needed. Provide instructions regarding a 24-hr urine sample to be collected at home starting in 7 days (Day 92 or R3/ET+7) (Section 7.5.1). If the Day 84 24-hr UFC result is > ULN, inform the subject that they will not need to collect this sample.
  - Schedule the next study visit (Visit F1).
- If the subject's most recent available 24-hr UFC result is > ULN, follow up with the subject via telephone in 13 days to assess for new AEs. Subjects who have ongoing AEs should be followed up as appropriate. After completing Visit A3/ET, subjects whose most recent 24-hr UFC is > ULN may begin treatment with another agent for Cushing's syndrome at the discretion of their physicians.

7.5. Follow-up Period

During the follow-up period, the continued safety of the subjects after discontinuation of study drug will be assessed.

7.5.1. Between Visits R3/A3/ET and F1

At the indicated study days, subjects whose Day 84 24-hr UFC result was ≤ ULN should:

- Day 92 (R3/ET+7): Begin a 24-hr urine collection.
- Day 93 (R3/ET+8): Take the 24-hr urine collection to the study site, or a visiting nurse will assist with processing the sample and shipping it to the central laboratory, per subject preference.

7.5.2. Follow-up, Visit F1 (End-of-Study (EoS); End of Trial)

The target study day for the follow-up (EoS; end-of-trial) visit is 13 days after Visit R3/A3/ET. Only subjects whose most recent available 24-hr UFC is ≤ ULN need to have a follow-up visit at the study site. All other subjects should be followed up via telephone to assess for new AEs and concomitant medications. Subjects who have ongoing AEs should be followed up as appropriate.

Subjects whose Day 92 24-hr UFC is ≤ ULN should continue to be followed up and have morning serum ACTH and 24-hr UFC assessed every 2-4 weeks until their 24-hr UFC is > ULN or until the Investigator and the Medical Monitor agree that the subject is stable.

At Visit F1 (EoS; end of trial), appropriate study site personnel should:

- Record adverse events and update medications.
- Record vital signs and weight.
- Perform a brief PE, with particular attention to assessing the subject for adrenal insufficiency.
- Collect blood samples for hematology, chemistry and hormones (11-DOC, 17-OHP, A, A4, ACTH, cortisol, DHEA, DHEAS, free T, P, renin, SHBG and total T).

  - All blood hormone collections should be performed between 6-10 AM (06:00-10:00), as close to 8 AM (08:00) as practicable.
  - Subjects need to be in a seated position for at least 15 minutes prior to collection of blood hormone levels so that renin and aldosterone levels are stable.

- If the subject is a woman of childbearing potential, collect a urine sample and perform a urine pregnancy test (preferred; or submit a serum or urine sample to a laboratory for pregnancy testing if required by your institution/IRB/EC).
- If the subject's most recent available 24-hr UFC result is ≤ ULN, then:
  - Provide instructions regarding a 24-hr urine sample to be collected at home within 2-4 weeks after the previous sample.
  - Schedule the next study visit (unscheduled follow-up).
- At the completion of Visit F1 and all follow-ups, once the 24-hr UFC is > ULN, discharge the subject from the study.

8. QUALITY CONTROL AND ASSURANCE

Before any subjects can be consented at an investigational site and prior to the conduct of any protocol-specific procedures, formal training of investigational site personnel will be conducted. The Investigator and all relevant investigational site staff are to be trained on all aspects of the study 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 Council 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. 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 study are provided in Section 10.5. During the course of the study, investigational sites, the study database and all associated study 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. STATISTICS

9.1. General Considerations

A Statistical Analysis Plan that includes a more technical and detailed description of the planned statistical analyses will be prepared prior to unblinding of the double-blind randomized withdrawal period of the study.

9.2. Sample Size

A sample size of 16 enrolled patients in the open-label dose-escalation period is sufficient per clinical considerations. No formal sample size calculation was performed.

