# CLINICAL STUDY PROTOCOL
# PRODUCT NAME: NEVANIMIBE HYDROCHLORIDE
# STUDY NUMBER: ATR-101-202

## A Multicenter Dose-Titration Open-Label Study of Nevanimibe Hydrochloride for the Treatment of Classic Congenital Adrenal Hyperplasia

**Study Phase: 2b**

**IND Number: 122745**

**EudraCT Number: 2017-004878-34**

**NCT Number: NCT03669549**

**Indication: Classic Congenital Adrenal Hyperplasia**

**Sponsor: Millendo Therapeutics US, Inc.**

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

**Original Protocol: 22 February 2018**

**Global Protocol Amendment 1: 13 March 2018**

**Czech Republic Country-Specific Amendment 1: 11 June 2018**

**France Country-Specific Amendment 1: 25 June 2018**

**Global Protocol Amendment 2: 31 May 2019**

**Confidentiality Statement**

# INVESTIGATOR'S AGREEMENT

**Study Title**: A Multicenter Dose-Titration Open-Label Study of Nevanimibe Hydrochloride for the Treatment of Classic Congenital Adrenal Hyperplasia

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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 US, 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 Multicenter Dose-Titration Open-Label Study of Nevanimibe Hydrochloride for the Treatment of Classic Congenital Adrenal Hyperplasia

**SPONSOR SIGNATURE**

I have read and approve the protocol and appendices. My signature, in conjunction with the signature of the Investigator, confirms the agreement of both parties that the clinical trial will be conducted in accordance with the protocol and all applicable laws and regulations, including, but not limited to, the 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: PMohideen

Date: June 4, 2019

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Ann Arbor, MI 48104

# SYNOPSIS

**Name of Sponsor/Company:** Millendo Therapeutics US, Inc.

**Name of Investigational Product:** Nevanimibe hydrochloride (formerly known as ATR-101)

**Study Number:** ATR-101-202

**Title of Study:** A Multicenter Dose-Titration Open-Label Study of Nevanimibe Hydrochloride for the Treatment of Classic Congenital Adrenal Hyperplasia

**Phase of Development:** 2b

**Objectives**:

Primary: To evaluate the efficacy and safety of orally administered nevanimibe hydrochloride for the treatment of classic congenital adrenal hyperplasia

Secondary:

- To assess the changes in adrenal cortical steroids and steroid intermediates
- To determine the pharmacokinetic (PK) parameters of nevanimibe and its major metabolite(s)
- To assess the PK/pharmacodynamic (PD) relationships of nevanimibe and its major metabolite(s)

**Study Design:**

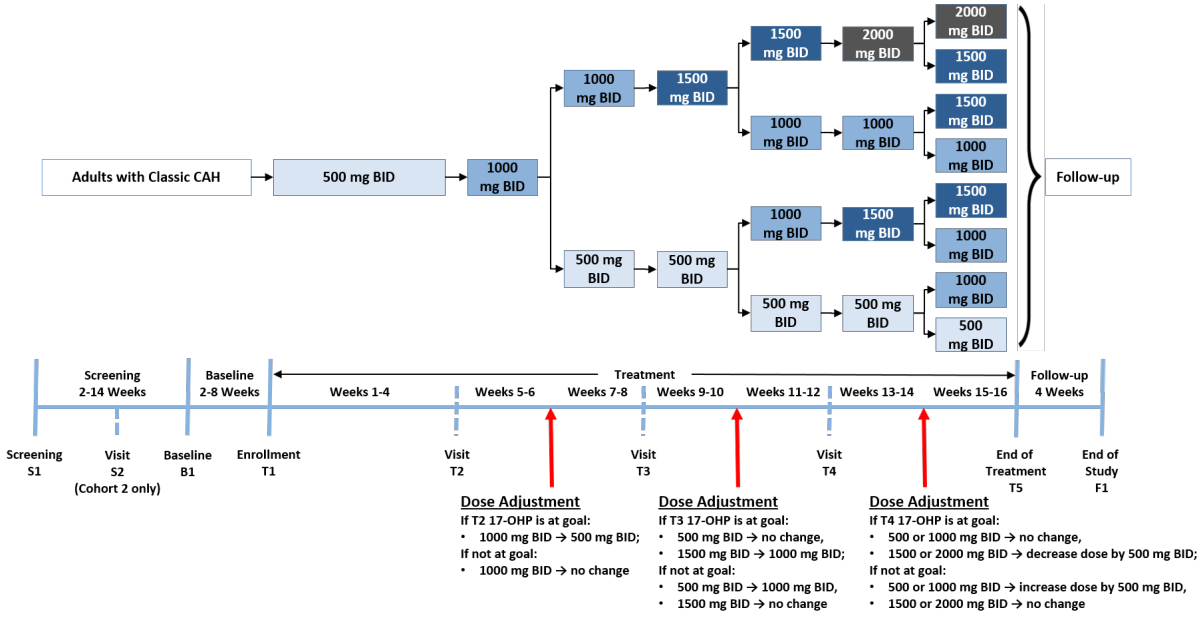
This is a multicenter, intra-subject dose-titration open-label study of nevanimibe hydrochloride (HCl) for the treatment of classic congenital adrenal hyperplasia (CAH). Following a Screening Period of approximately 2-14 weeks, eligible subjects will enter a Baseline Period of approximately 2-8 weeks and then a 16-week Treatment Period. During the Treatment Period, subjects will receive nevanimibe HCl twice daily (BID) for 16 weeks. All subjects will begin dosing with nevanimibe HCl 500 mg BID. Titration of nevanimibe HCl will depend upon the 17-OHP response, which will be assessed every 4 weeks during the Treatment Period. The dosing regimens are intended to achieve and maintain 17-OHP ≤ 2x the upper limit of normal (ULN) (the primary endpoint) on the lowest possible dose of nevanimibe HCl while actively up-titrating if 17-OHP is > 2x ULN. Thus, subjects who are found to have met the primary endpoint (i.e., on the previous lower dose of nevanimibe HCl) based on their most recent serum 17-OHP value will have their nevanimibe HCl dose down-titrated to the dose on which they met the endpoint. Four doses of nevanimibe HCl (500 mg BID, 1000 mg BID, 1500 mg BID, and 2000 mg BID) are available for use in the study. A study schematic is shown in Figure 1.

After signing informed consent, subjects with classic CAH will enter the Screening Period to assess preliminary eligibility for the study based on the inclusion and exclusion criteria. In addition, pertinent information will be collected such as past medical history, demographic data, and prior and current medications. Laboratory tests will be done as part of study eligibility.

Subjects with a serum 17-OHP ≥ 4x ULN (Cohort 1) at the initial screening visit (Visit S1) will proceed to the Baseline Visit (Visit B1). Cohort 1 subjects will not make any changes in their daily maintenance glucocorticoid dose throughout the study (except, for example, for emergency, stress dose requirements). Subjects with a serum 17-OHP < 4x ULN (Cohort 2) AND a daily maintenance glucocorticoid dose in the suppressive range (≥ the equivalent of approximately 12 mg hydrocortisone/$m^2$ body surface area—see Appendix 3) at the initial screening visit (Visit S1) will have their glucocorticoid dose decreased by the equivalent of approximately 5 mg hydrocortisone or 1 mg prednisone or prednisolone (see Appendix 2). They will then return for Visit S2 to have their 17-OHP level rechecked approximately 2 to 4 weeks after their glucocorticoid dose was changed. If their serum 17-OHP level from Visit S2 is ≥ 4x ULN, they will proceed to the Baseline Visit (Visit B1). If not, the case should be discussed with the Medical Monitor; if appropriate, the subject may undergo

further glucocorticoid dose adjustment and subsequent assessment of serum 17-OHP levels during the Screening Period. The Screening Period may last from approximately 2-14 weeks.

**Figure 1: Study Schematic**




At the Baseline Visit (Visit B1), additional laboratory tests will be done as part of study eligibility. In addition, subjects will be instructed on the use of an electronic diary (eDiary) for recording their glucocorticoid, mineralocorticoid (if applicable), and study drug doses (and, for premenopausal women, start dates of menstrual periods) during the study. The most recent serum 17-OHP level should be ≥ 4x ULN for all subjects prior to Visit B1. Any subject whose Visit B1 serum 17-OHP is < 4x ULN should be discussed with the Medical Monitor prior to enrolling in the study. Cohort 2 subjects may require further decreases in glucocorticoid dose and subsequent assessment of serum 17-OHP during the Baseline Period (see Appendix 2). No study drug will be given during the Baseline Period. The Baseline Period may last from approximately 2-8 weeks.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria may be enrolled into the 16-week Treatment Period. Enrollment in either Cohort 1 or Cohort 2 may be capped at the Sponsor's discretion to ensure that a sufficient number of subjects are enrolled into both cohorts.

All enrolled subjects will receive open-label active treatment with nevanimibe HCl orally starting at a dose of 500 mg BID. The first dose of nevanimibe HCl will be given at the study site at Visit T1 (Day 1; Enrollment). All subjects will receive nevanimibe HCl 500 mg BID for Treatment Period Weeks 1-4 (Day 1 to Day 28).

At Visit T2 (Day 29), all subjects will have their nevanimibe HCl dose automatically up-titrated to 1000 mg BID. At Visits T3 (Day 57) and T4 (Day 85), subjects whose most recent predose serum 17-OHP met the primary endpoint will remain on the nevanimibe HCl dose on which they met the endpoint; and subjects whose most recent predose serum 17-OHP did not meet the primary endpoint will have their nevanimibe HCl dose increased to the next higher dose level.

The serum 17-OHP samples require ~10 days to process. When the predose serum 17-OHP results are available following Visits T2, T3, and T4, they will be used to titrate the nevanimibe HCl dose as follows:

- Subjects whose predose serum 17-OHP is ≤ 2x ULN (primary endpoint is met) will have their nevanimibe HCl dose decreased to the dose on which they most recently met the endpoint if they underwent a dose increase at their most recent treatment period site visit.
- Subjects whose predose serum 17-OHP is > 2x ULN (primary endpoint is not met) will have their nevanimibe HCl dose increased to the next higher dose level if they did not already undergo a dose increase at their most recent treatment period site visit.
- All other subjects will remain on their current nevanimibe HCl dose.

During the Treatment Period, nevanimibe HCl doses may also be down-titrated by the Investigator if needed based on safety and tolerability with approval of the Medical Monitor.

The 4-week Follow-up Period will commence immediately after the subject completes the Treatment Period. No study drug will be given during the Follow-up Period. The last study visit will take place at the completion of the Follow-up Period.

A detailed schedule of study assessments is provided in Appendix 1. An algorithm for maintenance glucocorticoid dose down-titration and subsequent monitoring of serum 17-OHP levels for eligibility during the Screening and Baseline periods is provided in Appendix 2.

**Duration of Study:**

Approximately 24-42 weeks (Screening Period of 2-14 weeks, Baseline Period of 2-8 weeks, Treatment Period of 16 weeks, and Follow-up Period of 4 weeks)

**Number of Sites:** Approximately 10-12 in Israel, Europe, and South America

**Number/Type of Subjects (planned):**

Approximately 20-24 evaluable adults with a documented history of classic CAH will be enrolled

**Diagnosis and Main Criteria for Inclusion:**

Inclusion Criteria:

1. Provision of signed and dated informed consent prior to any study-specific procedures
2. Men and women 18 to 80 (70 in the Czech Republic) years of age (inclusive) at the time of informed consent
3. Documented historical diagnosis of classic CAH due to 21-hydroxylase deficiency based on either or both of the following criteria:
   - Documented genetic mutation in the CYP21A2 enzyme consistent with a diagnosis of classic CAH
   - Historical documentation of elevated 17-OHP (e.g., in infancy or following a cosyntropin/ACTH stimulation test)
4. Serum 17-OHP ≥ 4x ULN during the Baseline Period
   - Premenopausal women in the follicular phase of the menstrual cycle must have serum 17-OHP ≥ 4x follicular phase ULN
   - Premenopausal women in the luteal phase of the menstrual cycle must have serum 17-OHP ≥ (4x follicular phase ULN + (luteal phase ULN – follicular phase ULN))
5. Chronic glucocorticoid replacement therapy for at least 6 consecutive months prior to Screening
6. Stable glucocorticoid and mineralocorticoid regimen for at least 4 weeks prior to the Screening (S1), Baseline (B1), and Enrollment (T1) Visits
7. For subjects who undergo maintenance glucocorticoid dose adjustment between Screening and Enrollment, stable serum 17-OHP levels (adjusted as needed for menstrual cycle phase) prior to Enrollment, defined as the most recent 2 values being within 30% of each other (calculated as 100 × (1 – (smaller value/larger value)))

8. Female subjects of childbearing potential must consent to use two medically acceptable methods of contraception, excluding depot progesterone, throughout the study period and for 30 days after the last dose of study treatment during any sexual intercourse with a fertile male partner (in France: Fertile subjects (male and female) must consent to use two medically acceptable methods of contraception, excluding depot progesterone, throughout the study period and for 30 days after the last dose of study treatment during any sexual intercourse with a fertile partner of the opposite sex)

Exclusion Criteria:

1. Nonclassic CAH
2. Other causes of adrenal insufficiency such as Addison's disease or adrenalectomy; or classic CAH with serum 17-OHP < 4x ULN and daily maintenance glucocorticoid dose in the adrenal insufficiency range (e.g., ≤ 8-10 mg hydrocortisone/$m^2$ body surface area per day)
3. Surgery within the previous three months prior to screening or planned surgery during study participation. Minor procedures are permitted (e.g., removal of skin tags or other minor dermatological procedures)
4. History of active cancer requiring medical or surgical therapy within the past 6 months (with the exception of successfully treated non-metastatic basal cell or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix)
5. Female subjects must not be currently pregnant or breastfeeding or have conceived or given birth within 3 months of Screening
6. Abnormal laboratory tests at Screening:
   - ALT or AST > 2x ULN
   - Bilirubin > 1.5x ULN
   - Serum creatinine > 1.5x ULN
7. Positive screen for HIV, hepatitis B surface antigen or hepatitis C antibody at Screening
8. An average QTcF value of > 470 (450 in France) msec at Screening
9. Current or ongoing use of any prohibited concomitant medications (Section 5.8)
10. History of substance abuse within the past 1 year prior to informed consent
11. Positive toxicology screening test for substances of abuse, other than marijuana
12. Known allergy to nevanimibe HCl (formerly known as ATR-101)
13. Participation in any study of an investigational drug within 30 days (or 5 half-lives of the investigational drug, whichever is longer) prior to Screening
14. 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 (e.g., myocardial infarction (MI) or cerebrovascular accident/transient ischemic attack (CVA/TIA) within the past 6 months)

**Investigational Product, Dosage and Mode of Administration:**

Clinical supplies of nevanimibe HCl will be provided as 500-mg tablets for oral administration.

**Reference Therapy, Dosage and Mode of Administration:** None

**Study Endpoints:**

Primary Efficacy Endpoint: The primary efficacy endpoint is the overall response rate within each cohort, defined as the percentage of subjects achieving serum 17-OHP targets as follows:

- Men and postmenopausal women: 17-OHP ≤ 2x ULN
- Premenopausal women:
  - Follicular phase: 17-OHP ≤ 2x follicular phase ULN

- Luteal phase: 17-OHP ≤ (2x follicular phase ULN + (luteal phase ULN – follicular phase ULN))

Safety Endpoints: Safety endpoints include the incidence of treatment-emergent adverse events (AEs) and serious adverse events (SAEs), as well as values and changes from baseline in clinical laboratory tests, vital signs, physical examinations, and electrocardiogram (ECG) parameters.

Pharmacokinetic Endpoints:

The PK and PD endpoints include the following; additional PK and PD endpoints may be described in the SAP.

- The $C_{max}$, $T_{max}$, $AUC_{0-4}$, and other PK parameters of nevanimibe and its major metabolite(s) (as appropriate and as the data allow)
- The relationship between the $C_{max}$ and $AUC_{0-4}$ of nevanimibe and its major metabolite(s) in relation to the change in 17-OHP levels (as appropriate and as the data allow)

**Statistical Methods:**

Sample Size:

Based on results of the previous Phase 2 study of nevanimibe HCl in classic CAH (ATR-101-201), the sample size of approximately 20-24 evaluable subjects is considered to be sufficient for assessing whether nevanimibe HCl at doses of 500-2000 mg BID has clinically meaningful efficacy in the treatment of classic CAH. An evaluable subject is defined as a subject who has efficacy data following at least 8 weeks of continuous dosing with nevanimibe HCl.

Efficacy Analyses:

Only observed case data will be used for the efficacy summaries. The levels of adrenal steroids, steroid intermediates, and other measured hormones will be summarized using descriptive statistics, including number of non-missing observations (n), mean and/or median, standard deviation (SD) and/or percentiles, minimum (min), maximum (max) and 90% confidence intervals, if applicable. The analysis will be performed by value and by change from baseline in the value, where appropriate, for each time point, overall, by nevanimibe HCl dose, and by cohort. The percentage of subjects achieving serum 17-OHP targets, the primary endpoint, will be summarized overall and by cohort. The study will be considered positive if 40% or more of enrolled subjects in either cohort achieve the primary endpoint.

Safety Analyses:

Only observed case data will be used for safety summaries. The summarization of AEs will include treatment-emergent AEs (TEAEs; defined as AEs that begin or worsen after the first dose of study drug). TEAEs and treatment-emergent SAEs will be summarized by MedDRA system organ class and preferred term, severity, and relationship to study drug, overall, by nevanimibe HCl dose, and by cohort. Deaths and discontinuations due to AEs will each be summarized, overall, by nevanimibe HCl dose, and by cohort. Clinical safety laboratory results, PE findings, vital signs, and ECG readings will be summarized by value and by change from baseline in the value, where appropriate, for each time point, overall, by nevanimibe HCl dose, and by cohort using summary statistics for continuous parameters, including number of non-missing observations (n), mean and/or median, standard deviation (SD) and/or percentiles, minimum (min), and maximum (max). Frequencies and percentages as well as shift tables will be prepared for categorical parameters.

Pharmacokinetic Analyses:

Individual subject PK data will be analyzed along with pooling of subjects' data at each dose level. Individual PK parameters will be computed to the extent allowed by the PK data collection times. Tabular summaries will be provided using descriptive summary statistics. PK/PD analyses will be detailed in the Statistical Analysis Plan.