9.3. Analysis Populations

Efficacy – The primary efficacy analysis population will be the Intent-to-Treat (ITT) population, based on all subjects who are randomized to the double-blind randomized withdrawal period and take at least one dose of double-blind study drug. The modified ITT (mITT) population, based on all subjects who complete at least 2 weeks in the double-blind randomized withdrawal period of the study, will be used for additional analyses. For efficacy analyses, subjects will be included in the treatment group to which they were randomized.

Safety – The safety population will include all treated subjects. Safety analyses will be based on the safety population. For the safety analyses for the double-blind randomized withdrawal period, subjects randomized to the placebo group who receive ATR-101 will be included in the treatment group of the active study drug that they received.

Pharmacokinetic – The PK population will include all subjects with measurable drug concentrations. PK analyses will be based on the PK population.

9.4. 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.

9.5. Treatment

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

9.6. Efficacy

9.6.1. Efficacy Endpoints

9.6.1.1. Primary Efficacy Endpoint

- The proportion of subjects with either a normal 24-hr UFC or a reduction in 24-hr UFC of ≥ 50% relative to their baseline value at the end of the double-blind randomized withdrawal period

9.6.1.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints will include the following. If the data allow, unless otherwise specified in the Statistical Analysis Plan, the endpoints will be evaluated for each post-baseline

visit, at the end of the open-label dose-escalation period and at the end of the double-blind randomized withdrawal period, for the ITT population as a whole and for each baseline UFC stratum.

- The proportion of subjects with a normal 24-hr UFC at the end of the double-blind randomized withdrawal period
- The proportion of subjects with a reduction in 24-hr UFC of ≥ 50% relative to their baseline value at the end of the double-blind randomized withdrawal period
- The proportion of subjects with a normal 24-hr UFC at the end of the open-label dose-escalation period and at the end of the additional open-label dosing period
- The proportion of subjects with a reduction in 24-hr UFC of ≥ 50% relative to their baseline value at the end of the open-label dose-escalation period and at the end of the additional open-label dosing period
- The change and percentage change in the 24-hr UFC from randomization at the end of the double-blind randomized withdrawal period
- The change and percentage change in the 24-hr UFC from baseline at the end of the open-label dose-escalation period and at the end of the additional open-label dosing period
- The proportion of subjects with a normal late night salivary cortisol at the end of the double-blind randomized withdrawal period
- The proportion of subjects with a normal late night salivary cortisol at the end of the open-label dose-escalation period and at the end of the additional open-label dosing period
- The change and percentage change in the late night salivary cortisol from randomization at the end of the double-blind randomized withdrawal period
- The change and percentage change in the late night salivary cortisol from baseline at the end of the open-label dose-escalation period and at the end of the additional open-label dosing period
- The change and percentage change from baseline in blood hormone levels, including 11-DOC, 17-OHP, A, A4, ACTH, cortisol, DHEA, DHEAS, free T, P, renin, SHBG and total T
- The change from baseline in fasting glucose, insulin, lipid panel, systolic blood pressure, diastolic blood pressure and BMI

9.6.2. Efficacy Analysis Methodology

9.6.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint, the proportion of subjects with either a normal 24-hr UFC or a reduction in UFC of ≥ 50% relative to their baseline value at the end of the double-blind randomized withdrawal period, will be evaluated using the Cochran-Mantel-Haenszel (CMH) test, controlling for baseline 24-hr UFC stratum.

Note: the baseline 24-hr UFC is calculated as the mean of all 24-hr UFC levels obtained within the 28 days prior to enrollment into the open-label dose-escalation period.

9.6.2.2. Secondary Efficacy Endpoints

No further adjustments for multiple group comparisons, multiple additional endpoints or multiple subgroups of interest are planned.

Responder analyses and other categorical analyses will be based on the CMH test or Fisher's exact test, as appropriate and if the data allow. Continuous endpoints will be evaluated using ANCOVA or ANOVA model methodology, as appropriate and if the data allow.

9.6.2.3. Exploratory Endpoints

Additional efficacy endpoints may be pre-specified in the Statistical Analysis Plan, including sensitivity analyses associated with drug compliance and missing data issues.

9.7. Safety

9.7.1. Safety Endpoints

Safety endpoints will include the incidence of treatment-emergent adverse events and serious adverse events, as well as changes from baseline in clinical laboratory tests, vital signs, PEs and ECG parameters.

9.7.2. Safety Analyses

Adverse events counts (overall, as well as by severity, causality and seriousness) will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Descriptive statistics and shift tables will be used to summarize continuous laboratory, blood pressure and ECG parameters. Counts and shift tables will be used for categorical lab parameters.

9.8. Pharmacokinetics and Pharmacodynamics

9.8.1. Pharmacokinetic and Pharmacodynamic Endpoints

- The C_{max}, T_{max}, AUC, $t_{1/2}$ and other PK parameters of ATR-101 and its major metabolites (as appropriate and as the data allow)
- The relationship between C_{max} and AUC vs. the percentage change in 24-hr UFC; other PK/PD relationships may be explored as appropriate and as data allow

9.8.2. Pharmacokinetic and Pharmacodynamic Analyses

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}, AUC_{0-4} and trough levels.

Individual subject PK data will be analyzed along with pooling of subjects' data at each dose level. Individual PK parameters will be derived using the WinNonlin software, and table summaries will be provided using descriptive summary statistics. PK/PD analyses will be detailed in the Statistical Analysis Plan.

9.9. Interim Analysis

No interim analysis is planned for this study.

10. ADMINISTRATIVE CONSIDERATIONS

10.1. Institutional Review Board (IRB)/Ethics Committee (EC)

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/EC. A letter from the IRB/EC indicating approval of the Investigator and study site must be submitted to the study Sponsor. All reviews and approval by the IRB/EC will be in accordance with Title 21 of the Code of Federal Regulations (CFR), Part 56. Initial IRB approval and all materials approved by the IRB for this study including the subject consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

The Investigator will promptly report any new information that may adversely affect the safety of subjects or the conduct of the study to the IRB/EC. Similarly, the Investigator will submit written summaries of the study status to the IRB/EC annually, or more frequently if requested. Upon completion of the study, the Investigator will provide the IRB/EC 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 Investigator 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 Investigator 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 Investigator in the Investigator study file.

It should be emphasized to the subject that he or she is at liberty to either discontinue study drug 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 study will be made available for review by authorized representatives of the Sponsor and/or submitted to the IRB/EC and regulatory authorities.

Prior to any screening procedures being performed, 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 Investigator regularly for monitoring purposes. The CRA will be allowed, on request, to inspect the various records of the study (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 study, 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 Investigator agrees to cooperate with the CRA to ensure that problems detected during these monitoring visits are resolved.

Before an investigational site can consent a subject into the study, a representative of Millendo Therapeutics, Inc. will evaluate the investigational study site to assess the site including but not limited to:

- Determine the adequacy of the facilities including the site's ability to carry out the protocol
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence and the responsibilities of Millendo Therapeutics, Inc. or its representatives. This will also be documented in a Clinical Study Agreement between Millendo Therapeutics, Inc. and the Investigator.

During the study, a monitor from Millendo Therapeutics, Inc. or representative will have regular contacts with the investigational site, for the following but not limited to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms and that investigational product accountability checks are being performed

- Perform source data verification. This includes a comparison of the data in the case report forms with the subject's medical records at the hospital or practice and other records relevant to the study. This will require direct access to all original records for each subject (e.g. clinic charts).
- Record and report any protocol deviations not previously sent to Millendo Therapeutics, Inc.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to Millendo Therapeutics, Inc. and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

10.6. Audits and Inspections

Authorized representatives of Millendo Therapeutics, Inc., a regulatory authority, an Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. Millendo Therapeutics, Inc. may perform Clinical Quality Assurance (CQA) audit randomly at a sample of clinical sites, or for cause as warranted. The purpose of a Millendo Therapeutics, Inc. CQA audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed and accurately reported according to the protocol, GCP guidelines of the ICH and any applicable regulatory requirements. These audits will be independent of routine monitoring by the CRA and initiated with prior written notification provided to the site.