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# LIST OF ABBREVIATIONS

| Abbreviation | Explanation |
|---|---|
| 17-OHP | 17-hydroxyprogesterone |
| A4 | androstenedione |
| ACAT1 | acyl-CoA:cholesterol *O*-acyltransferase 1 |
| ACC | adrenocortical carcinoma |
| ACTH | adrenocorticotropic hormone |
| AE | adverse event |
| ALK-P | alkaline phosphatase |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| AST | aspartate aminotransferase |
| aPTT | activated partial thromboplastin time |
| AUC | area under the concentration-time curve |
| $AUC_{0-4}$ | area under the concentration-time curve from time zero to 4 h after dosing |
| $AUC_{0-4/D}$ | dose-normalized $AUC_{0-4}$, calculated as the ratio of $AUC_{0-4}$ to dose |
| $AUC_{0-\infty}$ | area under the concentration-time curve from time zero to infinity |
| $AUC_{0-t}$ | area under the concentration-time curve from time zero to the time of the last quantified concentration |
| $AUC_{\%extrap}$ | percentage of $AUC_{0-\infty}$ extrapolated |
| BID | twice daily |
| BMI | body mass index |
| BUN | blood urea nitrogen |
| CAH | congenital adrenal hyperplasia |
| CE | cholesteryl ester |
| CFR | Code of Federal Regulations |
| CL | clearance |
| CL/F | oral clearance calculated as dose/$AUC_{0-\infty}$ |
| CI | confidence interval |
| $C_{last}$ | last quantifiable drug concentration determined directly from individual concentration-time data |
| $C_{max}$ | maximum observed 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 |
| CFR | Code of Federal Regulations |

| Abbreviation | Explanation |
|---|---|
| CQA | clinical quality assurance |
| CPMP | Committee for Proprietary Medicinal Products |
| CRA | clinical research associate |
| CS | Cushing's syndrome |
| CSR | clinical study report |
| CVA | cerebrovascular accident |
| CYP | cytochrome P450 |
| DSMB | Drug Safety Monitoring Board |
| EC | ethics committee |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| eDiary | electronic diary |
| EoS | End-of-Study |
| EoT | End-of-Treatment |
| ET | early termination |
| FC | free cholesterol |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practices |
| HBsAg | hepatitis B surface antigen |
| HCl | hydrochloride |
| Hct | hematocrit |
| HCV | hepatitis C virus |
| HEENT | head, eyes, ears, nose and throat |
| Hgb | hemoglobin |
| HIV | human immunodeficiency virus |
| HPA | hypothalamic-pituitary-adrenal |
| ICF | informed consent form |
| ICH | International Council on Harmonisation |
| ID | identification |
| INR | international normalized ratio |
| IRB | institutional review board |
| $\lambda_z$ | terminal phase rate constant |
| MedDRA | Medical Dictionary for Regulatory Activities |

| Abbreviation | Explanation |
|---|---|
| MI | myocardial infarction |
| mITT | modified intention-to-treat |
| NOAEL | No Observed Adverse Effect Level |
| NYHA | New York Heart Association |
| P | progesterone |
| PCOS | polycystic ovary syndrome |
| PD | pharmacodynamic |
| PE | physical examination |
| PK | pharmacokinetic(s) |
| PP | per protocol |
| PT | prothrombin time or preferred term |
| 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 |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SGOT | serum glutamic oxaloacetic transaminase |
| SGPT | serum glutamic pyruvate transaminase |
| SOC | system organ class |
| SP | Safety Population |
| T | testosterone |
| $t_{1/2}$ | terminal phase half-life |
| TBili | total bilirubin |
| TEAE | treatment-emergent AE |
| TESAE | treatment-emergent SAE |
| TIA | transient ischemic attack |
| $T_{max}$ | observed time to reach maximum drug concentration |
| TMF | trial master file |
| ULN | upper limit of normal |
| US | United States |
| WBC | white blood cell |

# 1. INTRODUCTION

## 1.1. Background

Congenital adrenal hyperplasia (CAH) consists of genetic disorders affecting the synthesis of cortisol from the adrenal glands. CAH is categorized as being "classic" (associated with cortisol insufficiency) or "nonclassic" (associated with mild subclinical impairment of cortisol synthesis). The hallmark of classic CAH is the inability to produce cortisol. More than 90% of all classic CAH cases are due to defects in the cytochrome P450 enzyme steroid 21-hydroxylase, also known as 21-hydroxylase or CYP21A2. This enzyme facilitates the conversion of 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol, the immediate precursor of cortisol. Additionally, 21-hydroxylase is responsible for the conversion of progesterone to 11-deoxycorticosterone, the precursor of aldosterone (Dauber, 2010). The remaining cases (< 10%) of classic CAH are mainly due to four other enzyme deficiencies (i.e., P450scc, P450c17, 11β-hydroxylase, 3β-hydroxysteroid dehydrogenase), a defect in the cholesterol transfer protein StAR, and a defect in an electron-transfer protein (Sahakitrungruang, 2015).

In addition to the inability to produce cortisol, approximately 75% or more of classic CAH patients do not have the ability to produce mineralocorticoids (e.g., aldosterone) (Arlt, 2010; Auchus, 2010). Thus, adrenal steroid precursors (e.g., 17-OHP) accumulate proximal to these enzyme blocks and are shunted to the androgen pathway (e.g., androstenedione and testosterone), resulting in excess androgens.

Classic CAH is the most frequent of the congenital endocrine diseases (Arlt, 2010). The incidence has been consistently reported to be approximately 1 in 10,000 to 1 in 16,000 live births in most Caucasian populations (Krone, 2009; Merke, 2005). Incidence rates vary by ethnicity and geographic isolation of affected populations (Merke, 2005). Until the middle of the 20$^{th}$ century, individuals born with classic CAH died in childhood from glucocorticoid and mineralocorticoid deficiency. Today, universal newborn screening and methodologies to identify underlying genetic mutations along with sensitive methodologies to determine levels of steroids and steroid precursors have enabled accurate diagnosis and early treatment of classic CAH.

Treatment of classic CAH involves replacement of missing or deficient levels of naturally occurring glucocorticoids and/or mineralocorticoids with exogenous products. This has enabled individuals to live into adulthood and have a nearly normal life expectancy. However, management of classic CAH can be challenging since it is difficult to mimic the normal circadian fluctuations of glucocorticoids using exogenous glucocorticoid replacement therapy (Arlt, 2010). Additionally, classic CAH patients are often unable to adequately balance the high doses of exogenous glucocorticoids required to suppress excess androgen production while avoiding the iatrogenic side effects of high dose glucocorticoids (i.e., Cushing's syndrome). Thus, patients are caught between having excess androgens and the associated virilization and infertility issues (Auchus, 2010; Auchus, 2013; Auchus, 2015) and suffering from iatrogenic Cushing's syndrome. Women may also develop a secondary polycystic ovary syndrome (PCOS) that persists even after adrenal suppression (Barnes, 1994). Men may have complications of androgen excess manifesting as suppression of gonadotropins leading to testicular atrophy and infertility (Tiitinen, 2002). Additionally, up to 50% of men may have testicular adrenal rest tumors, which can become quite large and painful along with causing testicular dysfunction (Cabrera, 2001). In children, glucocorticoid management entails unique additional issues of achieving and maintaining a normal growth velocity and rate of skeletal maturation. Thus, there

are three major concerns for the management of adults with classic CAH: (1) prevention of adrenal and gonadal hyperplasia and neoplasia, (2) prevention of long-term consequences of adrenal replacement therapies, and (3) restoration of fertility in those who desire to have children (Auchus, 2010).

## 1.2. Rationale for the Use of Nevanimibe Hydrochloride in Congenital Adrenal Hyperplasia

Nevanimibe hydrochloride (HCl), formerly known as ATR-101, is a selective acyl-CoA:cholesterol *O*-acyltransferase 1 (ACAT1) inhibitor in development for the treatment of diseases that result from dysfunctional adrenal steroidogenesis. ACAT1 is a key enzyme functioning proximally in the adrenocortical steroidogenesis cascade. The unique effects of proximally inhibiting adrenocortical steroidogenesis suggest a novel approach to targeting the adrenal cortex with applications in rare (orphan) endocrine diseases caused by hormone dysregulation, such as classic CAH and Cushing's syndrome (CS), and in the oncology indication, adrenocortical carcinoma (ACC).

One of the first obligatory steps in adrenocortical steroidogenesis is the conversion of free cholesterol (FC) to cholesteryl ester (CE). Nevanimibe HCl prevents the esterification of FC to CE, thus inhibiting/preventing the accumulation of the CE reservoir required for normal adrenocortical steroidogenesis. At higher doses, the same mechanism of action results in additional activity that ultimately results in apoptotic effects on adrenocortical cells, including malignant cells. Therefore, nevanimibe HCl can be used in different indications based on the dose, where the lower dose range inhibits adrenocortical steroidogenesis while the higher dose range provides oncologic apoptotic effects (LaPensee, 2016).

Nevanimibe HCl inhibition of adrenal steroid and steroid intermediate synthesis may provide an extremely valuable tool for clinicians managing classic CAH. Inhibition of adrenal steroidogenesis across the androgen pathway would negate the need to suppress adrenocorticotropic hormone (ACTH) with supra-physiologic doses of glucocorticoid and would consequently prevent the risk of iatrogenic Cushing's syndrome. Classic CAH patients may then require only physiologic doses of glucocorticoid replacement. Use of nevanimibe HCl in the treatment of classic CAH is supported by extensive mechanism-of-action studies, robust non-clinical proof-of-concept data, exposure of approximately 60 patients with ACC in a Phase 1 study (ATR-101-001), and exposure of 10 patients with classic CAH in a previous Phase 2 study (ATR-101-201). Additional information may be found in the ATR-101 (nevanimibe HCl) Investigator's Brochure.

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

# 2. STUDY OBJECTIVES

## 2.1. Primary Objective

- To evaluate the efficacy and safety of orally administered nevanimibe HCl for the treatment of classic CAH

## 2.2. Secondary Objectives

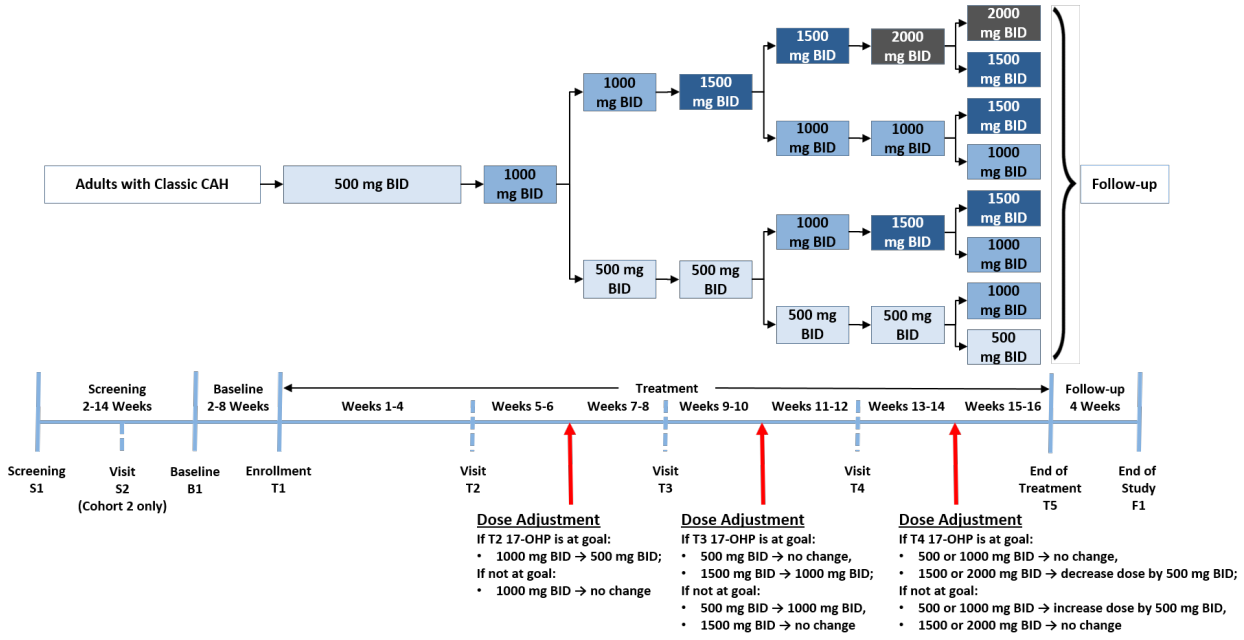
- To assess the changes in adrenal cortical steroids and steroid intermediates
- To determine the pharmacokinetic (PK) parameters of nevanimibe and its major metabolite(s)
- To assess the PK/pharmacodynamic (PD) relationships of nevanimibe and its major metabolite(s)

# 3. INVESTIGATIONAL PLAN

## 3.1. Overall Study Design

This is a multicenter, intra-subject dose-titration open-label study of nevanimibe HCl for the treatment of classic CAH. Following a Screening Period of approximately 2-14 weeks, eligible subjects will enter a Baseline Period of approximately 2-8 weeks and then a 16-week Treatment Period. During the Treatment Period, subjects will receive nevanimibe HCl twice daily (BID) for 16 weeks. All subjects will begin dosing with nevanimibe HCl 500 mg BID. After the 4-week 500 mg BID dosing period, serum samples for 17-OHP will be obtained at Visit T2 and the nevanimibe HCl dose will be automatically up-titrated to 1000 mg BID for all subjects. Although all subjects will receive nevanimibe HCl 1000 mg BID for Weeks 5 and 6, once the 17-OHP results from Visit T2 become available, the nevanimibe HCl dose for Weeks 7 and 8 will either remain at 1000 mg BID (if the Visit T2 predose serum 17-OHP is > 2x ULN) or be decreased to 500 mg BID (if the Visit T2 predose serum 17-OHP is ≤ 2x ULN). The dosing regimens are intended to achieve and maintain 17-OHP ≤ 2x the upper limit of normal (ULN) (the primary endpoint) on the lowest possible dose of nevanimibe HCl while actively up-titrating if 17-OHP is > 2x ULN. Thus, subjects who are found to have met the primary endpoint (i.e., on the previous lower dose of nevanimibe HCl) based on their most recent serum 17-OHP value will have their nevanimibe HCl dose down-titrated to the dose on which they met the endpoint. Subsequent dose adjustments will follow the same procedures. Four doses of nevanimibe HCl (500 mg BID, 1000 mg BID, 1500 mg BID, and 2000 mg BID) are available for use in the study. The study schematic is shown in Figure 1.

**Figure 1: Study Schematic**




### 3.1.1. Screening Period

After signing informed consent, subjects with classic CAH will enter the Screening Period to assess preliminary eligibility for the study based on the inclusion and exclusion criteria. In

addition, pertinent information will be collected such as past medical history, demographic data, and prior and current medications. Laboratory tests will be done as part of study eligibility.

Subjects with a serum 17-OHP ≥ 4x ULN (Cohort 1) at the initial screening visit (Visit S1) will proceed to the Baseline Visit (Visit B1). Cohort 1 subjects will not make any changes in their daily maintenance glucocorticoid dose throughout the study (except, for example, for emergency, stress dose requirements). Subjects with a serum 17-OHP < 4x ULN (Cohort 2) AND a daily maintenance glucocorticoid dose in the suppressive range (≥ the equivalent of approximately 12 mg hydrocortisone/$m^2$ body surface area—see Appendix 3) at the initial screening visit (Visit S1) will have their glucocorticoid dose decreased by the equivalent of approximately 5 mg hydrocortisone or 1 mg prednisone or prednisolone (see Appendix 2). They will then return for Visit S2 to have their 17-OHP level rechecked approximately 2 to 4 weeks after their glucocorticoid dose was changed. If their serum 17-OHP level from Visit S2 is ≥ 4x ULN, they will proceed to the Baseline Visit (Visit B1). If not, the case should be discussed with the Medical Monitor; if appropriate, the subject may undergo further glucocorticoid dose adjustment and subsequent assessment of serum 17-OHP levels during the Screening Period. The Screening Period may last from approximately 2-14 weeks.

### 3.1.2. Baseline Period

At the Baseline Visit (Visit B1), additional laboratory tests will be done as part of study eligibility. In addition, subjects will be instructed on the use of an electronic diary (eDiary) for recording their glucocorticoid, mineralocorticoid (if applicable), and study drug doses (and, for premenopausal women, start dates of menstrual periods) during the study. The most recent serum 17-OHP level should be ≥ 4x ULN for all subjects prior to Visit B1. Any subject whose Visit B1 serum 17-OHP is < 4x ULN should be discussed with the Medical Monitor prior to enrolling in the study. Cohort 2 subjects may require further decreases in glucocorticoid dose and subsequent assessment of serum 17-OHP during the Baseline Period (see Appendix 2). No study drug will be given during the Baseline Period. The Baseline Period may last from approximately 2-8 weeks.

### 3.1.3. Treatment Period

Subjects who meet all of the inclusion criteria and none of the exclusion criteria may be enrolled into the 16-week Treatment Period. Enrollment in either Cohort 1 or Cohort 2 may be capped at the Sponsor's discretion to ensure that a sufficient number of subjects are enrolled into both cohorts.

All enrolled subjects will receive open-label active treatment with nevanimibe HCl orally starting at a dose of 500 mg BID. The first dose of nevanimibe HCl will be given at the study site at Visit T1 (Day 1; Enrollment). All subjects will receive nevanimibe HCl 500 mg BID for Treatment Period Weeks 1-4 (Day 1 to Day 28). At Visit T2 (Day 29), blood for assessment of serum 17-OHP will be collected; all subjects will have their nevanimibe HCl dose automatically up-titrated to 1000 mg BID and will remain on this dose for Weeks 5-6 (Day 29 to Day 42). The Visit T2 (Day 29) serum 17-OHP samples require ~10 days to process and results should be available before the beginning of Week 7 (Day 43).

If the Visit T2 predose 17-OHP is ≤ 2x ULN (primary endpoint is met), subjects will have their nevanimibe HCl dose down-titrated from 1000 mg BID to 500 mg BID starting at Week 7 (Day 43) and remain on this dose until the end of Week 10 (Day 70). If the serum 17-OHP value

obtained at Visit T2 is > 2x ULN (primary endpoint is not met), the subject will continue on their current 1000 mg BID dose for Weeks 7-8 (Day 43 to Day 56) and will automatically up-titrate to 1500 mg BID for Weeks 9-10 (Day 57 to Day 70). At Visits T3 (Day 57) and T4 (Day 85), subjects whose most recent predose serum 17-OHP met the primary endpoint will remain on the nevanimibe HCl dose on which they met the endpoint. Subjects whose most recent predose serum 17-OHP did not meet the primary endpoint will have their nevanimibe HCl dose increased to the next higher dose level.

Following Visits T3 and T4, nevanimibe HCl dose adjustment will proceed in a similar manner as Visit T2. The serum 17-OHP samples require ~10 days to process. When the predose serum 17-OHP results are available, they will be used to titrate the nevanimibe HCl dose as follows:

- Subjects whose predose serum 17-OHP is ≤ 2x ULN (primary endpoint is met) will have their nevanimibe HCl dose decreased to the dose on which they most recently met the endpoint if they underwent a dose increase at their most recent treatment period site visit.
- Subjects whose predose serum 17-OHP is > 2x ULN (primary endpoint is not met) will have their nevanimibe HCl dose increased if they did not already undergo a dose increase at their most recent treatment period site visit.
- All other subjects will remain on their current nevanimibe HCl dose.

During the Treatment Period, nevanimibe HCl doses may also be down-titrated by the Investigator if needed based on safety and tolerability with approval of the Medical Monitor.

### 3.1.4. Follow-up Period

The 4-week Follow-up Period will commence immediately after the subject completes the Treatment Period. No study drug will be given during the Follow-up Period. The last study visit will take place at the completion of the Follow-up Period.

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 provided in Appendix 1. An algorithm for maintenance glucocorticoid dose down-titration and subsequent monitoring of serum 17-OHP levels for eligibility during the Screening and Baseline periods is provided in Appendix 2.

## 3.2. Rationale for Study Design

The previous Phase 2 CAH study (ATR-101-201) explored nevanimibe HCl doses ranging from 125 mg to 1000 mg BID, with each dose lasting 2 weeks followed by a 2-week placebo washout. Each subject had the opportunity to dose-escalate based on 17-OHP values assessed after each dose level. Eligible subjects had 17-OHP ≥ 4x ULN at screening (i.e., similar to Cohort 1). At baseline, the mean 17-OHP was 53x ULN (ranging from 7 to 187x ULN) for the 10 subjects who received nevanimibe HCl. In that study, although robust decreases in 17-OHP with nevanimibe HCl were observed, only two (20%) subjects were able to achieve 17-OHP levels ≤ 2x ULN. However, some of the largest percentage decreases in 17-OHP were observed in subjects with the highest baseline 17-OHP values. This finding was entirely consistent with the known mechanism of action for ATR-101, where depletion of the cholesteryl ester pool may require more than 2 weeks in subjects with markedly elevated 17-OHP (a correlation between larger

adrenal size and higher 17-OHP level has been reported in classic CAH subjects). Also, the cholesteryl ester stores may have been partially replenished during the 2-week placebo washout period that followed each ATR-101 dose period. Thus, hypotheses to be tested for this protocol include whether sustained, continuous dosing of nevanimibe HCl will result in greater efficacy and whether higher doses are needed to demonstrate this effect. Consequently, this protocol will evaluate longer periods of dosing at each dose level with an overall duration of 16 weeks, and explore higher doses of nevanimibe HCl (up to 2000 mg BID). Dosing will commence with nevanimibe HCl at 500 mg BID for 4 weeks prior to up-titrating to the 1000 mg BID dose, as the nevanimibe HCl 500 mg BID dose was well-tolerated in both the previous Phase 2 CAH study and in a previous drug-drug interaction study, and experience from previous studies suggests that study drug tolerability is improved by longer dosing.

The intra-subject dose escalation design is appropriate for the current stage of nevanimibe HCl development in an orphan indication such as classic CAH. A "traditional" randomized, parallel-arm, placebo-controlled trial would have severe limitations and would have the potential to generate indeterminate study results. In a traditional design, since only ~20 subjects in total are being recruited for this study and there are 4 nevanimibe HCl doses being tested, no more than ~5 subjects per arm would be feasible. If a placebo arm were to be included, then the number of subjects per arm could be no more than ~3. Additionally, there would need to be equal distribution between subjects in Cohort 1 and Cohort 2 within a given dose. Thus, each dose could have no more than ~2 subjects per cohort. With such small numbers, a single outlier (e.g., baseline 17-OHP, treatment effect, etc.) in a given cohort (within a dose arm) could completely skew the entire arm or render that cohort uninterpretable. In contrast, the design presented in this protocol avoids such challenges.

Use of nevanimibe HCl for subjects in Cohort 1 will attempt to demonstrate sustained decreases in 17-OHP with a target value of ≤ 2x ULN while continuing on their generally supra-physiologic (unchanged) glucocorticoid doses. For this cohort, demonstration of maintenance of 17-OHP with decreased glucocorticoid doses is not the goal of the present study, as it is not reasonable to decrease the glucocorticoid dose in subjects with 17-OHP values already elevated beyond 4x ULN; however, in a future study this would be attempted once 17-OHP levels are controlled. Conversely, increasing the glucocorticoid dose to suppress 17-OHP has presumably already been attempted, would result in further risk of iatrogenic Cushing's syndrome, and would also confound the simultaneous use of nevanimibe HCl.

Use of nevanimibe HCl in Cohort 2 is designed to demonstrate sustained decreases 17-OHP to a target value of ≤ 2x ULN while the subject receives glucocorticoid doses that are lower than their doses at screening. Although subjects in Cohort 2 have 17-OHP values at or very close to goal at screening (i.e., < 4x ULN), this comes at the "cost" of suppressive glucocorticoid doses and associated side effects. In this cohort, the temporary, purposeful rise in 17-OHP associated with a decrease in glucocorticoid dose toward non-suppressive levels (see Appendix 2) creates the potential for nevanimibe HCl to demonstrate a truly novel clinical therapy. Nevanimibe HCl could potentially create the optimal/ideal clinical situation that does not currently exist for classic CAH patients, i.e., control of 17-OHP with non-suppressive glucocorticoid doses. Ultimately, in a future study, a similar outcome to that of Cohort 1 could be demonstrated in Cohort 2 with a longer duration of treatment (i.e., the glucocorticoid dose could be decreased once the 17-OHP has reached the target level).

The dose range for this study is supported by the previous CAH Phase 2 study, extensive ACC Phase 1 data, and comprehensive non-clinical and *in vitro* studies conducted with nevanimibe HCl (additional information regarding the dose rationale may be found in Appendix 7 and in the ATR-101 (nevanimibe HCl) Investigator's Brochure).

The ACC Phase 1 study provides tremendous reassurance for the safety of the doses proposed, since both the dose levels and the duration of treatment have already far surpassed those being proposed in this protocol. The highest dose evaluated in the ACC study was 158.5 mg/kg/day, which is approximately 3x the highest dose proposed for this protocol for a 75-kg subject. In addition, the average duration of exposure was 58 days across the 14 nevanimibe HCl dose cohorts, with several subjects having received nevanimibe HCl for as long as 5 to 12 months at doses > 2000 mg BID. Nevanimibe HCl was extremely well tolerated in the ACC study population, which is markedly less robust (all had advanced stage cancer and most had undergone multiple prior treatment regimens) relative to the classic CAH patient population.

The dose rationale is further supported by the 13-week dog toxicity study with $AUC_{0\text{-}24\ hr}$ margins relative to the dog No Observed Adverse Effect Level (NOAEL) of 2.0 to 8.0 for the highest (2000 mg BID) and lowest (500 mg BID) nevanimibe HCl doses planned, respectively.

Acceptably managed classic CAH patients generally have mildly elevated, rather than completely normal, 17-OHP levels (Speiser, 2010). Thus, the overall goal of the study is to show clinically meaningful decreases in 17-OHP that are aligned with clinical practice goals. Two classic CAH patient populations have been identified: those with serum 17-OHP ≥ 4x ULN (Cohort 1) and those with serum 17-OHP < 4x ULN (Cohort 2) at screening. The vast majority of subjects are expected to be on suppressive (supra-physiologic) glucocorticoid doses at screening, but it is possible that potential subjects may have an elevated 17-OHP while on less than supra-physiologic glucocorticoid doses.

The study design and dose levels are appropriately supported by existing clinical and nonclinical data.

## 3.3. Efficacy Assessment

Efficacy will be assessed by changes in adrenal steroids and steroid intermediates. The percentage of subjects achieving serum 17-OHP targets will serve as the primary endpoint, as this adrenal steroid intermediate is used diagnostically and to aid in the management of exogenous glucocorticoid replacement therapy in clinical practice. However, absolute target values for 17-OHP or androgens do not currently exist in treatment guidelines put forth by any of the medical societies. The entry criterion for 17-OHP is set at ≥ 4 x ULN (for menstruating women, this criterion is adjusted for the menstrual cycle phase), which is intended to enroll subjects who are not optimally controlled while on exogenous glucocorticoid replacement therapy. The primary endpoint is aligned with the clinical goal of achieving a mildly elevated 17-OHP level, which for this study is defined as serum 17-OHP ≤ 2 x ULN. However, salivary 17-OHP and other key efficacy parameters in the androgen pathway (i.e., androstenedione, testosterone, and 11-ketotestosterone) will also serve to define efficacy.

ACTH levels will be assessed to determine potential effects on the hypothalamic-pituitary-adrenal (HPA) axis. Glucocorticoid replacement doses must be stable for at least 4 weeks prior to starting study drug, and are expected to remain unchanged during the treatment period (except, for example, for emergency, stress dose requirements), so no significant changes in ACTH are

anticipated. Confirmation of stable ACTH levels associated with decreases in 17-OHP and androgens will help to establish the pharmacodynamic effects of nevanimibe.

## 3.4. Safety Assessment

Safety will be assessed by monitoring adverse events, changes in PEs (including vital signs), changes in ECGs, and changes in laboratory parameters. Safety assessments will take place every 4 weeks during study participation.

Classic CAH subjects will have been enrolled into the study on stable glucocorticoid and mineralocorticoid regimens. Monitoring and management of replacement steroids should continue per usual clinical practice.

## 3.5. Criteria for Study Termination

The study is open-label and all laboratory results will be able to be viewed by the Investigator and Sponsor. The Sponsor will review pooled and individual subject data at regular intervals during the course of the study. In addition, a single occurrence of any the following safety events will trigger an expedited, *ad hoc* safety meeting of at least the Sponsor and the Medical Monitor:

- Marked elevations in transaminases or simultaneous elevations in hepatic transaminases and bilirubin (i.e., Hy's Law)
- Severe renal impairment
- Severe cardiovascular dysfunction such as arrhythmia or valvular dysfunction, or New York Heart Association (NYHA) Class III or IV heart failure.

If the Sponsor and the Medical Monitor determine that the event is drug-related and a clear safety signal has been identified, the Sponsor and the Medical Monitor will determine whether early termination of the study is warranted.

# 4. SELECTION AND WITHDRAWAL OF SUBJECTS

## 4.1. Study Population

The study population will consist of adult men and women with a documented history of classic CAH.

## 4.2. Inclusion Criteria

Each subject must meet all 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 to 80 (70 in the Czech Republic) years of age (inclusive) at the time of informed consent
3. Documented historical diagnosis of classic CAH due to 21-hydroxylase deficiency based on either or both of the following criteria:
   - Documented genetic mutation in the CYP21A2 enzyme consistent with a diagnosis of classic CAH
   - Historical documentation of elevated 17-OHP (e.g., in infancy or following a cosyntropin/ACTH stimulation test)
4. Serum 17-OHP ≥ 4x ULN during the Baseline Period
   - Premenopausal women in the follicular phase of the menstrual cycle must have serum 17-OHP ≥ 4x follicular phase ULN
   - Premenopausal women in the luteal phase of the menstrual cycle must have serum 17-OHP ≥ (4x follicular phase ULN + (luteal phase ULN – follicular phase ULN))
5. Chronic glucocorticoid replacement therapy for at least 6 consecutive months prior to Screening
6. Stable glucocorticoid and mineralocorticoid regimen for at least 4 weeks prior to the Screening (S1), Baseline (B1), and Enrollment (T1) Visits
7. For subjects who undergo maintenance glucocorticoid dose adjustment between Screening and Enrollment, stable serum 17-OHP levels (adjusted as needed for menstrual cycle phase) prior to Enrollment, defined as the most recent 2 values being within 30% of each other (calculated as 100 × (1 – (smaller value/larger value)))
8. Female subjects of childbearing potential must consent to use two medically acceptable methods of contraception, excluding depot progesterone, throughout the study period and for 30 days after the last dose of study treatment during any sexual intercourse with a fertile male partner (in France: Fertile subjects (male and female) must consent to use two medically acceptable methods of contraception, excluding depot progesterone, throughout the study period and for 30 days after the last dose of study treatment during any sexual intercourse with a fertile partner of the opposite sex)

## 4.3. Exclusion Criteria

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

1. Nonclassic CAH
2. Other causes of adrenal insufficiency such as Addison's disease or adrenalectomy; or classic CAH with serum 17-OHP < 4x ULN and daily maintenance glucocorticoid dose in the adrenal insufficiency range (e.g., ≤ 8-10 mg hydrocortisone/$m^2$ body surface area per day)

3. Surgery within the previous three months prior to screening or planned surgery during study participation. Minor procedures are permitted (e.g., removal of skin tags or other minor dermatological procedures)
4. History of active cancer requiring medical or surgical therapy within the past 6 months (with the exception of successfully treated non-metastatic basal cell or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix)
5. Female subjects must not be currently pregnant or breastfeeding or have conceived or given birth within 3 months of Screening
6. Abnormal laboratory tests at Screening:
   - ALT or AST > 2x ULN
   - Bilirubin > 1.5x ULN
   - Serum creatinine > 1.5x ULN
7. Positive screen for HIV, hepatitis B surface antigen or hepatitis C antibody at Screening
8. An average QTcF value of > 470 (450 in France) msec at Screening
9. Current or ongoing use of any prohibited concomitant medications (Section 5.8)
10. History of substance abuse within the past 1 year prior to informed consent
11. Positive toxicology screening test for substances of abuse, other than marijuana
12. Known allergy to nevanimibe HCl (formerly known as ATR-101)
13. Participation in any study of an investigational drug within 30 days (or 5 half-lives of the investigational drug, whichever is longer) prior to Screening
14. 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 (e.g., myocardial infarction (MI) or cerebrovascular accident/transient ischemic attack (CVA/TIA) within the past 6 months)

## 4.4. 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 AE 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.

Enrolled subjects who withdraw from the study prior to the T5/End-of-Treatment (EoT) visit should return to the study site for an Early Termination (ET) visit, which consists of the same procedures as at T5/EoT. 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 6.10. 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 will not be replaced. All enrolled subjects will be fully accounted for and documented in the final clinical study report (CSR).

# 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). This number will be utilized to identify the subject throughout the study. 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

Nevanimibe HCl Drug Product is supplied as a 500-mg strength tablet for oral administration. Each subject will receive sufficient nevanimibe HCl Drug Product Tablets to provide dosing for a 4-week period with extra tablets to account for scheduling visit windows and unforeseen events. The tablet formulation is described in Table 1.

**Table 1: Investigational Product**

| | **Investigational Product** |
|---|---|
| **Product Name** | Nevanimibe hydrochloride |
| **Dosage Form** | tablet |
| **Unit Dose** | 500 mg |
| **Route of Administration** | Oral |
| **Physical Description** | White or orange, film-coated oval biconvex tablets with no markings [1] |
| **Inactive Ingredients** | Mannitol, microcrystalline cellulose, croscarmellose sodium, pregelatinized starch, hypromellose, magnesium stearate, and Opadry II white or Opadry II orange [1] |
| **Manufacturer** | Corealis Pharma, Inc. (white tablets) or Patheon, part of Thermo Fisher Scientific (orange tablets) [1] |

[1] The white tablets and the orange tablets are identical in strength, specification, composition, and components, except for the coating films. The white tablets are currently in use, and the orange tablets are expected to be available after 1 January 2020.

For more information regarding the nevanimibe HCl tablet, refer to the most recent version of the ATR-101 (nevanimibe HCl) Investigator's Brochure.

## 5.3. Study Drug Administration

All enrolled subjects who enter the Treatment Period will begin dosing with nevanimibe HCl 500 mg BID. During the Treatment Period, a sufficient number of bottles of nevanimibe HCl 500-mg tablets will be supplied to last until at least the subject's next scheduled study visit (see Pharmacy Manual). Table 2 presents the tablets and dosing regimen by dose level. An additional bottle or bottles may be dispensed to provide sufficient nevanimibe HCl in case of potential up-titration or for unanticipated scheduling issues.

**Table 2 Nevanimibe HCl Dose Levels and Tablet Doses**

| Dose Level | Nevanimibe HCl Dose | Nevanimibe HCl Tablet Strength Dispensed | Nevanimibe HCl Dosing |
|---|---|---|---|
| 1 | 500 mg BID | 500 mg | 1 tablet BID |
| 2 | 1000 mg BID | 500 mg | 2 tablets BID |
| 3 | 1500 mg BID | 500 mg | 3 tablets BID |
| 4 | 2000 mg BID | 500 mg | 4 tablets BID |

BID: twice daily; HCl: hydrochloride

### 5.3.1. Timing and Administrative Dosing Conditions

Study drug should be taken approximately 12 hours apart (twice per day dosing). The time of day that the dose is taken should be as consistent as possible (e.g., every morning at 8 AM (08:00) and every evening at 8 PM (20:00)). Using the eDiary, subjects should record the actual time of their doses of study drug (if applicable), glucocorticoid, and mineralocorticoid (if applicable), particularly those taken on the day prior to and the day of study visits. On the morning of study visits, including at Visit T5/EoT, subjects should wait to take their morning doses of study drug (if applicable), glucocorticoid, and mineralocorticoid (if applicable) until directed by personnel at the study site.

Study drug should be taken with a non-alcoholic beverage (except grapefruit juice) 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.

The first dose of each dose level will be administered at the site with food. See the Pharmacy Manual for more details.

### 5.3.2. Titration of Nevanimibe HCl Dose

At Visit T2 (Day 29), all subjects will have their nevanimibe HCl dose up-titrated from 500 mg BID to 1000 mg BID and will also have serum 17-OHP levels obtained. Based on the results of the Visit T2 serum 17-OHP level (expected to be available prior to Day 43, the start of Week 7), if the primary endpoint was not achieved on the nevanimibe HCl 500 mg BID dose, the subject will continue on 1000 mg BID (for Weeks 7-8; Days 43-56) and automatically up-titrate to 1500 mg BID for Weeks 9-10, Days 57-70. If the primary endpoint was achieved, appropriate study site personnel will contact the subject via telephone prior to Day 43 to instruct them on down-titrating their nevanimibe HCl dose from 1000 mg BID to 500 mg BID (for Weeks 7-10; Days 43-70). Note: subjects should change to their updated dose the day they are contacted by the site to do so; they do not need to wait until Day 43 to start the updated dose. The primary endpoint is defined as follows:

- Men and postmenopausal women: 17-OHP ≤ 2x ULN
- Premenopausal women:
  - Follicular phase: 17-OHP ≤ 2x follicular phase ULN
  - Luteal phase: 17-OHP ≤ (2x follicular phase ULN + (luteal phase ULN – follicular phase ULN))

At Visits T3 (Day 57) and T4 (Day 85), all subjects will again have their serum 17-OHP levels obtained. The serum 17-OHP samples require ~10 days to process. When the predose serum 17-OHP results are available following Visits T3 and T4, appropriate study site personnel will contact the subjects via telephone to instruct them on any potential dose adjustments:

- Subjects whose predose serum 17-OHP is ≤ 2x ULN (primary endpoint is met) will have their nevanimibe HCl dose decreased to the dose on which they most recently met the endpoint if they underwent a dose increase at their most recent treatment period site visit.
- Subjects whose predose serum 17-OHP is > 2x ULN (primary endpoint is not met) will have their nevanimibe HCl dose increased to the next higher dose level if they did not already undergo a dose increase at their most recent treatment period site visit.
- All other subjects will remain on their current nevanimibe HCl dose.

Note: subjects should change to their updated dose the day they are contacted by the site to do so; they do not need to wait until 14 days after their scheduled treatment period site visit to start the updated dose.

### 5.3.3. Drug Holidays and Down-Titration

During the Treatment Period, the nevanimibe HCl dose may be down-titrated and/or a "drug holiday" taken at any time (independent of study visit schedule) for safety-related reasons. However, such events should be discussed with the Medical Monitor ahead of time, whenever feasible, or after the fact to align on the treatment regimen/plan moving forward.

### 5.3.4. Missed Doses

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

### 5.3.5. Compliance

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

### 5.3.6. Blinding

This is an open-label study. Neither Investigators nor subjects will be blinded to treatment.

## 5.4. Study Drug Packaging and Labeling

The formulation and bulk packaging of nevanimibe HCl will be conducted according to standard procedures. The drug product will be packaged and labeled by Millendo Therapeutics US, Inc.'s designated contract packager and labeler according to regulatory requirements.