The Investigator should contact Millendo Therapeutics, Inc. immediately if contacted by a regulatory agency about an inspection.

10.7. Case Report Forms and Study Records

This study 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 study 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 study.

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.

All unused study materials are to be returned or destroyed as instructed by Millendo Therapeutics, Inc. after the study has been completed.

10.8. Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) is not planned for this study since all subjects will receive treatment with ATR-101 during the intra-subject dose-escalation period and the overall small size of the study generally limits the value of pooling data across the study population. All Investigators will have the ability to assess benefit:risk for each of their subjects in almost real time. The 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 and assesses safety every 2 weeks.

10.9. 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.

10.10. Access to Source Documentation

The Investigator 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 Millendo Therapeutics, Inc. 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 Therapeutics, Inc. or their appointed representatives. Subject confidentiality will be protected at all times.

10.11. Data Generation and Analysis

Data processing and management will be performed by Millendo Therapeutics, Inc. or its designee. Data will be promptly entered into the study database by the site 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 Millendo Therapeutics, Inc. and/or submitted to the IRB/EC and regulatory authorities.

10.12. Retention of Records

Copies of all study documents should be retained by the Investigator 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. The Investigator must inform the Sponsor and obtain agreement prior to study documents being moved or destroyed. It is the responsibility of Millendo Therapeutics, Inc. to inform the Investigator/institution as to when these documents no longer need to be retained. The final database will be archived by the Millendo Therapeutics, Inc. according to regulatory requirements.

10.13. Financial Disclosure

Investigators and Subinvestigators are required to provide full disclosure of any financial relationship to the Sponsor or its designee(s) prior to participation in any study-related activities. Additionally, Investigators and Subinvestigators 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 study and for 1 year after completion of the study. For additional guidance, refer to 21 CFR 312.53(c) (4), 312.64(d), 812.43(c) (5), 812.110(d).

10.14. Premature Termination of the Study

If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators/institutions and the regulatory authority(s) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/EC will also be promptly informed and provided with the reason(s) for the termination or suspension by Millendo Therapeutics, Inc. or by the Investigator/institution, as specified by the applicable regulatory requirement(s).

10.15. 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.”

10.16. 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.

10.17. 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/EC 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 Investigator 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 EC, 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).

11. LIST OF REFERENCES

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4. Etxabe J, Vazquez J. Morbidity and mortality in Cushing's disease: an epidemiological approach. Clin Endocrinol 1994;40(4);479-84.
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7. Nieman LK, Biller BMK, Findling JW, et al. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2015;100(8):2807-2831.
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12. APPENDICES

APPENDIX 1. STUDY SCHEDULE

Table 6: Study Schedule, Screening and Open-Label Dose-Escalation Periods

	Screening	Open-Label Dose-Escalation Period													
Study Day:†	**-56 to -1**	**1**	**13**	**14**	**15**	**27**	**28**	**29**	**41**	**42**	**43**	**50**	**51**	**52**	**56**
Visit:†	**S1**	**T1**			**T2**			**T3**			**tel**				
Study Drug Dose:*	**None**	**ATR-101 250 mg BID**			**ATR-101 500 mg BID**			**ATR-101 1000 mg BID**							
Informed Consent	X														
Inclusion/Exclusion	X	X													
Medical History & Demographics	X														
Vital Signs, Height and Weight[a]	X	X			X			X							
Physical Examination[b]	X	X			X			X							
12-lead ECG	X														
Hematology & Chemistry	X	X			X			X							
PT, aPTT, INR, Insulin, HbA1c, Lipids[c]	X														
Serology (HBsAg, HCV, HIV)	X														
Blood Hormone Levels[d]	X	X			X			X							
Plasma PK[e]		X			X			X							
Serum/Urine Pregnancy Test[f]	X	X			X			X							
Urinalysis/Urine Drug Screen[g]	X	X													
Begin 24-Hr Urine Collection[h]	XX[h]		X	X		X	X		X	X		X	X		X
Early Morning Salivary Cortisol[i]	XX[i]		X	X		X	X		X	X		X	X		X
Late Night Salivary Cortisol[i]	XX[i]		X	X		X	X		X	X		X	X		X
Submit Completed 24-Hr Urine Collections and Saliva Collections to Central Lab[h,i]	XX[h,i]				X			X			X			X	
Enrollment into Open-Label Dose-Escalation Period		X													
Dispense Study Drug		X			X			X							
Collect Study Drug/Assess Compliance					X			X							
Prior and Concomitant Medications	X	X			X			X			X				
Adverse Events[k]		X			X			X			X				

Footnotes are located at the end of Appendix 1.

Table 7: Study Schedule, Double-Blind Randomized Withdrawal Period and Follow-Up Period

	Double-Blind Randomized Withdrawal Period									Follow-Up Period		
Study Day:†	**57**	**64**	**65**	**66**	**71**	**79**	**80**	**84**	**85**	**92^**	**93^**	**98^**
Visit:†	**R1**				**R2**				**R3 EoT/ ET**			**F1 EoS**
Study Drug Dose:*	**ATR-101 1000 mg BID or Placebo**								**None**			
Inclusion/Exclusion	X§											
Vital Signs and Weight	X				X				X			X^
Physical Examination[b]	X				X				X			X^
12-lead ECG	X								X			
Hematology & Chemistry	X				X				X			X^
PT, aPTT, INR, Insulin, HbA1c, Lipids[c]	X								X			
Blood Hormone Levels[d]	X				X				X			X^
Plasma PK[e]	X				X				X			
Serum/Urine Pregnancy Test[f]	X				X				X			X^
Urinalysis	X								X			
Begin 24-Hr Urine Collection[h]		X	X			X		X		X^		
Early Morning Salivary Cortisol[i]		X	X			X		X				
Late Night Salivary Cortisol[i]		X	X			X		X				
Submit Completed 24-Hr Urine Collections and/or Saliva Collections to Central Lab[h,i]	X			X			X		X		X^	
Dispense Study Drug	X				X							
Collect Study Drug/Assess Compliance	X				X				X			
Enrollment into Double-Blind Randomized Withdrawal Period	X§											
Study Completion Assessment[j]					X							
Prior and Concomitant Medications	X				X				X			X
Adverse Events[k]	X				X				X			X

Footnotes are located at the end of Appendix 1.

Table 8: Study Schedule, Additional Open-Label Dosing Period and Follow-Up Period

	Additional Open-Label Dosing Period								Follow-Up Period		
Study Day:†	**57**	**69**	**70**	**71**	**79**	**80**	**84**	**85**	**92^**	**93^**	**98^**
Visit:†	**A1**			**A2**				**A3 EoT/ ET**			**F1 EoS**
Study Drug Dose:*	**ATR-101 1000 mg BID**							**None**			
Inclusion/Exclusion	X§										
Vital Signs and Weight	X			X				X			X^
Physical Examination[b]	X			X				X			X^
12-lead ECG	X							X			
Hematology & Chemistry	X			X				X			X^
PT, aPTT, INR, Insulin, HbA1c, Lipids[c]	X							X			
Blood Hormone Levels[d]	X			X				X			X^
Plasma PK[e]	X			X				X			
Serum/Urine Pregnancy Test[f]	X			X				X			X^
Urinalysis	X							X			
Begin 24-Hr Urine Collection[h]		X	X		X		X		X^		
Early Morning Salivary Cortisol[i]		X	X		X		X				
Late Night Salivary Cortisol[i]		X	X		X		X				
Submit Completed 24-Hr Urine Collections and/or Saliva Collections to Central Lab[h,i]	X			X		X		X		X^	
Dispense Study Drug	X			X							
Collect Study Drug/Assess Compliance	X			X				X			
Enrollment into Additional Open-Label Dosing Period	X§										
Prior and Concomitant Medications	X			X				X			X
Adverse Events[k]	X			X				X			X