## 5.5. Study Drug Storage and Accountability

Study drug must be kept in a secure 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 (or designee) 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 the Sponsor (or designee) or destruction. Total study site accountability will be conducted at the end of the study and the Investigator (or designee) 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) of the subject to whom the study drug was dispensed
- The dates the study drug was dispensed
- 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 nevanimibe HCl will be provided in the Pharmacy Manual.

## 5.6. Investigational Product Retention at the Study Site

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 will assure 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.

## 5.7. Concomitant Medications

Use of concomitant medications should be kept to a minimum during the study. However, if concomitant medications are considered necessary for subject welfare, they may be given at the discretion of the Investigator. During the study, any medication given other than the study drug (including blood transfusions, parenteral fluids, over-the-counter medications, and herbal preparations) 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.

Glucocorticoid and mineralocorticoid replacement are critical concomitant medications used in classic CAH. Subjects must continue to receive glucocorticoid and mineralocorticoid (if applicable) according to their individual regimens established prior to enrolling in the study. Other than as specified in Appendix 2, the regimen should remain as stable and unchanged as possible to minimize potential confounding effects on efficacy outcome measures. However, changes are permitted to ensure subject safety. It is not expected that nevanimibe HCl will result

in a need for increased doses of glucocorticoid replacement, as the glucocorticoid synthetic pathway is already compromised in classic CAH. Therefore, decreasing cortisol precursors (i.e., 17-OHP) should not result in increased glucocorticoid requirements over the treatment period.

The timing of glucocorticoid replacement therapy may have an impact on the measurement of 17-OHP. Consequently, on clinic days when blood and/or saliva samples for adrenal steroids/steroid intermediates are to be collected, the morning dose of replacement steroids (glucocorticoid and mineralocorticoid) must not be taken until after the sample collection as this could confound efficacy endpoint measures. Glucocorticoid and mineralocorticoid replacement doses should be taken after samples are obtained for laboratory assessments. Similarly, when subjects collect salivary 17-OHP profiles at home, the first (~8 AM/08:00) sample should be obtained prior to the morning dose of replacement steroids. See Section 6.11 for additional details on the timing of blood and saliva samples.

Approximately 75% of classic CAH subjects have deficiency in the mineralocorticoid pathway in addition to the glucocorticoid pathway (Auchus, 2010). Thus, the majority of subjects in this study are anticipated to be on mineralocorticoid replacement. Nevanimibe HCl inhibition of the mineralocorticoid pathway for these subjects should not have an effect on mineralocorticoid replacement therapy. Subjects who enter the study with sufficiently intact endogenous mineralocorticoid production may be impacted by suppression of this pathway by nevanimibe HCl. Pharmacological doses of glucocorticoids, especially shorter acting ones such as hydrocortisone, also confer mineralocorticoid activity and the need for additional replacement mineralocorticoid is not always required (Speiser, 2010). However, mineralocorticoid replacement should be initiated as soon as possible if there is suspicion of insufficiency.

## 5.8. Prohibited and Restricted Medications

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

Concurrent use of medications that are known to prolong the QT/QTc interval at therapeutic exposures and those that only cause prolonged QT intervals in unusual circumstances (e.g., overdosage) may be used with caution (Appendix 4, Lists A, B and C).

Nevanimibe is metabolized by CYP3A4 and is a moderate inhibitor of CYP3A4. As a consequence, nevanimibe may interfere with the metabolism of other medicines that are metabolized by CYP3A4. In addition, the metabolism of nevanimibe 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 5 and should be used with caution if they are known to interact with weak or moderate CYP3A4 inhibitors.

Nevanimibe may be an inhibitor of P-glycoprotein and OATP1B1. *In vitro* data indicate that nevanimibe may compete with certain drugs for P-glycoprotein in the intestinal lumen. Consequently, the drugs listed in Appendix 6 should be used with caution, as they may impact nevanimibe exposure or vice versa. Note that some of these drugs may also appear in Appendices 3 or 4.

## 5.9. Precautions and Warnings

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

# 6. STUDY ASSESSMENTS

## 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, study procedures and visits during the Treatment Period have a window of ±2 days. Study procedures and visits during the Screening, Baseline, and Follow-up Periods have a window of ±7 days, although up to ~14 weeks may be allowed for Screening and up to ~8 weeks may be allowed for Baseline (e.g., for additional glucocorticoid dose adjustment or stabilization of Cohort 2 subjects—see Appendix 2) with approval of the Medical Monitor. If a study visit occurs early or late, the timing of subsequent visits may be re-anchored.

## 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 (IRB)/Ethics Committee (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 all assessable study inclusion/exclusion criteria will be done at/after the Screening visit (Visit S1) and before enrolling the subject at Visit T1.

## 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 (F1/End-of-Study (EoS) visit), as well as any replacement glucocorticoids and mineralocorticoids taken during the 4 weeks prior to Screening. Glucocorticoid and mineralocorticoid replacement are critical concomitant medications used in classic CAH and will be captured on a separate eCRF from other concomitant therapies. Any other treatments given during the study other than nevanimibe HCl, including blood transfusions, parenteral fluids, over-the-counter medications, and herbal preparations, are also considered to be concomitant therapies and must be recorded on the concomitant medications eCRF.

## 6.6. Electronic Diary

At Visit B1, subjects will be instructed in the use of the eDiary for recording glucocorticoid, mineralocorticoid, and/or study drug doses. Premenopausal women will also be instructed in the use of the eDiary for recording the start dates of their menstrual periods. The eDiary entries will be used to help assess compliance with glucocorticoid and study drug dosing and, in premenopausal women, they will be used to help assess menstrual cycle phase. The eDiary may also be used to provide reminders to subjects.

## 6.7. 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 throughout the study.

Systolic and diastolic blood pressure should be taken in the same arm per subject 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 and do not need to be documented as protocol deviations.

Body weight will be obtained at each study visit. Height will be assessed only at Screening. Body mass index will be calculated based on body weight and height.

## 6.8. Physical Examination

A complete PE will be obtained at Visits S1, T1, and T5/EoT. A brief PE will be performed at Visits T2, T3, T4, and F1/EoS, with particular attention to assessing the subjects for adrenal insufficiency. At any time, 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 physical examination: HEENT, respiratory, cardiovascular, gastrointestinal/hepatobiliary (specifically the presence of hepatomegaly or splenomegaly will be assessed), musculoskeletal, neurological, dermatologic, and any areas pertinent to any adverse events (AEs) and positives from review of systems. 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.

## 6.9. Electrocardiography and Determination of QTc

All subjects will have 12-lead ECGs performed at Visits S1 and T5/EoT. 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 interval is greater than 470 (450 in France) 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 (450 in France) 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 (450 in France) 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 interval determination unreliable by standard means, the QT interval will be corrected by the method of Rautaharju et al. (Zhou, 1992; Rautaharju, 2004).

## 6.10. Adverse Events, Serious Adverse Events and Reporting

### 6.10.1. 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 informed consent form until the last study visit or 30 days after the last dose of study drug, whichever is later. (Any serious adverse event (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, the specific 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 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 ATR-101 (nevanimibe HCl) Investigator's Brochure currently in force.

### 6.10.2. Assessing Severity of Adverse Events

The assessment of severity must be provided by the Investigator and based on the Investigator's clinical judgment. 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 an SAE. Refer to Section 6.10.4.1 for the definition of an SAE.

### 6.10.3. 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 AE 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.

### 6.10.4. Serious Adverse Events

#### 6.10.4.1. Definition of Serious Adverse Event

A serious adverse event (SAE) 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

  Notes:

  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 hospitalizations 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.

#### 6.10.4.2. Reporting SAEs – Procedure for Investigators

Initial Reports

Adverse events and all information regarding SAEs, whether reported by the subject or observed by the investigator/study personnel, must be documented in the subject's medical record and reported by recording all pertinent information on the eCRF AE/SAE Forms in the electronic data capture (EDC) system.

SAEs, regardless of causality assessment, must be collected beginning 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 longer. All SAEs must be reported within the EDC system by the study site. Study site personnel should complete the eCRF AE/SAE Form in the EDC system and the investigator should assess the causality **within 24 hours** of knowledge of the event (this refers to any AE that meets any of the aforementioned seriousness criteria). Via the EDC system, Clinical Safety will receive the report in parallel via email at clinicalsafety@biomapas.eu. 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.

The minimum information required for the initial SAE report is covered by the eCRF AE/SAE Form. If requested by Clinical Safety, SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports and other documents (see Follow-up Reports, below).

Clinical Safety contact information for this study is as follows:

- If the EDC system is unavailable, the SAE will be reported via telephone at +370 37 383 227
- For urgent safety issues, call the Medical Monitor at +370 37 383 238

Follow-up Reports

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

Within 24 hours of receipt of follow-up information, the Investigator must update the eCRF AE/SAE Form within the EDC system. Any requested supporting documentation (e.g., subject discharge summary or autopsy reports) should be submitted to Clinical Safety via e-mail at clinicalsafety@biomapas.eu or fax at +370 37 352 321. All personal data must be redacted prior to submission; instead, please provide the study number (Millendo ATR-101-202) and the subject ID on each document. If the follow-up information changes the Investigator's assessment of causality, this should also be noted in the follow-up section within the eCRF AE/SAE form.

The Investigator should notify the IRB/EC of the occurrence of the SAE, in writing, in accordance with local requirements. A copy of this communication must be filed in the Investigator's files for this study.

### 6.10.5. Pregnancy Reporting

Any pregnancy that occurs 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 using the Pregnancy Form within the EDC system within 24 hours of being notified. Via the EDC system, Clinical Safety will receive the report in parallel via email at clinicalsafety@biomapas.eu. **The contact information for reporting pregnancies is the same as for reporting SAEs** (Section 6.10.4.2).

A subject becoming pregnant while on study drug will immediately be withdrawn from the study and early termination (ET) 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 Clinical Safety as specified in the Safety Manual. 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.

### 6.10.6. 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.

## 6.11. Laboratory Tests

Blood, saliva, and urine samples for assessments of clinical laboratory parameters and/or PK will be obtained as shown in the study schedule in Appendix 1. For each study visit, the first hormone sample collection that is obtained at the study site should be done between 6-10 AM (06:00-10:00), as close to 8 AM (08:00) as practicable. Additionally, at study visits, blood and corresponding saliva samples will be obtained at approximately the same time (±15 minutes) to facilitate correlation of results.

On days that saliva samples are collected, the timing of glucocorticoid doses, mineralocorticoid doses (if applicable), nevanimibe HCl doses (if applicable), and saliva sample collections should be kept consistent as much as possible per subject. For salivary profiles collected on Days -8, 22, 50, 78, and 106, samples should be obtained at approximately 8 AM (08:00), noon (12:00), 4 PM (16:00), 8 PM (20:00), and 10-11 PM (22:00-23:00). At Visits T1, T2, T3, and T4, samples will be collected at the study site at approximately 8 AM (08:00), 10 AM (10:00), and noon (12:00).

The 8 AM (8:00) sample should be collected prior to the subjects' morning dose of glucocorticoid and mineralocorticoid (if applicable) and will also be assessed for P (in premenopausal women only) and cortisol. The timing of the 8 AM (08:00), 10 AM (10:00), noon (12:00) samples should be adjusted to correspond to just before (within 30 minutes before), 2 hours after, and 4 hours after (respectively) administration of the morning glucocorticoid, mineralocorticoid (if applicable) and/or study drug (if applicable) doses. In general, the samples should be collected prior to relevant glucocorticoid and mineralocorticoid (if applicable) doses if possible.

### 6.11.1. Clinical Laboratory Assessments

Testing of clinical laboratory samples will be carried out by the central clinical laboratory using validated methods and will include the tests listed in Table 3. In addition, stored serum and plasma samples may be assayed for parameters relevant to hormone metabolism (no DNA samples will be stored). Total blood volumes to be collected will be provided in the Laboratory Manual. 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 6.10).

**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, alkaline phosphatase, alanine aminotransferase (ALT; SGPT), aspartate aminotransferase (AST; SGOT), blood urea nitrogen (BUN), calcium, creatinine, glucose, total bilirubin, total protein, electrolytes (magnesium, sodium, potassium, chloride, bicarbonate) |
| Coagulation | PT, aPTT, INR |
| Plasma or Serum Hormones | 17-hydroxyprogesterone, androstenedione, adrenocorticotropic hormone, cortisol, progesterone, total testosterone, and 11-ketotestosterone |
| Salivary Hormones | 17-hydroxyprogesterone, progesterone (premenopausal women “08:00” sample only), and cortisol (“08:00” sample only) |
| Urinalysis | appearance, bilirubin, color, glucose, ketones, leukocyte esterase, nitrite, occult blood, pH, protein, specific gravity, urobilinogen; microscopic examination will be performed if leukocyte esterase, nitrite, and/or occult blood are positive |
| Other | HBsAg, HCV, HIV, urine drug screen |

aPTT, activated partial thromboplastic time; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INR, international normalized ratio; PT, prothrombin time

### 6.11.2. Pharmacokinetic Assessments

Testing of PK samples will be carried out by the central PK laboratory using validated methods. 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 hour postdose have a window of ±5 min and subsequent time points have a window of ±10 min. At Treatment Period visits, study drug and replacement glucocorticoid and mineralocorticoid (if applicable) doses are expected to be administered at approximately the same time. At Treatment Period visits, actual dosing times of nevanimibe HCl, glucocorticoids, and mineralocorticoids (if applicable) must be recorded using the eDiary; and actual times of PK sampling must be recorded on the eCRF.

**Table 4: Pharmacokinetic Sampling Time Points**

| Visit | Sampling Time Points (Morning Dose Only) |
|---|---|
| T1, T2, T3, T4, T5/EoT | 0 hours (trough, within 30 min predose); and<br>1 hour (±5 min), 2 hours (±10 min), 3 hours (±10 min) and 4 hours (±10 min) postdose |

Specific collection and shipment procedures for PK samples are provided in the Laboratory Manual.

PK parameters will be computed using non-compartmental methods. The PK parameters outlined in Table 5 will be estimated for nevanimibe and its major metabolite(s) as data permit and as appropriate. PK parameters may also be estimated for replacement glucocorticoids and/or mineralocorticoids as appropriate.

**Table 5: Pharmacokinetic Parameters**

| | |
|---|---|
| $C_{last}$ | last quantifiable drug concentration determined directly from individual concentration-time data |
| $C_{max}$ | maximum observed 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 |
| $T_{max}$ | observed time to reach maximum drug concentration |
| $AUC_{0-4}$ | 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 |
| $AUC_{0-t}$ | 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 |
| $\lambda_z$ | terminal phase rate constant, estimated by linear regression through the terminal phase of the log concentration-time profile |
| $t_{½}$ | terminal phase half-life, calculated as:<br>$t½ = \frac{\ln(2)}{\lambda z}$ |
| $AUC_{0-\infty}$ | area under the concentration-time curve from time zero to infinity (first dose only), calculated as $AUC_{0-4} + C_{last}/\lambda_z$ |
| $AUC_{\%extrap}$ | percentage of $AUC_{0-\infty}$ extrapolated, represented as $(1 - AUC_{0-t}/AUC_{0-\infty}) \times 100$ |
| CL/F | oral clearance calculated as:<br>$dose/AUC_{0-\infty}$ (Day 1 only) |

### 6.11.3. Pharmacodynamic Assessments

The relationship between $C_{max}$, $T_{max}$, $AUC_{0-4}$ and other PK parameters with efficacy assessments will be explored as appropriate and as data allow.

### 6.11.4. 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

Subjects do not need to be fasting prior to any of the study visits. For each study visit, the first hormone sample collection that is obtained at the study site should be done between 6-10 AM (06:00-10:00), as close to 8 AM (08:00) as practicable.

The day *before* each study visit, subjects should pay particular attention to noting the actual time of their last doses of glucocorticoid and study drug (if applicable). On the morning of study visits, including Visit T5/EoT, subjects should wait to take their morning doses of study drug (if applicable), glucocorticoid, and mineralocorticoid (if applicable) until directed by personnel at the study site.

Study visit designations (S1, B1, T1, F1, etc.) are shown in the detailed schedule of study assessments provided in Appendix 1. Please note that below and in Appendix 1, the assigned Study Day is the first day of the corresponding Study Week. For example, the Day 85 visit occurs following 12 full weeks of dosing with study drug, at the beginning of Week 13.

## 7.1. Screening Period

During the Screening Period, the eligibility of the subjects is assessed. The Screening Period may last from approximately 2-14 weeks, depending on whether the subject is in Cohort 1 or Cohort 2, and on the number of maintenance glucocorticoid dose adjustments required for Cohort 2 subjects. The Screening Period concludes with the start of the Baseline Period.

Prior to the Screening visit, appropriate study site personnel should:

- Remind the subjects that on the morning of the Screening visit, they should wait to take their morning doses of glucocorticoid and mineralocorticoid (if applicable) until directed by site personnel at the study site.
- Remind the subjects to bring their glucocorticoid and mineralocorticoid (if applicable) containers to each study visit.

### 7.1.1. Visit S1

The Screening visit can be conducted approximately 2-14 weeks prior to the Baseline visit. 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.
- Obtain and record medical history, demographic data and prior and current medications. If the subject is a premenopausal woman, obtain the start date of her last menstrual period.
- Record any AEs that occurred after informed consent was signed.
- Record the date and time of the subject's last dose of glucocorticoid prior to the visit.
- Record vital signs, height and weight.
- Perform a complete PE.

- Obtain a 12-lead ECG.
- Review all assessable inclusion and exclusion criteria.
- Within 30 minutes prior to administration of morning replacement glucocorticoid and mineralocorticoid (if applicable) doses, collect blood samples for hematology, chemistry, PT, aPTT, INR, HBsAg, HCV, HIV, 17-OHP, P, cortisol, and (for female subjects of childbearing potential only) a serum pregnancy test.
  - For each study visit, the first hormone sample collection that is obtained at the study site should be done between 6-10 AM (06:00-10:00), as close to 8 AM (08:00) as practicable.
  - Hormones should not be collected if the subject already took their replacement glucocorticoid and/or mineralocorticoid dose that morning; instead, the sample collection should be rescheduled for the next day or as soon as is feasible.
  - Note: The serum 17-OHP may be repeated one time at the Investigator's discretion if there is reason to suspect the results are inaccurate.
- Collect a urine sample for urinalysis and urine drug screen.
- Ask the subject to self-administer their morning replacement glucocorticoid and mineralocorticoid (if applicable) doses. Record the time of glucocorticoid and mineralocorticoid (if applicable) administration.
- If the subject is a premenopausal woman, instruct the subject to make note of the first day of each of her menstrual periods during the study.
- Remind the subjects that on the morning of their next study visit, they should wait to take their morning dose of glucocorticoid and mineralocorticoid (if applicable) until directed by site personnel at the study site.
- Remind the subjects to bring their glucocorticoid and mineralocorticoid (if applicable) containers to their next study visit.

### 7.1.2. After Visit S1

Within approximately 2 weeks after Visit S1, appropriate study site personnel should:

- Review all assessable inclusion and exclusion criteria.
- Review serum 17-OHP results (see Appendix 2).
- Contact the subject via telephone to:
  - Record AEs and update medications. If the subject is a premenopausal woman, obtain the start date of her last menstrual period.
  - If serum 17-OHP is ≥ 4x ULN (Cohort 1), schedule the subject for the Baseline visit, Visit B1.
  - If serum 17-OHP is < 4x ULN (Cohort 2), assess the subject's maintenance glucocorticoid replacement dose in equivalent mg of hydrocortisone/$m^2$ body surface area (see Appendix 3).