Footnotes are located at the end of Appendix 1.

† Study assessments, procedures and visits from T1-R3/A3/ET have a window of + 2 days. All other study assessments, procedures and visits have a window of ± 7 days. Day 1 of the study is defined as the day the subject first receives study drug in the clinic. Subjects who are discontinued from the study should undergo an ET visit, which consists of the same procedures as R3/A3. Target study day numbers provided are for subjects who complete the full duration of the study.

^ Subjects whose Day 84 24-hr UFC is ≤ ULN should collect a repeat 24-hr UFC starting 7 days after R3/A3/ET. If the repeat 24-hr UFC is also ≤ ULN, the subject should return for a follow-up visit at the study site 13 days after R3/A3/ET. Only subjects whose most recent 24-hr UFC is ≤ ULN need to have a follow-up visit at the study site. Such subjects should continue to be followed up and have morning serum ACTH and 24-hr UFC assessed every 2-4 weeks until their 24-hr UFC is > ULN or until the Investigator and the Medical Monitor agree that the subject is stable. All other subjects should be followed-up via a telephone call (instead of having a follow-up visit at the study site).

* Subjects should take the evening dose of study drug with food the evening prior to study visits during the open-label intra-subject dose-escalation period, the double-blind randomized withdrawal period, and the additional open-label dosing period. On the morning of study visits (except S1, R3/A3/ET and F1), subjects should not take their study drug until directed by study site personnel. Subjects should document the time of their last study drug dose prior to each visit.

§ Prior to randomization into the double-blind randomized withdrawal period or enrollment into the additional open-label dosing period, subjects should be evaluated for meeting randomization criteria. A subject is eligible to enter the double-blind randomization period if the mean Day 50/51 24-hr UFC is ≤ ULN or is ≤ 50% of the baseline value. Subjects whose mean Day 50/51 24-hr UFC does not meet either of these criteria are eligible to enter the additional open-label dosing period.

[a] Height at screening only.

[b] A complete physical examination (PE) will be performed at S1, T1, R1/A1 and R3/A3/ET. A brief PE will be performed at T2, T3, R2/A2 and F1, with particular attention to assessing the subjects for adrenal insufficiency. At all other visits, targeted PEs may be performed if needed based on adverse events and positives from review of systems.

[c] Subjects should be fasting after 10 PM (22:00; water and maintenance medications allowed) the evening prior to S1, R1/A1 and R3/A3/ET.

[d] Blood hormone levels to be assessed include 11-DOC, 17-OHP, A, A4, ACTH, cortisol, DHEA, DHEAS, free T, P, renin, SHBG and total T. All blood hormone levels should be drawn in the morning, as close to 8 AM (08:00) as practicable and between the hours of 6-10 AM (06:00-10:00). During the screening period, subjects who require a wash-out of medications that affect cortisol levels should NOT have their hormone levels drawn until they have completed the required wash-out.

[e] At each study visit from T1 to R2/A2, a trough PK level will be collected within 30 minutes prior to dosing. At T1, T2, and T3, plasma for PK assessments will then be collected 1, 2, 3 and 4 hours post-dose. At R3/A3/ET, a trough PK level will be collected (no study drug will be dosed).

[f] Pregnancy tests will be performed on female subjects of childbearing potential only. A serum pregnancy test will be performed at S1; a urine pregnancy test will be performed at all other visits unless otherwise required by the institution/IRB/EC.