- If ≥ 12 mg/m$^2$, reduce the dose by the equivalent of approximately 5 mg hydrocortisone or 1 mg prednisone or prednisolone, and schedule the subject to return for Visit S2 approximately 2-4 weeks after the dose change.
- If < 12 mg/m$^2$, discuss the case with the Medical Monitor; screen-fail the subject if no further glucocorticoid dose reduction is possible.

– Remind the subjects that on the morning of their next study visit, they should wait to take their morning dose of glucocorticoid and mineralocorticoid (if applicable) replacement until directed by site personnel at the study site.

– Remind the subjects to bring their glucocorticoid and mineralocorticoid (if applicable) containers to their next study visit.

### 7.1.3. Visit S2 (Cohort 2 Subjects Only)

Subjects in Cohort 1 should skip Visit S2 and proceed to the Baseline Visit (Visit B1).

Subjects in Cohort 2 should undergo Visit S2 at least 2 weeks after the last decrease in their maintenance glucocorticoid dose.

At the S2 visit, appropriate study site personnel should:

- Record AEs and update medications. If the subject is a premenopausal woman, obtain the start date of her last menstrual period.
- Record the date and time of the subject's last dose of glucocorticoid prior to the visit.
- Record vital signs and weight.
- Within 30 minutes prior to administration of morning replacement glucocorticoid and mineralocorticoid (if applicable) doses, collect blood samples for 17-OHP, P, and cortisol.
  - For each study visit, the first hormone sample collection that is obtained at the study site should be done between 6-10 AM (06:00-10:00), as close to 8 AM (08:00) as practicable.
  - Hormones should not be collected if the subject already took their replacement glucocorticoid and/or mineralocorticoid dose that morning; instead, the sample collection should be rescheduled for the next day or as soon as is feasible.
- For female subjects of childbearing potential only, collect a urine sample and perform a urine pregnancy test.
- Ask the subject to self-administer their morning replacement glucocorticoid and mineralocorticoid (if applicable) doses. Record the time of glucocorticoid and mineralocorticoid (if applicable) administration.
- Schedule the next study visit (Visit B1) to occur at least 4 weeks after the subject's last maintenance glucocorticoid dose change.
- Remind the subjects that on the morning of their next visit, they should wait to take their morning dose of glucocorticoid and mineralocorticoid (if applicable) until directed by site personnel at the study site.
- Remind the subjects to bring their glucocorticoid and mineralocorticoid (if applicable) containers to their next study visit.

#### 7.1.4. After Visit S2 (Cohort 2 Subjects Only)

Within approximately 2 weeks after Visit S2, prior to Visit B1, appropriate study site personnel should review serum 17-OHP results for Cohort 2 subjects (see Appendix 2):

- If serum 17-OHP is ≥ 4x ULN, the subject should return for the Baseline visit, Visit B1, as scheduled.
- If serum 17-OHP is < 4x ULN, assess the subject's maintenance glucocorticoid replacement dose in equivalent mg of hydrocortisone/$m^2$ body surface area (see Appendix 3) and discuss the case with the Medical Monitor.
  - If ≥ 12 mg/$m^2$, with agreement of the Medical Monitor, it may be possible to further reduce the dose by the equivalent of approximately 5 mg hydrocortisone or 1 mg prednisone or prednisolone. The subject should then return for an Unscheduled visit approximately 2-4 weeks after the dose change (i.e., when the Investigator assesses that the subject's hormone levels have stabilized) to assess 17-OHP levels. Further management should be discussed and agreed with the Medical Monitor.
  - If < 12 mg/$m^2$, discuss the case with the Medical Monitor; screen-fail the subject if no further glucocorticoid dose reduction is possible.

## 7.2. Baseline Period

Subjects who meet all assessable inclusion and exclusion criteria, whose last 17-OHP obtained during the Screening Period was ≥ 4x ULN and last maintenance glucocorticoid dose change occurred at least 4 weeks prior, may enter the Baseline Period.

#### 7.2.1. Visit B1 (Day -14; Week -2)

Prior to Visit B1, the Investigator should review whether the subject continues to be eligible for the study. If not, the subject should be screen-failed from the study. Please note that the Screening serum cortisol level result does not need to be available for the subject to proceed with Visit B1.

At Visit B1, appropriate study site personnel should:

- Record AEs and update medications.
- Record the date and time of the subject's last dose of glucocorticoid prior to the visit.
- Record vital signs and weight.
- Within 30 minutes prior to administration of morning replacement glucocorticoid and mineralocorticoid (if applicable) doses, collect blood samples for hormones (17-OHP, P, cortisol, A4, ACTH, total testosterone, and 11-ketotestosterone), and collect saliva samples for 17-OHP, P, and cortisol.
  - For each study visit, the first hormone sample collection that is obtained at the study site should be done between 6-10 AM (06:00-10:00), as close to 8 AM (08:00) as practicable.
  - Hormones should not be collected if the subject already took their replacement glucocorticoid and/or mineralocorticoid dose that morning; instead, the sample collection should be rescheduled for the next day or as soon as is feasible.

- For female subjects of childbearing potential only, collect a urine sample and perform a urine pregnancy test.
- Instruct the subject on the use of the eDiary for recording glucocorticoid, mineralocorticoid, and/or study drug doses. If needed, provision a device for accessing the eDiary.
- If the subject is a premenopausal woman, instruct her on the use of the eDiary for recording the start date of her last menstrual period, and ask her to record the start date of her last menstrual period using the eDiary.
- Ask the subject to self-administer their morning replacement glucocorticoid and mineralocorticoid (if applicable) doses.
- Ask the subject to record the time of glucocorticoid and mineralocorticoid (if applicable) administration using the eDiary.
- Remind the subjects to collect a salivary 17-OHP profile within approximately one week prior to the next study visit (Visit T1).
- Schedule the next study visit (Visit T1).
- Remind the subjects to record the actual time of their doses of glucocorticoid and mineralocorticoid (if applicable), particularly those taken on the day prior to their next visit, using the eDiary. If the subject is a premenopausal woman, also remind her to record the start date of her menstrual periods.
- Remind the subjects that on the morning of their next visit, they should wait to take their morning doses of glucocorticoid and mineralocorticoid (if applicable) until directed by site personnel at the study site.

#### 7.2.2. After Visit B1

Within 2 weeks after Visit B1, prior to Visit T1, review serum 17-OHP results (see Appendix 2):

- If 17-OHP is ≥ 4x ULN:
  - If the subject met criteria for Cohort 1 based on the S1 serum 17-OHP, the subject should return for the Enrollment visit, Visit T1, as scheduled.
  - If the subject met criteria for Cohort 2 based on the S1 serum 17-OHP, assess stability of 17-OHP.
    - For the purposes of this study, "stable" serum 17-OHP levels following a glucocorticoid dose reduction are defined as the most recent two 17-OHP levels prior to enrollment being with 30% of each other (calculated as 100 × (1 – (smaller value/larger value))).
    - If 17-OHP levels are stable, the subject should return for the Enrollment visit, Visit T1, as scheduled.
    - If 17-OHP levels are not stable, discuss the case with the Medical Monitor, and consider obtaining a repeat serum 17-OHP level(s). Once the repeat 17-OHP levels are ≥ 4x ULN and meet stability criteria, the subject may proceed to the Enrollment visit, Visit T1.

- If 17-OHP is < 4x ULN:
  - If the subject met criteria for Cohort 2 based on the S1 serum 17-OHP, assess the subject's maintenance glucocorticoid replacement dose in equivalent mg of hydrocortisone/m2 body surface area (see Appendix 3) and discuss the case with the Medical Monitor.
    - If ≥ 12 mg/m2, with agreement of the Medical Monitor, it may be possible to reduce the dose by the equivalent of approximately 5 mg hydrocortisone or 1 mg prednisone or prednisolone. The subject should then return for an Unscheduled visit at least 2 weeks after the dose change to assess 17-OHP levels. Further management should be discussed and agreed with the Medical Monitor.
    - If < 12 mg/$m^2$, discuss the case with the Medical Monitor.
  - In the unlikely event that a subject in Cohort 1 (based on the S1 serum 17-OHP), has 17-OHP < 4x ULN, discuss the case with the Medical Monitor.

## 7.3. Treatment Period

Subjects who meet all the inclusion criteria and none of the exclusion criteria for the study may enter the Treatment Period.

### 7.3.1. Visit T1 (Day 1; Week 1; Enrollment)

Prior to Visit T1, the Investigator should review whether the subject continues to be eligible for the study. If not, the subject should be failed from the study. Please note that the Visit B1 serum cortisol, A4, ACTH, total T, and 11-ketoT results, as well as the salivary hormone results, do not need to be available for the subject to proceed with Visit T1.

At Visit T1, appropriate study site personnel should:

- Record AEs and update medications.
- Review the subject's eDiary entries and reinforce instruction on the use of the eDiary as needed.
- Confirm that the subject has recorded the date and time of their last doses of glucocorticoid and mineralocorticoid (if applicable) prior to the visit using the eDiary. If not, ask the subject to record the information.
- If the subject is a premenopausal woman, confirm that she has recorded the start date of her last menstrual period using the eDiary. If not, ask her to record the information.
- Record vital signs and weight.
- Perform a complete PE.
- Within 30 minutes prior to administration of study drug and morning replacement glucocorticoid and mineralocorticoid (if applicable) doses, collect blood samples for hematology, chemistry, hormones (17-OHP, P, cortisol, A4, ACTH, total testosterone, and 11-ketotestosterone), PK, and a serum storage sample; and collect a saliva sample for 17-OHP, P, and cortisol.

  - For each study visit, the first hormone sample collection that is obtained at the study site should be done between 6-10 AM (06:00-10:00), as close to 8 AM (08:00) as practicable.
  - Hormones should not be collected if the subject already took their replacement glucocorticoid and/or mineralocorticoid dose that morning; instead, the sample collection and enrollment should be rescheduled for the next day or as soon as is feasible.
  - Note: On days when both a salivary 17-OHP profile and saliva for 17-OHP, P, and cortisol are being collected, only single "8 AM" ("08:00"), "10 AM" ("10:00"), and "noon" ("12:00") saliva samples should be collected.
- Collect a urine sample for urinalysis.
- For female subjects of childbearing potential only, collect a urine sample and perform a urine pregnancy test.
- Confirm that the subject meets all of the inclusion criteria and none of the exclusion criteria.
- Enroll the subject.
- Dispense study drug and instruct the subject on self-administration of study drug orally twice per day.
  - All subjects will start nevanimibe HCl 500 mg BID.
- Ask the subject to self-administer study drug with food and a nonalcoholic beverage (excluding grapefruit juice) while at the study site.
- Ask the subject to self-administer their morning replacement glucocorticoid and mineralocorticoid (if applicable) doses.
- Ask the subject to record the time of study drug, glucocorticoid, and mineralocorticoid (if applicable) administration using the eDiary.
- Collect plasma PK samples and serum 17-OHP samples at 1, 2, 3 and 4 hours after administration of study drug. Collect saliva samples for 17-OHP at 2 and 4 hours after administration of study drug. Record the time of each sample collection.
- Schedule the next study visit (Visit T2).
- Remind the subjects to record the actual time of their doses of glucocorticoid, mineralocorticoid (if applicable), and study drug, particularly those taken on the day prior to their next visit, using the eDiary. If the subject is a premenopausal woman, also remind her to record the start date of her menstrual periods.
- Remind the subjects that on the morning of their next visit, they should wait to take their morning doses of study drug, glucocorticoid, and mineralocorticoid (if applicable) until directed by site personnel at the study site.
- Remind the subjects to bring all their study drug containers, including the used ones, to their next study visit.
- Remind the subjects to bring their glucocorticoid and mineralocorticoid (if applicable) containers to their next study visit.

### 7.3.2. Telephone Visit Between Visits T1 and T2 (Day 15; Week 3)

On approximately Day 15, between Visits T1 and T2, appropriate study site personnel should contact the subject via telephone to:

- Record AEs and update medications. If the subject is a premenopausal woman, obtain the start date of her last menstrual period.
- Remind the subject to collect saliva samples for assessing their salivary 17-OHP profile approximately one week prior to their next visit.
- Remind the subjects that they will need to record the actual time of their doses of glucocorticoid, mineralocorticoid (if applicable), and study drug, particularly those taken on the day prior to their next visit, using the eDiary. If the subject is a premenopausal woman, also remind her to record the start date of her menstrual periods.
- Remind the subjects that on the morning of their next visit, they should wait to take their morning doses of study drug, glucocorticoid, and mineralocorticoid (if applicable) until directed by site personnel at the study site.
- Remind the subjects to bring all their study drug containers, including the used ones, to their next study visit.
- Remind the subjects to bring their glucocorticoid and mineralocorticoid (if applicable) containers to their next study visit.

### 7.3.3. Visit T2 (Day 29; Week 5)

At Visit T2, appropriate study site personnel should:

- Record AEs and update medications.
- Review the subject's eDiary entries and reinforce instruction on the use of the eDiary as needed.
- Confirm that the subject has recorded the date and time of their last doses of glucocorticoid, mineralocorticoid (if applicable), and study drug prior to the visit using the eDiary. If not, ask the subject to record the information.
- If the subject is a premenopausal woman, confirm that she has recorded the start date of her last menstrual period using the eDiary. If not, ask her to record the information.
- Record vital signs and weight.
- Perform a brief PE, with particular attention to assessing the subject for adrenal insufficiency.
- Within 30 minutes prior to administration of study drug and morning replacement glucocorticoid and mineralocorticoid (if applicable) doses, collect blood samples for hematology, chemistry, hormones (17-OHP, P, cortisol, A4, ACTH, total testosterone, and 11-ketotestosterone), PK, and a serum storage sample; and collect a saliva sample for 17-OHP, P, and cortisol.
  - For each study visit, the first hormone sample collection that is obtained at the study site should be done between 6-10 AM (06:00-10:00), as close to 8 AM (08:00) as practicable.

  - Hormones should not be collected if the subject already took their replacement glucocorticoid and/or mineralocorticoid dose that morning; instead, the sample collection should be rescheduled for the next day or as soon as is feasible.

- For female subjects of childbearing potential only, collect a urine sample and perform a urine pregnancy test.
- Collect study drug and assess compliance.
- Dispense study drug and reinforce self-administration of study drug orally twice per day.
  - All subjects will start nevanimibe HCl 1000 mg BID.
- Ask the subject to self-administer study drug with food and a nonalcoholic beverage (excluding grapefruit juice) while at the study site.
- Ask the subject to self-administer their morning replacement glucocorticoid and mineralocorticoid (if applicable) doses.
- Ask the subject to record the time of study drug, glucocorticoid, and mineralocorticoid (if applicable) administration using the eDiary.
- Collect plasma PK samples and serum 17-OHP samples at 1, 2, 3 and 4 hours after administration of study drug. Collect saliva samples for 17-OHP at 2 and 4 hours after administration of study drug. Record the time of each sample collection.
- Schedule the next study visit (Visit T3).
- Remind the subjects that they will need to record the actual time of their doses of glucocorticoid, mineralocorticoid (if applicable), and study drug, particularly those taken on the day prior to their next visit, using the eDiary. If the subject is a premenopausal woman, also remind her to record the start date of her menstrual periods.
- Remind the subjects that on the morning of their next visit, they should wait to take their morning doses of study drug, glucocorticoid, and mineralocorticoid (if applicable) until directed by site personnel at the study site.
- Remind the subjects to bring all their study drug containers, including the used ones, to their next study visit.
- Remind the subjects to bring their glucocorticoid and mineralocorticoid (if applicable) containers to their next study visit.

#### 7.3.4. Telephone Visit Prior to Treatment Day 43 (Week 7)

Prior to Day 43, between Visits T2 and T3, appropriate study site personnel should contact the subject via telephone to:

- Record AEs and update medications. If the subject is a premenopausal woman, obtain the start date of her last menstrual period.
- Review serum 17-OHP results from Visit T2 to determine whether the subject met the primary endpoint on their previous nevanimibe HCl dose. The primary endpoint is defined as having been met as follows:

  - Men and postmenopausal women: 17-OHP ≤ 2x ULN
  - Premenopausal women:
    - Follicular phase: 17-OHP ≤ 2x follicular phase ULN
    - Luteal phase: 17-OHP ≤ (2x follicular phase ULN + (luteal phase ULN – follicular phase ULN))
- Adjust the nevanimibe HCl dose if needed as follows:
  - If the subject met the primary endpoint, ask the subject to decrease their nevanimibe HCl dose from 1000 mg BID to 500 mg BID (i.e., their previous dose immediately prior to Visit T2).
  - If the subject did not meet the primary endpoint, ask the subject to remain on their current nevanimibe HCl dose of 1000 mg BID.
- Remind the subject to collect saliva samples for assessing their salivary 17-OHP profile approximately one week prior to their next visit.
- Remind the subjects that they will need to record the actual time of their doses of glucocorticoid, mineralocorticoid (if applicable), and study drug, particularly those taken on the day prior to their next visit, using the eDiary. If the subject is a premenopausal woman, also remind her to record the start date of her menstrual periods.
- Remind the subjects that on the morning of their next visit, they should wait to take their morning doses of study drug, glucocorticoid, and mineralocorticoid (if applicable) until directed by site personnel at the study site.
- Remind the subjects to bring all their study drug containers, including the used ones, to their next study visit.
- Remind the subjects to bring their glucocorticoid and mineralocorticoid (if applicable) containers to their next study visit.

#### 7.3.5. Visit T3 (Day 57; Week 9)

At Visit T3, appropriate study site personnel should:

- Record AEs and update medications.
- Review the subject's eDiary entries and reinforce instruction on the use of the eDiary as needed.
- Confirm that the subject has recorded the date and time of their last doses of glucocorticoid, mineralocorticoid (if applicable), and study drug prior to the visit using the eDiary. If not, ask the subject to record the information.
- If the subject is a premenopausal woman, confirm that she has recorded the start date of her last menstrual period using the eDiary. If not, ask her to record the information.
- Record vital signs and weight.
- Perform a brief PE, with particular attention to assessing the subject for adrenal insufficiency.

- Within 30 minutes prior to administration of study drug and morning replacement glucocorticoid and mineralocorticoid (if applicable) doses, collect blood samples for hematology, chemistry, hormones (17-OHP, P, cortisol, A4, ACTH, total testosterone, and 11-ketotestosterone), PK, and a serum storage sample; and collect a saliva sample for 17-OHP, P, and cortisol.
  - For each study visit, the first hormone sample collection that is obtained at the study site should be done between 6-10 AM (06:00-10:00), as close to 8 AM (08:00) as practicable.
  - Hormones should not be collected if the subject already took their replacement glucocorticoid and/or mineralocorticoid dose that morning; instead, the sample collection should be rescheduled for the next day or as soon as is feasible.
- For female subjects of childbearing potential only, collect a urine sample and perform a urine pregnancy test.
- Collect study drug and assess compliance.
- Dispense study drug and reinforce self-administration of study drug orally twice per day.
  - Subjects on nevanimibe HCl 1000 mg BID will start nevanimibe HCl 1500 mg BID.
  - Subjects on nevanimibe HCl 500 mg BID will continue nevanimibe HCl 500 mg BID.
- Ask the subject to self-administer study drug with food and a nonalcoholic beverage (excluding grapefruit juice) while at the study site.
- Ask the subject to self-administer their morning replacement glucocorticoid and mineralocorticoid (if applicable) doses.
- Ask the subject to record the time of study drug, glucocorticoid, and mineralocorticoid (if applicable) administration using the eDiary.
- Collect plasma PK samples and serum 17-OHP samples at 1, 2, 3 and 4 hours after administration of study drug. Collect saliva samples for 17-OHP at 2 and 4 hours after administration of study drug. Record the time of each sample collection.
- Schedule the next study visit (Visit T4).
- Remind the subjects that they will need to record the actual time of their doses of glucocorticoid, mineralocorticoid (if applicable), and study drug, particularly those taken on the day prior to their next visit, using the eDiary. If the subject is a premenopausal woman, also remind her to record the start date of her menstrual periods.
- Remind the subjects that on the morning of their next visit, they should wait to take their morning doses of study drug, glucocorticoid, and mineralocorticoid (if applicable) until directed by site personnel at the study site.
- Remind the subjects to bring all their study drug containers, including the used ones, to their next study visit.
- Remind the subjects to bring their glucocorticoid and mineralocorticoid (if applicable) containers to their next study visit.

### 7.3.6. Telephone Visit Prior to Treatment Day 71 (Week 11)

Prior to Day 71, between Visits T3 and T4, appropriate study site personnel should contact the subject via telephone to:

- Record AEs and update medications. If the subject is a premenopausal woman, obtain the start date of her last menstrual period.
- Review serum 17-OHP results from Visit T3 to determine whether the subject met the primary endpoint on the nevanimibe HCl dose that they were taking just prior to Visit T3. The primary endpoint is defined as having been met as follows:
  - Men and postmenopausal women: 17-OHP ≤ 2x ULN
  - Premenopausal women:
    - Follicular phase: 17-OHP ≤ 2x follicular phase ULN
    - Luteal phase: 17-OHP ≤ (2x follicular phase ULN + (luteal phase ULN – follicular phase ULN))
- Adjust the nevanimibe HCl dose if needed as follows:
  - If the subject met the primary endpoint, and their nevanimibe HCl dose had been up-titrated at Visit T3, ask the subject to decrease their nevanimibe HCl dose to their previous dose (i.e., their dose immediately prior to Visit T3).
  - If the subject did not meet the primary endpoint, and their nevanimibe HCl dose had not been up-titrated at Visit T3, ask the subject to increase their nevanimibe HCl dose to the next higher dose level.
  - All other subjects should remain on their current dose of nevanimibe HCl (the dose assigned at Visit T3).
- Remind the subject to collect saliva samples for assessing their salivary 17-OHP profile approximately one week prior to their next visit.
- Remind the subjects that they will need to record the actual time of their doses of glucocorticoid, mineralocorticoid (if applicable), and study drug, particularly those taken on the day prior to their next visit, using the eDiary. If the subject is a premenopausal woman, also remind her to record the start date of her menstrual periods.
- Remind the subjects that on the morning of their next visit, they should wait to take their morning doses of study drug, glucocorticoid, and mineralocorticoid (if applicable) until directed by site personnel at the study site.
- Remind the subjects to bring all their study drug containers, including the used ones, to their next study visit.
- Remind the subjects to bring their glucocorticoid and mineralocorticoid (if applicable) containers to their next study visit.

### 7.3.7. Visit T4 (Day 85; Week 13)

At Visit T4, appropriate study site personnel should:

- Record AEs and update medications.
- Review the subject's eDiary entries and reinforce instruction on the use of the eDiary as needed.
- Confirm that the subject has recorded the date and time of their last doses of glucocorticoid, mineralocorticoid (if applicable), and study drug prior to the visit using the eDiary. If not, ask the subject to record the information.
- If the subject is a premenopausal woman, confirm that she has recorded the start date of her last menstrual period using the eDiary. If not, ask her to record the information.
- Record vital signs and weight.
- Perform a brief PE, with particular attention to assessing the subject for adrenal insufficiency.
- Within 30 minutes prior to administration of study drug and morning replacement glucocorticoid and mineralocorticoid (if applicable) doses, collect blood samples for hematology, chemistry, hormones (17-OHP, P, cortisol, A4, ACTH, total testosterone, and 11-ketotestosterone), PK, and a serum storage sample; and collect a saliva sample for 17-OHP, P, and cortisol.
  - For each study visit, the first hormone sample collection that is obtained at the study site should be done between 6-10 AM (06:00-10:00), as close to 8 AM (08:00) as practicable.
  - Hormones should not be collected if the subject already took their replacement glucocorticoid and/or mineralocorticoid dose that morning; instead, the sample collection should be rescheduled for the next day or as soon as is feasible.
- For female subjects of childbearing potential only, collect a urine sample and perform a urine pregnancy test.
- Collect study drug and assess compliance.
- Dispense study drug and reinforce self-administration of study drug orally twice per day.
  - Subjects whose Visit T3 predose serum 17-OHP met the primary endpoint should continue on the nevanimibe HCl dose on which they met the endpoint.
  - Subjects whose Visit T3 predose serum 17-OHP did not meet the primary endpoint should have their current nevanimibe HCl dose up-titrated to the next higher dose.
- Ask the subject to self-administer study drug with food and a nonalcoholic beverage (excluding grapefruit juice) while at the study site.
- Ask the subject to self-administer their morning replacement glucocorticoid and mineralocorticoid (if applicable) doses.
- Ask the subject to record the time of study drug, glucocorticoid, and mineralocorticoid (if applicable) administration using the eDiary.

- Collect plasma PK samples and serum 17-OHP samples at 1, 2, 3 and 4 hours after administration of study drug. Collect saliva samples for 17-OHP at 2 and 4 hours after administration of study drug. Record the time of each sample collection.
- Schedule the next study visit (Visit T4).
- Remind the subjects that they will need to record the actual time of their doses of glucocorticoid, mineralocorticoid (if applicable), and study drug, particularly those taken on the day prior to their next visit, using the eDiary. If the subject is a premenopausal woman, also remind her to record the start date of her menstrual periods.
- Remind the subjects that on the morning of their next visit, they should wait to take their morning doses of study drug, glucocorticoid, and mineralocorticoid (if applicable) until directed by site personnel at the study site.
- Remind the subjects to bring all their study drug containers, including the used ones, to their next study visit.
- Remind the subjects to bring their glucocorticoid and mineralocorticoid (if applicable) containers to their next study visit.

### 7.3.8. Telephone Visit Prior to Treatment Day 99 (Week 13)

Prior to Day 99, between Visits T4 and T5, appropriate study site personnel should contact the subject via telephone to:

- Record AEs and update medications. If the subject is a premenopausal woman, obtain the start date of her last menstrual period.
- Review serum 17-OHP results from Visit T4 to determine whether the subject met the primary endpoint on the nevanimibe HCl dose that they were taking just prior to Visit T4. The primary endpoint is defined as having been met as follows:
  - Men and postmenopausal women: 17-OHP ≤ 2x ULN
  - Premenopausal women:
    - Follicular phase: 17-OHP ≤ 2x follicular phase ULN
    - Luteal phase: 17-OHP ≤ (2x follicular phase ULN + (luteal phase ULN – follicular phase ULN))
- Adjust the nevanimibe HCl dose if needed as follows:
  - If the subject met the primary endpoint, and their nevanimibe HCl dose had been up-titrated at Visit T4, ask the subject to decrease their nevanimibe HCl dose to their previous dose (i.e., their dose immediately prior to Visit T4).
  - If the subject did not meet the primary endpoint, and their nevanimibe HCl dose had not been up-titrated at Visit T4, ask the subject to increase their nevanimibe HCl dose to the next higher dose level.
  - All other subjects should remain on their current dose of nevanimibe HCl (the dose assigned at Visit T4).

- Remind the subject to collect saliva samples for assessing their salivary 17-OHP profile approximately one week prior to their next visit.
- Remind the subjects that they will need to record the actual time of their doses of glucocorticoid, mineralocorticoid (if applicable), and study drug, particularly those taken on the day prior to their next visit, using the eDiary. If the subject is a premenopausal woman, also remind her to record the start date of her menstrual periods.
- Remind the subjects that on the morning of their next visit, they should wait to take their morning doses of study drug, glucocorticoid, and mineralocorticoid (if applicable) until directed by site personnel at the study site.
- Remind the subjects to bring all their study drug containers, including the used ones, to their next study visit.
- Remind the subjects to bring their glucocorticoid and mineralocorticoid (if applicable) containers to their next study visit.

#### 7.3.9. Visit T5 (Day 113; Week 17; End-of-Treatment)

At Visit T5, appropriate study site personnel should:

- Record AEs and update medications.
- Review the subject's eDiary entries and reinforce instruction on the use of the eDiary as needed.
- Confirm that the subject has recorded the date and time of their last doses of glucocorticoid, mineralocorticoid (if applicable), and study drug prior to the visit using the eDiary. If not, ask the subject to record the information.
- If the subject is a premenopausal woman, confirm that she has recorded the start date of her last menstrual period using the eDiary. If not, ask her to record the information.
- Record vital signs and weight.
- Perform a complete PE.
- Obtain a 12-lead ECG.
- Within 30 minutes prior to administration of study drug and morning replacement glucocorticoid and mineralocorticoid (if applicable) doses, collect blood samples for hematology, chemistry, PT, aPTT, INR, hormones (17-OHP, P, cortisol, A4, ACTH, total testosterone, and 11-ketotestosterone), PK, and a serum storage sample; and collect a saliva sample for 17-OHP, P, and cortisol.
  - For each study visit, the first hormone sample collection that is obtained at the study site should be done between 6-10 AM (06:00-10:00), as close to 8 AM (08:00) as practicable.
  - Hormones should not be collected if the subject already took their replacement glucocorticoid and/or mineralocorticoid dose that morning; instead, the sample collection should be rescheduled for the next day or as soon as is feasible (the subject should also continue taking study drug BID until the Visit T5 hormone samples are collected).
- Collect a urine sample for urinalysis.

- For female subjects of childbearing potential only, collect a urine sample and perform a urine pregnancy test.
- If the subject does not have sufficient remaining study drug to administer a single dose, or did not bring their study drug to the study visit, dispense study drug.
- Ask the subject to self-administer study drug with food and a nonalcoholic beverage (excluding grapefruit juice) while at the study site.
- Ask the subject to self-administer their morning replacement glucocorticoid and mineralocorticoid (if applicable) doses.
- As the subject to record the time of study drug, glucocorticoid, and mineralocorticoid (if applicable) administration using the eDiary.
- Collect study drug and assess compliance.
- Collect plasma PK samples and serum 17-OHP samples at 1, 2, 3 and 4 hours after administration of study drug. Collect saliva samples for 17-OHP at 2 and 4 hours after administration of study drug. Record the time of each sample collection.
- Schedule the next study visit (Visit F1).
- Remind the subjects that they will need to record the actual time of their doses of glucocorticoid and mineralocorticoid (if applicable), particularly those taken on the day prior to their next visit, using the eDiary. If the subject is a premenopausal woman, also remind her to record the start date of her menstrual periods.
- Remind the subjects that on the morning of their next visit, they should wait to take their morning doses of glucocorticoid and mineralocorticoid (if applicable) until directed by site personnel at the study site.
- Remind the subjects to bring their glucocorticoid and mineralocorticoid (if applicable) containers to their next study visit.

## 7.4. Follow-up Period

During the 4-week follow-up period, the continued safety of the subjects after discontinuation of study drug will be assessed.

### 7.4.1. Visit F1 (Day 141; Week 21; Follow-up Visit)

The Follow-up Visit should occur approximately 4 weeks after completion of the EoT visit.

At Visit F1/EoS, appropriate study site personnel should:

- Record AEs and update medications.
- Review the subject's eDiary entries.
- Confirm that the subject has recorded the date and time of their last doses of glucocorticoid and mineralocorticoid (if applicable) prior to the visit using the eDiary. If not, ask the subject to record the information.
- If the subject is a premenopausal woman, confirm that she has recorded the start date of her last menstrual period using the eDiary. If not, ask the subject to record the information.

- Record vital signs and weight.
- Perform a brief PE, with particular attention to assessing the subject for adrenal insufficiency.
- Within 30 minutes prior to administration of morning replacement glucocorticoid and mineralocorticoid (if applicable) doses, collect blood samples for hematology, chemistry, and hormones (17-OHP, P, cortisol, A4, ACTH, total testosterone, and 11-ketotestosterone).
  - For each study visit, the first hormone sample collection that is obtained at the study site should be done between 6-10 AM (06:00-10:00), as close to 8 AM (08:00) as practicable.
  - Hormones should not be collected if the subject already took their replacement glucocorticoid and/or mineralocorticoid dose that morning; instead, the sample collection should be rescheduled for the next day or as soon as is feasible.
- For female subjects of childbearing potential only, collect a urine sample and perform a urine pregnancy test.
- Ask the subject to self-administer their morning replacement glucocorticoid and mineralocorticoid (if applicable) doses.
- Ask the subject to record the time of glucocorticoid and mineralocorticoid (if applicable) administration using the eDiary.
- Collect any provisioned devices.
- Once all Visit F1 procedures have been completed, discharge the subject from the study.

## 7.5. Early Termination (ET)

Enrolled subjects who withdraw from the study prior to the EoT visit should return to the study site for an ET visit, which consists of the same procedures as at EoT. Any provisioned devices should also be collected.

# 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 clinical research associate (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 separate Statistical Analysis Plan that includes a more technical and detailed description of the planned statistical analyses will be prepared prior to final database lock.

## 9.2. Sample Size

Based on results of the previous Phase 2 study of nevanimibe HCl in classic CAH (ATR-101-201), the sample size of approximately 20-24 evaluable subjects is considered to be sufficient for assessing whether nevanimibe HCl at doses of 500-2000 mg BID has clinically meaningful efficacy in the treatment of classic CAH. No formal sample size calculation was done. An evaluable subject is defined as a subject who has efficacy data following at least 8 weeks of continuous dosing with nevanimibe HCl.

## 9.3. Analysis Populations

Efficacy – The modified Intent-to-Treat (mITT) Population, used for all the efficacy summaries, is defined as all enrolled subjects who received at least one dose of study drug and had at least one post-baseline serum 17-OHP value.

Per Protocol – The Per Protocol (PP) Population, used for all the efficacy summaries, is defined as all enrolled subjects who received at least one dose of study drug, had at least one post-baseline serum 17-OHP value, and did not have any major protocol deviations that would compromise assessment of efficacy.

Safety – The Safety Population, used for all the safety summaries, is defined as all enrolled subjects who received at least one dose of study drug.

Pharmacokinetic – The Pharmacokinetic (PK) Population will include all subjects with measurable study drug concentrations. PK analyses will be based on the PK Population.

## 9.4. Disposition and Baseline Characteristics

Disposition, including reason for discontinuation from the study, will be summarized. Demographic information and subject characteristics including, but not limited to, race, age, baseline vital signs, and baseline glucocorticoid and mineralocorticoid replacement will also be summarized for each analysis population. For categorical variables, frequencies (n) and percentages (%) will be provided. Continuous variables will be summarized by number of non-missing observations (n), mean and/or median, standard deviation (SD) and/or percentiles, minimum (min), and maximum (max). If applicable, 90% confidence intervals will be calculated.

## 9.5. Efficacy

### 9.5.1. Efficacy Endpoints

#### 9.5.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the overall response rate within each cohort, defined as the percentage of subjects achieving serum 17-OHP targets as follows:

- Men and postmenopausal women: 17-OHP ≤ 2x ULN
- Premenopausal women:

- Follicular phase: 17-OHP ≤ 2x follicular phase ULN
- Luteal phase: 17-OHP ≤ (2x follicular phase ULN + (luteal phase ULN – follicular phase ULN))

#### 9.5.1.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints will be defined in the SAP. There are no prespecified efficacy targets for the secondary efficacy endpoints.

### 9.5.2. Efficacy Analysis Methodology

#### 9.5.2.1. Analysis of the Efficacy Endpoints

Only observed case data will be used for the efficacy summaries. The levels of adrenal steroids, steroid intermediates, and other measured hormones will be summarized for the mITT and PP populations using descriptive statistics, including number of non-missing observations (n), mean and/or median, standard deviation (SD) and/or percentiles, minimum (min), maximum (max) and 90% confidence intervals, if applicable. The analysis will be performed by value and by change from baseline in the value, where appropriate, for each time point, overall, by nevanimibe HCl dose, and by cohort. The percentage of subjects achieving serum 17-OHP targets, the primary endpoint, will be summarized overall and by cohort. The study will be considered positive if 40% or more of enrolled subjects in either cohort achieve the primary endpoint.

#### 9.5.2.2. Exploratory Efficacy Endpoints

Additional efficacy endpoints may be prespecified in the SAP, including sensitivity analyses associated with drug compliance and missing data issues.

## 9.6. Safety

### 9.6.1. Safety Endpoints

Safety endpoints include the incidence of treatment-emergent AEs and SAEs, as well as the values and changes from baseline in clinical laboratory tests, vital signs, PEs and ECG parameters. There are no prespecified targets for the safety endpoints.

### 9.6.2. Safety Analyses

No inferential statistical analyses will be performed on the safety data from this study. The Safety Population will be used for all summaries of safety data. Only observed case data will be used. The summarization of AEs will include treatment-emergent AEs (TEAEs; defined as AEs that begin or worsen after the first dose of study drug). TEAEs and treatment-emergent SAEs (TESAEs) will be summarized by MedDRA system organ class (SOC) and preferred term (PT), severity, and relationship to study drug, overall, by nevanimibe HCl dose, and by cohort. Deaths and discontinuations due to AEs will each be summarized, overall, by nevanimibe HCl dose, and by cohort. Clinical safety laboratory results, PE findings, vital signs, and ECG readings will be summarized by value and by change from baseline in the value, where appropriate, for each time point, overall, by nevanimibe HCl dose, and by cohort using summary statistics for continuous parameters, including number of non-missing observations (n), mean and/or median, standard deviation (SD) and/or percentiles, minimum (min), and maximum (max). Frequencies and percentages as well as shift tables will be prepared for categorical parameters.

## 9.7. Pharmacokinetics and Pharmacodynamics

### 9.7.1. Pharmacokinetic and Pharmacodynamic Endpoints

The PK and PD endpoints include the following:

- The $C_{max}$, $T_{max}$, $AUC_{0-4}$ and other PK parameters of nevanimibe and its major metabolite(s) (as appropriate and as the data allow)
- The relationship between the $C_{max}$ and $AUC_{0-4}$ of nevanimibe and its major metabolite(s) in relation to the change in 17-OHP levels (as appropriate and as the data allow)

Additional PK and PD endpoints may be described in the SAP.

### 9.7.2. Pharmacokinetic and Pharmacodynamic Analyses

The analysis of the PK and PD parameters will be performed on the PK Population. PK assessments will be performed at each dose level to determine exposures to nevanimibe and its major metabolite(s) and to profile PK/PD relationships. PK assessments will include $C_{max}$, $T_{max}$, $AUC_{0-4}$ 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 computed to the extent allowed by the PK data collection times. Tabular summaries will be provided using descriptive summary statistics, including number of non-missing observations (n), arithmetic mean and/or geometric mean and/or median, standard deviation (SD) and/or standard error (SE), minimum (min), and maximum (max). PK/PD analyses will be detailed in the Statistical Analysis Plan.