[g] Urine drug screen at S1 only for cocaine, amphetamines and opioids.

[h] TWO 24-hr urine collections for UFC should be performed during the screening period within 28 days of enrollment into the open-label dose-escalation period and results reviewed for eligibility prior to enrollment. Subjects who require wash-out of medications should perform these collections AFTER wash-out. Subjects whose Day 84 24-hr UFC is ≤ ULN will perform a 24-hr urine collection on Day 92. A visiting nurse may assist with processing and shipping the Screening and Day 41, 42, 50, 51, 64 (if applicable), 65 (if applicable), 79, and 92 (if applicable) urine collections to the central laboratory; or the subject may submit these to the study site for shipping to the central laboratory, per subject preference (all other collections should be brought by the subject to the next visit at the study site).

[i] TWO early morning (30-45 minutes after awakening for the day) and TWO late night (10 PM - 12 AM; 22:00-00:00) saliva collections for salivary cortisol should be performed during the screening period within 28 days of enrollment into the open-label dose-escalation period and results reviewed for eligibility prior to enrollment. Subjects who require wash-out of medications should perform these collections AFTER wash-out. A visiting nurse may assist with processing and shipping the Screening and Day 41, 42, 50, 51, 64 (if applicable), 65 (if applicable), and 79 saliva collections to the central laboratory; or the subject may submit these to the study site for shipping to the central laboratory, per subject preference (all other collections should be brought by the subject to the next visit at the study site).

[j] For subjects in the double-blind randomized withdrawal period, if the mean Day 64/65 24-hr UFC result is available prior to or at the time of R2, study completion assessment will be performed: if subjects are found to have met criteria for completing the study (i.e., 24-hr UFC is > 1.3 x ULN and has also increased by > 50% relative to the mean Day 50/51 24-hr UFC), R3 will be conducted, rather than R2 (i.e., the subject will skip R2). If the mean Day 64/65 24-hr UFC does not meet criteria for completing the study, or the result is not available at the time of R2, the subject will proceed with R2.

[k] Adverse events will be collected from the time the subject signs the informed consent form until the last study visit or 30 days after the last dose of study drug, whichever is later.

11-DOC, 11-deoxycorticosterone; 17-OHP, 17-hydroxyprogesterone; A, aldosterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; aPTT, activated partial thromboplastic time; demog, demographics; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; ECG, electrocardiogram; ET, Early Termination; excl, exclusion; HbA1c, hemoglobin A1c; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; incl, inclusion; INR, international normalized ratio; P, progesterone; PE, physical examination; PK, pharmacokinetic(s) (samples); PT, prothrombin time; SHBG, sex hormone binding globulin; T, testosterone; tel, telephone visit; UFC, urinary free cortisol; ULN, upper limit of normal

APPENDIX 2. DRUGS THAT PROLONG THE QT/QTC INTERVAL

Appendix 2, List A. Drugs that prolong the QT interval

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 US
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 US
Citalopram	Celexa®	Anti-depressant/depression	
Clarithromycin	Biaxin®	Antibiotic/bacterial infection	
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 US
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®	Antidepressant/major depression/anxiety disorders	
Escitalopram	Lexapro®	Antidepressant/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 IV administration or overdosage
Ibutilide	Corvert®	Anti-arrhythmic/abnormal heart rhythm	Females > Males
Levomethadyl	Orlaam®	Opiate agonist/pain control, narcotic dependence	Not available in US
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®	Antilipidemic/hypercholesterolemia	No longer available in US
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 US
Terfenadine	Seldane®	Antihistamine/allergic rhinitis	No longer available in US
Thioridazine	Mellaril®	Anti-psychotic/schizophrenia	
Vandetanib	Caprelsa®	Anti-cancer/thyroid cancer	