## 9.8. 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 central 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/EC approval and all materials approved by the IRB/EC 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 (Committee for Proprietary Medicinal Products/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.

## 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 US, 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 US, Inc. or its representatives. This will also be documented in a Clinical Study Agreement between Millendo Therapeutics US, Inc. and the Investigator.

During the study, a monitor from Millendo Therapeutics US, 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 US, Inc.

- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to Millendo Therapeutics US, Inc. and those SAEs that met criteria for reporting have been forwarded to the IRB/EC.

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 US, Inc., a regulatory authority, an EC, or an IRB may visit the site to perform audits or inspections, including source data verification. Millendo Therapeutics US, Inc. may perform Clinical Quality Assurance (CQA) audits from time to time at a random sample of clinical sites, or for cause as warranted. The purpose of a Millendo Therapeutics US, 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, Good Clinical Practice guidelines of the International Council on Harmonization 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 must contact Millendo Therapeutics US, Inc. immediately if contacted by a regulatory agency about an inspection.

## 10.7. Case Report Forms and Study Records

This study will utilize an EDC 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 EDC 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., the provider of PK analyses) 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 US, Inc. after the study has been completed.

## 10.8. Data Safety Monitoring Board

The study is open-label and all laboratory results will be able to be viewed by the Investigator and Sponsor. Consequently, a Data Safety Monitoring Board (DSMB) is not planned for this study.

## 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 US, 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 US, 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 US, 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 US, 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 US, 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 US, 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 US, 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/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).

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# 12. APPENDICES

# APPENDIX 1. STUDY SCHEDULE

**Table 6: Schedule of Assessments**

| **Study Period:** | **Screening 2-14 Weeks** | | | **Baseline 2-8 Weeks** | | **Treatment 16 Weeks** | | | | | | | | | | | | | **Follow-up 4 Weeks** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Target Study Day:**[a] | **-56** | **-42** | **-28** | **-14** | **-8** | **1** | **15** | **22** | **29** | **<43** | **50** | **57** | **<71** | **78** | **85** | **<99** | **106** | **113** | **141** |
| **Study Week:**[a] | **-8** | **-6** | **-4** | **-2** | **-1** | **1** | **3** | **4** | **5** | **7** | **8** | **9** | **11** | **12** | **13** | **15** | **16** | **17** | **21** |
| **Visit:**[a,b] | **S1** | **tel** | **S2**[a] | **B1** | | **T1** | **tel** | | **T2** | **tel** | | **T3** | **tel** | | **T4** | **tel** | | **T5/EoT** | **F1/EoS** |
| Informed Consent | X | | | | | | | | | | | | | | | | | | |
| Inclusion/ Exclusion Criteria | X | X | | | | X | | | | | | | | | | | | | |
| Medical History & Demographics | X | | | | | | | | | | | | | | | | | | |
| Vital Signs, Height and Weight[c] | X | | X | X | | X | | | X | | | X | | | X | | | X | X |
| Physical Examination[d] | X | | | | | X | | | X | | | X | | | X | | | X | X |
| 12-lead ECG | X | | | | | | | | | | | | | | | | | X | |
| Hematology & Chemistry | X | | | | | X | | | X | | | X | | | X | | | X | X |
| PT, aPTT, INR | X | | | | | | | | | | | | | | | | | X | |
| Viral Screen | X | | | | | | | | | | | | | | | | | | |
| Serum 17-OHP, P, and Cortisol[e] | X | | X | X | | X | | | X | | | X | | | X | | | X | X |
| Other Blood Hormones (A4, ACTH, total T, and 11-ketoT)[e] | | | | X | | X | | | X | | | X | | | X | | | X | X |
| Salivary 17-OHP, P, and Cortisol[e,f] | | | | X | | X | | | X | | | X | | | X | | | X | |
| Salivary 17-OHP Profile[f] | | | | | X | X | | X | X | | X | X | | X | X | | X | X | |
| Urinalysis | X | | | | | X | | | | | | | | | | | | X | |
| Urine Drug Screen | X | | | | | | | | | | | | | | | | | | |
| Pregnancy Test[g] | X | | X | X | | X | | | X | | | X | | | X | | | X | X |
| Start Date of Last Menstrual Period[g,h] | X | X | X | X | | X | X | | X | X | | X | X | | X | X | | X | X |
| GC Dose Adjustment (if needed)[i] | | X | | | | | | | | | | | | | | | | | |
| eDiary Instruction/Review[h] | | | | X | | X | | | X | | | X | | | X | | | X | X |
| Enrollment | | | | | | X | | | | | | | | | | | | | |
| Dispense and Dose Study Drug[b] | | | | | | X | | | X | | | X | | | X | | | X[b] | |
| Dose Titration Assessment[j] | | | | | | | X | | | X | | | X | | | X | | | |
| Study Drug Compliance | | | | | | | | | X | | | X | | | X | | | X | |
| Dose GC and MC at Site[b] | X | | X | X | | X | | | X | | | X | | | X | | | X | X |
| Plasma PK and Serum Storage[k] | | | | | | X | | | X | | | X | | | X | | | X[b] | |
| Medications and Adverse Events[l] | X | X | X | X | | X | X | | X | X | | X | X | | X | X | | X | X |

[a] Study procedures and visits during the Treatment Period have a window of ±2 days. Study procedures and visits during the Screening, Baseline, and Follow-up Periods have a window of ±7 days. Only Cohort 2 subjects should undergo Visit S2; Cohort 1 subjects should skip Visit S2 and proceed to the Baseline Visit (Visit B1). Subjects who discontinue the study during the Treatment Period prior to Visit T5/EoT should undergo an ET visit, which consists of the same procedures as Visit T5/EoT. Please note that the assigned Study Day is the first day of the corresponding Study Week. Additionally, target study days shown for Screening and Baseline are for a hypothetical Cohort 2 subject who requires 1 GC dose down-titration during Screening and none during Baseline, and has 17-OHP checked 2 weeks after GC dose down-titration; however, regardless of the assigned Study Day/Week, with agreement of the Medical Monitor, the duration of the Screening and Baseline Periods may be adjusted based on the needs of the individual subject.

[b] Subjects should note the actual time of their doses of study drug (if applicable), GC, and MC (if applicable), particularly those taken on the day prior to and the day of study visits. On the morning of study visits, subjects should wait to take their morning doses of study drug (if applicable) and GC and MC (if applicable) replacement until directed by personnel at the study site. On the morning of Visit T5, subjects who do not have sufficient remaining study drug to administer a single dose may be dispensed study drug if needed.

[c] Height will be assessed at Visit S1 only.

[d] A complete PE will be performed at Visits S1, T1, and T5/EoT. A brief PE will be performed at Visits T2, T3, T4 and F1/EoS.

[e] For each study visit, the first blood and saliva hormone sample should be collected in the morning prior to the subjects' morning dose of GC and MC (if applicable) replacement, as close to 8 AM (08:00) as practicable and between the hours of 6-10 AM (06:00-10:00). For Cohort 2 subjects who undergo GC dose adjustment, results from the serum 17-OHP samples obtained during Screening and Baseline will be used to assess stability of 17-OHP. Cohort 2 subjects who undergo GC dose adjustment, whose subsequent serum 17-OHP results during Screening and Baseline do not indicate stable levels, should be discussed with the Medical Monitor (see Appendix 2). At Visits T1, T2, T3, T4, and T5/EoT, blood sample collections for 17-OHP will also occur approximately 1, 2, 3, and 4 hours after administration of the morning replacement glucocorticoid, mineralocorticoid (if applicable) and/or study drug (if applicable) doses.

[f] A salivary 17-OHP profile should be collected by the subjects on Days -8, 22, 50, 78, and 106. These samples should be obtained at approximately 8 AM (08:00), noon (12:00), 4 PM (16:00), 8 PM (20:00), and 10-11 PM (22:00-23:00). At Visits T1, T2, T3, T4, and T5, saliva samples for 17-OHP will be collected at the study site at approximately 8 AM (08:00), 10 AM (10:00), and noon (12:00). The 8 AM (8:00) sample should be collected prior to the subjects' morning dose of GC and MC (if applicable) and will also be assessed for P (in premenopausal women only) and cortisol. The timing of the 8 AM (08:00), 10 AM (10:00) (if applicable), and noon (12:00) samples should be adjusted to correspond to just before, 2 hours after, and 4 hours after (respectively) administration of the morning replacement glucocorticoid, mineralocorticoid (if applicable) and/or study drug (if applicable) doses.

[g] On the days marked, a pregnancy test will be done on female subjects of childbearing potential only. A serum pregnancy test will be done at Screening; a urine pregnancy test will be done at Visit S2 (if applicable), B1, T1, T2, T3, T4, T5/EoT, and F1/EoS. The start date of the subject's last menstrual period will be obtained for premenopausal women only.

[h] Subjects will use the eDiary to record their glucocorticoid and mineralocorticoid (if applicable) doses (and, for premenopausal women, start dates of menstrual periods) from B1 to F1, and will also record their study drug doses from T1 to T5. The eDiary may also be used to provide reminders to subjects.

[i] Subjects with a 17-OHP level from Visit S1 < 4x ULN (Cohort 2) and a daily maintenance GC dose ≥ the equivalent of approximately 12 mg hydrocortisone/$m^2$ body surface area (see Appendices 2 and 3) will be contacted approximately 2 weeks after Visit S1 to have their GC dose decreased by the equivalent of approximately 5 mg hydrocortisone or 1 mg prednisone or prednisolone. They will then return for Visit S2 at least 2 weeks later. If their 17-OHP level from Visit S2 is ≥ 4x ULN, they will enter the Baseline period; if not, the case should be discussed with the Medical Monitor.

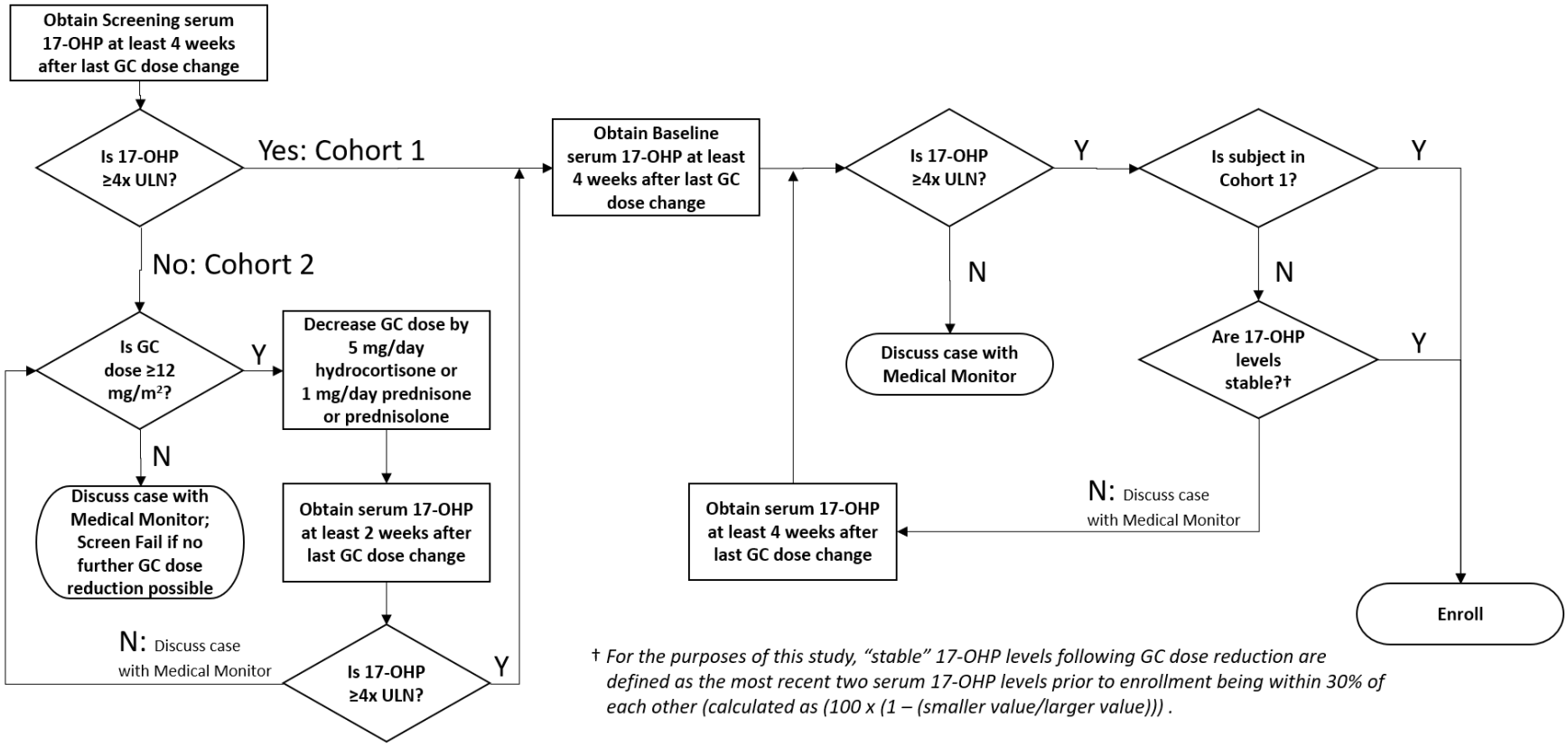
[j] All subjects will undergo an up-titration of study drug dose at Visit T2, and subjects whose predose serum 17-OHP levels obtained at the most recent scheduled treatment period visit did not meet the primary endpoint will also undergo an up-titration of study drug dose at Visits T3 and T4. Approximately 2 weeks after each of these visits, the Investigator will review the laboratory results from the visits and determine whether the subject should continue their existing dose of nevanimibe HCl or have their dose titrated.

[k] At Visits T1, T2, T3, T4, and T5/EoT, a trough ("0-hour") PK level and a serum storage sample will be collected within 30 minutes prior to dosing, and plasma for PK assessments will also be collected 1, 2, 3, and 4 hours postdose.

[l] AEs 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.

17-OHP: 17-hydroxyprogesterone; A4: androstenedione; ACTH: adrenocorticotropic hormone; AE: adverse event; aPTT: activated partial thromboplastin time; ECG: electrocardiogram; EoS: End-of-Study; EoT: End-of-Treatment; ET: early termination; GC: glucocorticoid; INR: international normalized ratio; MC: mineralocorticoid; P: progesterone; PE: physical examination; PK: pharmacokinetic(s) (samples); PT: prothrombin time; T: testosterone; tel: telephone visit

# APPENDIX 2. GLUCOCORTICOID (GC) DOSE ADJUSTMENT ALGORITHM




† *For the purposes of this study, "stable" 17-OHP levels following GC dose reduction are defined as the most recent two serum 17-OHP levels prior to enrollment being within 30% of each other (calculated as (100 x (1 – (smaller value/larger value))) .*

# APPENDIX 3. CALCULATION OF GLUCOCORTICOID DOSE AS EQUIVALENT MG OF HYDROCORTISONE/M$^2$ BODY SURFACE AREA

## I. Steps for Calculating Glucocorticoid Dose as Equivalent mg of Hydrocortisone/m$^2$ Body Surface Area

1. Calculate the daily glucocorticoid dose in equivalent mg of hydrocortisone (see Table 7 below).
2. Calculate the body surface area using the DuBois equation (see below).
3. Divide the daily glucocorticoid dose in equivalent mg of hydrocortisone by the body surface area in m$^2$.

## II. Conversion of Glucocorticoid Doses

**Table 7: Conversion of Various Glucocorticoids to Equivalent mg of Hydrocortisone**

| Glucocorticoid: | Equivalent Doses (mg) | Conversion Factor | Equivalent mg Hydrocortisone |
|---|---|---|---|
| Hydrocortisone | 20 | 1 | 20 |
| Prednisone | 4 | 5 [1] | 20 |
| Prednisolone | 4 | 5 [2] | 20 |
| Dexamethasone | 0.25 | 80 [3] | 20 |

[1] Hindmarsh PC. 2009. Management of the child with congenital adrenal hyperplasia. *Best Pract Res Clin Endocrinol Metab* 23(2):193-208

[2] Finkielstain GP, Kim MS, Sinaii N, Nishitani M, Van Rysin C, Hill SC, Reynolds JC, Hanna RM, Merke DP. 2012. *J Clin Endocrinol Metab* 97(12):4429-38

[3] Rivkees SA, Crawford JD. 2000. Dexamethasone treatment of virilizing congenital adrenal hyperplasia: The ability to achieve normal growth. *Pediatrics* 106:767–773

## III. Calculation of Body Surface Area

Where weight is in kilograms and height is in centimeters:

Body Surface Area = $W^{0.425} \times H^{0.725} \times 0.007184$

Du Bois D, Du Bois EF. 1916. A formula to estimate the approximate surface area if height and weight be known. *Archives of Internal Medicine* 17(6): 863-71

The body surface area can also be obtained by entering the weight and height at the following website: http://www-users.med.cornell.edu/~spon/picu/calc/bsacalc.htm

# APPENDIX 4. DRUGS THAT PROLONG THE QT/$QT_C$ INTERVAL

**Appendix 4, List A. Drugs that prolong the QT interval, to be used with caution**

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

**Appendix 4, LIST B. Drugs with conditional risk of QT prolongation, to be used with caution**

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

**Appendix 4, LIST C. Drugs with possible risk of QT prolongation, to be used with caution**

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

# APPENDIX 5. DRUGS KNOWN TO INTERACT WITH CYP3A4

**SUBSTRATES: 3A4, 5, 7**

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

**Anti-arrhythmics:**
quinidine-OH (not 3A5)

**Benzodiazepines:**
alprazolam
diazepam-3OH
midazolam
triazolam

**Immune Modulators:**
cyclosporine
tacrolimus (FK506)

**HIV Antivirals:**
indinavir
nelfinavir
ritonavir
saquinavir

**Prokinetics:**
cisapride

**Antihistamines:**
astemizole
chlorpheniramine
terfenadine

**Calcium Channel Blockers:**
amlodipine
diltiazem
felodipine
lercanidipine
nifedipine
nisoldipine
nitrendipine
verapamil

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

**6β-OH Steroids:**
estradiol
hydrocortisone
progesterone
testosterone

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

**Appendix 5. Drugs known to interact with CYP3A4, continued.**

**INHIBITORS 3A4,5,7**

**HIV Antivirals:**
indinavir
nelfinavir
ritonavir

**Antibiotics**
clarithromycin
itraconazole
ketoconazole
nefazodone
saquinavir
telithromycin
aprepitant
erythromycin
fluconazole

**Grapefruit juice**

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

**INDUCERS 3A4,5,7**

**HIV Antivirals**:
efavirenz
nevirapine

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

# APPENDIX 6. DRUGS THAT MAY INTERACT WITH P-GLYCOPROTEIN

| Transporter | MDR1/PgP |
|---|---|
| Gene | *ABCB1* |
| Amiodarone | S/Inhib |
| Amitriptyline | Inhib |
| Amprenavir | Induc |
| Astemizole | Inhib |
| Atorvastatin | S/Inhib |
| Boceprevir | S/Inhib |
| Bromocriptine | Inhib |
| Carvedilol | Inhib |
| Chlorpromazine | Inhib |
| Clarithromycin | Inhib |
| Clotrimazole | Induc |
| Cyclosporine | S/Inhib |
| Desipramine | Inhib |
| Dexverapamil | Inhib |
| Diltiazem | S/Inhib |
| Dipyridamole | Inhib |
| Disulfiram | Inhib |
| Doxepin | Inhib |
| Erythromycin | S/Inhib |
| Fluphenazine | Inhib |
| Glibenclamide | Inhib |
| Haloperidol | Inhib |
| Imipramine | Inhib |
| Indinavir | S/Induc |
| Itraconazole | S/Inhib |
| Ketoconazole | Inhib |
| Lidocaine | S/Inhib |
| Lovastatin | S/Inhib |
| Maprotiline | Inhib |
| Mefloquine | Inhib |
| Meperidine | Inhib |
| Methadone | Inhib |
| Mibefradil | Inhib |
| Midazolam | Inhib |
| Mifepristone | Inhib |
| Nelfinavir | S/Induc |

| Transporter | MDR1/PgP |
|---|---|
| Gene | *ABCB1* |
| 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-transporters

# APPENDIX 7. DOSE RATIONALE

The dose range for nevanimibe HCl (hereafter, nevanimibe) in this Phase 2b congenital adrenal hyperplasia (CAH) study is supported by previously completed clinical studies (i.e., the previous CAH Phase 2 study, the Phase 1 maximum tolerated dose (MTD) study in adrenocortical carcinoma (ACC), and healthy volunteer Phase 1 drug-drug interaction and food interaction studies) as well as comprehensive non-clinical and *in vitro* programs. Extensive clinical and non-clinical pharmacokinetic data have also been generated that further support the clinical dose rationale across the nevanimibe development program.