Appendix 2, List B. Drugs with conditional risk of QT prolongation

Generic Name	Brand Name	Class/Clinical Use	Comments
Amisulpride	Solian® and others	Antipsychotic, atypical	Risk of TdP with overdosage - 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 with overdosage
Diphenhydramine	Nytol®	Antihistamine/allergic rhinitis, insomnia	Risk of QT increase/TdP with overdosage
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®	Antidepressant/depression	
Fluoxetine	Prozac®	Antidepressant/depression	
Galantamine	Reminyl®	Cholinesterase inhibitor /dementia, Alzheimer's	
Imipramine	Norfranil®	Tricyclic antidepressant/depression	Risk of TdP with overdosage
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®	Antidepressant/depression	
Protriptyline	Vivactil®	Tricyclic antidepressant/depression	
Ritonavir	Norvir®	Protease inhibitor/HIV	
Sertraline	Zoloft®	Antidepressant/depression	
Solifenacin	VESIcare®	muscarinic receptor antagonist/treatment of overactive bladder	
Trazodone	Desyrel®	Antidepressant/depression, insomnia	
Trimethoprim-Sulfa	Septra® or Bactrim®	Antibiotic/bacterial infection	
Trimipramine	Surmontil®	Tricyclic antidepressant/depression	

Appendix 2, List C. Drugs with possible risk of QT prolongation

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 US
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/IV forms no longer available in US and Canada
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	Antidepressant	
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 with 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 US
Sertindole	Serdolect®	Antipsychotic, atypical/anxiety, schizophrenia	Not available in US
Sertindole	Serlect®	Antipsychotic, atypical/anxiety, schizophrenia	Not available in US
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®	Antidepressant/depression	
Voriconazole	VFend®	Anti-fungal/anti-fungal	
Ziprasidone	Geodon®	Anti-psychotic/schizophrenia	

APPENDIX 3. 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
cilostazol
cocaine
codeine
dapsone
dexamethasone
dextromethorphan
docetaxel
domperidone
eplerenone
fentanyl
finasteride
gleevec
haloperidol
irinotecan
LAAM
lidocaine
methadone
nateglinide
ondansetron
pimozide
propranolol
quetiapine
quinine
risperidone
rivaroxaban
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

Appendix 3. Drugs known to interact with CYP3A4, continued.

INDUCERS 3A4,5,7

HIV Antivirals:	**Miscellaneous**	
efavirenz	barbiturates	phenytoin
nevirapine	carbamazepine	pioglitazone
	glucocorticoids	rifabutin
	modafinil	rifampin
	oxcarbazepine	St. John's wort
	phenobarbital	troglitazone

Adapted from © Cytochrome P450 Drug Interaction Table
www.drug-interactions.com

APPENDIX 4. DRUGS THAT MAY INTERACT WITH P-GLYCOPROTEIN

Transporter	MDR1/P-gp
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. John's 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-transporter

APPENDIX 5. PROCEDURES FOR EMERGENCY UNBLINDING

Study drug for this study will be managed using an online interactive web response system (IWRS). Each user will have a unique username and passcode to access the IWRS.

Each site will additionally be provided with a 6-digit emergency unblinding code. Site users will be carefully trained to store the unblinding code in a secure but accessible location. Each code will be valid for one emergency unblinding action. A new code will be generated and sent to the site once an unblinding action has been carried out, or if the original code is lost. If a site performs an unblinding, all applicable audit-trail data is captured (username, participant number, unblinding date, etc.).

In order to unblind the treatment assignment for a subject, a site user would:

- Log in to the IWRS
- Provide the subject ID and birth date of the subject for whom unblinding is requested
- Provide the 6-digit emergency unblinding code

The IWRS would then provide the treatment group to which the subject was assigned.

APPENDIX 6. ENDOCRINE SOCIETY CLINICAL PRACTICE GUIDELINE ON THE DIAGNOSIS AND TREATMENT OF ADRENAL INSUFFICIENCY (INCLUDING HYPOALDOSTERONISM)