Nevanimibe is a selective acyl-CoA: cholesterol acyltransferase 1 (ACAT1) inhibitor. ACAT1 is highly expressed in the adrenal cortex, where it catalyzes the formation of cholesteryl esters (CE) from cholesterol and acyl-coenzyme A. In the adrenal glands, CEs serve as a substrate reservoir for steroid biosynthesis. Nevanimibe distributes preferentially to the adrenal glands relative to other tissues and disrupts adrenal cholesterol homeostasis via inhibition of ACAT1 (LaPensee, 2016). At low doses/exposures, nevanimibe results in reduction of the CE reservoir and leads to reduced synthesis of adrenal steroids. At higher doses and correspondingly higher exposures, nevanimibe causes further disruption of the normal cholesterol:CE ratio, leading to endoplasmic reticulum stress and, if left unchecked, activation of the unfolded protein response (LaPensee, 2016). Thus, nevanimibe may be used at the lower dose range for endocrine indications such as CAH and Cushing's syndrome (CS), while the higher dose range may be used for ACC.

Based on extensive work conducted to elucidate the mechanism of action, the nevanimibe clinical development program followed a step-wise, strategic approach to dose selection. The clinical program began with the ACC indication, where the benefit:risk allowed for more aggressive dose escalation given the severity and aggressiveness of the disease. The endocrine indications CAH and CS started after initiation of the ACC Phase 1 MTD study and used a lower dose range aligned with the nevanimibe mechanism of action (i.e., inhibition of adrenal steroidogenesis). The robust safety dataset generated in the ACC Phase 1 MTD study provided tremendous reassurance for the endocrine studies since ACC subjects had already been treated with markedly higher nevanimibe doses for much longer periods of time relative to the doses and treatment periods currently used in the endocrine studies. Additionally, the ACC patient population in the nevanimibe study is considered to be significantly less robust relative to the CAH and CS populations, yet nevanimibe was still very well tolerated. A comprehensive overview of the dosing rationale for the CAH Phase 2b study is presented below; additional details can be found in the Investigators' Brochure.

The previous CAH Phase 2 study (N=10) enrolled adults with classic CAH and uncontrolled 17-hydroxyprogesterone (17-OHP) levels. The study was designed to evaluate whether nevanimibe added to the subjects' usual maintenance glucocorticoid doses would result in improved control of 17-OHP levels, and used nevanimibe doses of 125 mg BID, 250 mg BID, 500 mg BID, 750 mg BID and 1000 mg BID in a single-blind, intra-subject dose escalation design. A 14-day nevanimibe treatment period was used for each dose level followed immediately by a 14-day placebo washout period. Seven of the 10 subjects demonstrated biological activity (i.e., decrease in 17-OHP) at multiple nevanimibe dose levels, with most subjects up-titrating to the 1000 mg BID dose. Nevanimibe was very well tolerated in the previous CAH Phase 2 study with no safety events of note. It was hypothesized that continuous dosing beyond 2 weeks and/or higher doses may result in a more robust treatment effect. This CAH Phase 2b study will build upon the

previous Phase 2 data by using doses of 500 mg BID, 1000 mg BID, 1500 mg BID and 2000 mg BID. The combination of sustained dosing and higher doses should provide a more definitive assessment of the efficacy of nevanimibe in CAH subjects.

The nevanimibe 1500 mg BID and 2000 mg BID doses in this CAH Phase 2b study are supported by the ACC Phase 1 MTD study (N=63) with long-term exposures and extensive PK data. The ACC Phase 1 MTD study used a dose range of 1.6 to 158.5 mg/kg/day (equivalent to approximately 11,900 mg/day for a 75-kg individual). Multiple conditions for oral administration were used in attempts to increase nevanimibe exposure to the greatest extent possible. A once daily, powder-in-capsule formation was used for the first 7 dose cohorts; a tablet formulation twice per day (BID) with a non-diet cola to maintain acidic stomach conditions was used for Cohorts 8 to 11; and Cohorts 12-14 were dosed with food BID. Even at the highest dose (158.5 mg/kg/day) a MTD could not be defined as dose-limiting toxicities (DLT) did not occur. Only two DLTs were reported during the entire study: a grade 3 elevation of liver enzymes in a subject with pre-existing liver disease (occurring at 102.4 mg/kg/day) and grade 3 vomiting and diarrhea (occurring at 37.3 mg/kg/day). Some "hints" of efficacy were reported with prolonged periods of stable disease observed in multiple subjects (Figure 1). Although a MTD could not be defined, the Sponsor voluntarily halted the study due to low grade, chronic gastrointestinal side effects (e.g., nausea, diarrhea) secondary to the large number of tablets required (i.e., 158.5 mg/kg/day = ~24 tablets per day, each 500 mg tablet being 19 mm x 8 mm in size). A dose of 128.2 mg/kg/day (equivalent to approximately 9600 mg/day for a 75-kg individual) was declared as the "maximum feasible dose" that could be taken on a long-term, chronic basis. This dose is approximately 2.5x higher than the highest dose being used in the CAH Phase 2b study. Thus, the ACC data provides a wide safety margin.

Dosing in the CAH Phase 2b study will commence with nevanimibe HCl at a dose of 500 mg BID, as this dose was well-tolerated in both the previous Phase 2 CAH study and in a previous drug-drug interaction study, and experience from previous studies suggests that study drug tolerability is improved by longer dosing. A 3- to 6-fold multiple exists between the 1000-2000-mg BID doses in this CAH Phase 2b study and the highest dose used in the ACC Phase 1 MTD study. The CAH Phase 2b doses of 1000 mg BID, 1500 mg BID and 2000 mg BID are equivalent to approximately 27, 40 and 53 mg/kg/day, respectively, for a 75-kg individual. In comparison, the relevant doses in the ACC Phase 1 MTD study were 23.3 (n=5), 25.6 (n=6), 37.3 (n=6), 51.2 (n=3), 60.6 (n=5), 97.9 (n=4 with cola; n=6 with food), 102.4 (n=4), 128.2 (n=5) and 158.5 (n=4) mg/kg/day. Thus, a total of 48 ACC subjects have been treated at doses close to or greater than those being used in the CAH Phase 2b study. Thirty-one of these 47 subjects remained on study drug until the time of the first assessment for disease progression at the month 2 visit. Subjects who were found to have ACC disease progression at the month 2 visit did not continue in the study. In fact, the majority of study dropouts were driven by disease progression at various time points and not adverse events. Nine subjects remained on study drug for at least 3 months, with 8 subjects having at least 4 months of exposure. The longest durations of exposure were 8, 12, and 13 months at dose levels of 102.4, 60.6, and 97.9 mg/kg/day, respectively. This robust safety dataset in human subjects provides strong reassurance of safety for the lower nevanimibe doses and shorter duration of treatment in the CAH Phase 2b study. Figure 2 presents dose and duration of exposure for the entire ACC study population.

**Figure 2: Nevanimibe Doses and Exposure Duration by Dose Cohort, Part 1 of 2**

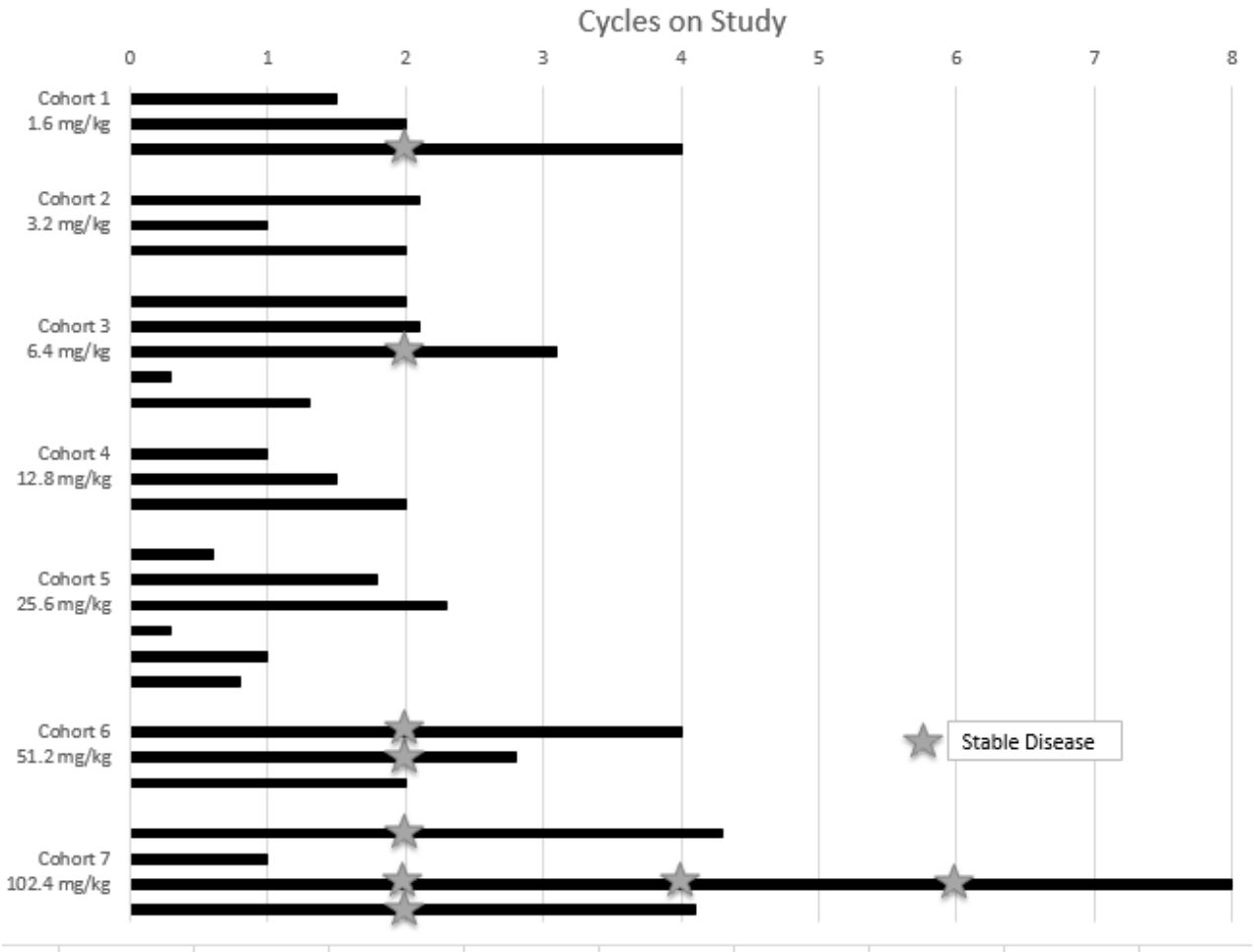
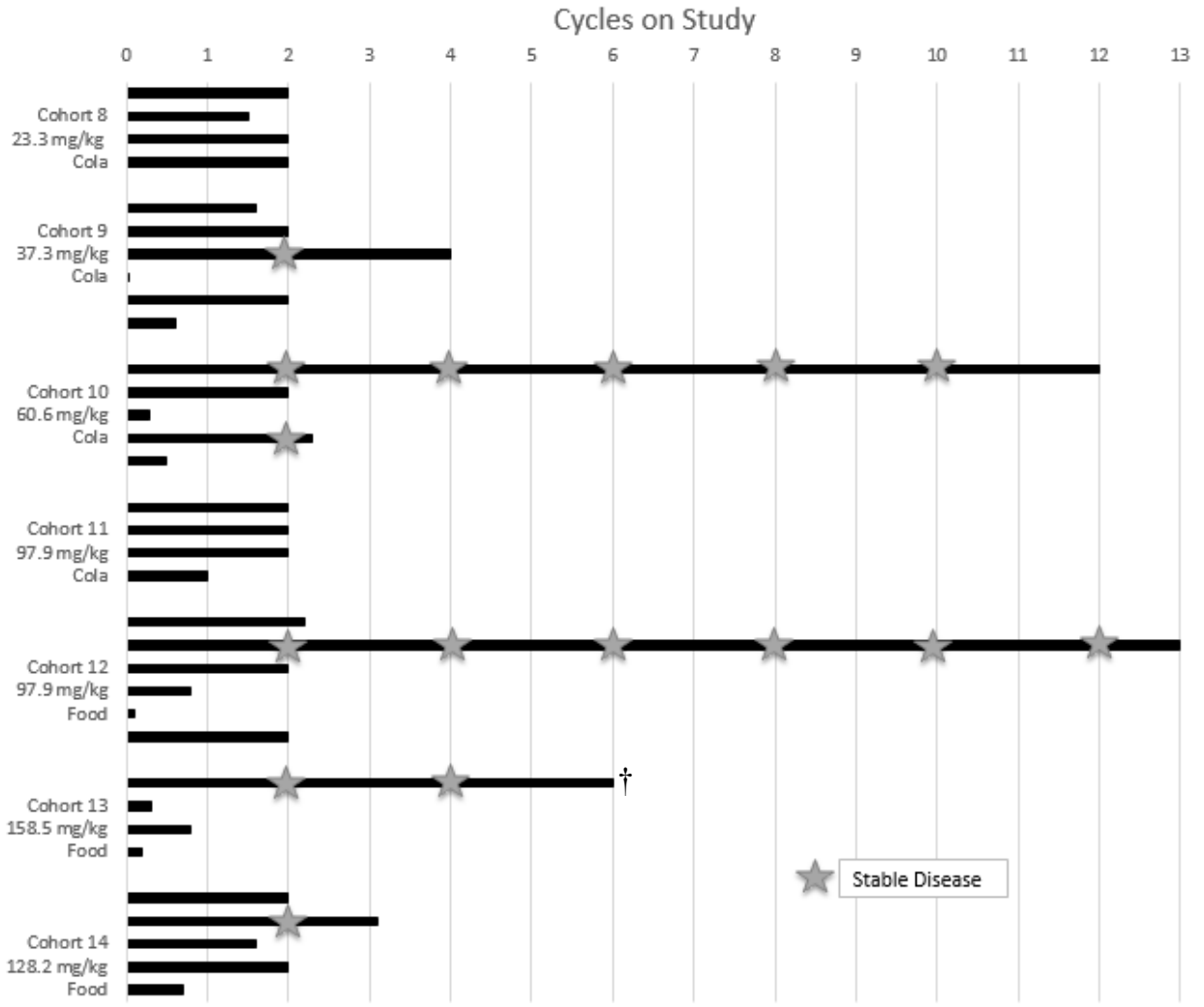


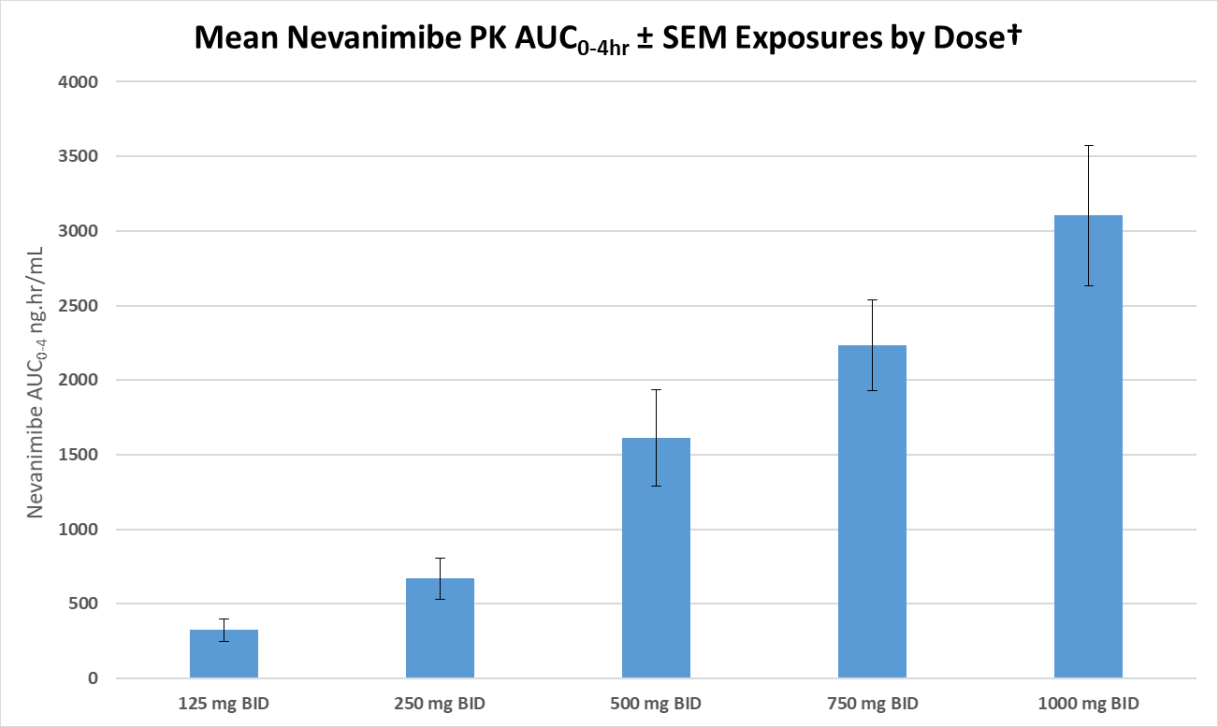
**Figure 2: Nevanimibe Doses and Exposure Duration by Dose Cohort, Part 2 of 2**




† Each cycle was approximately 28 days in duration. This subject was on nevanimibe 158.5 mg/kg/day for Cycle 1, 128.2 mg/kg/day for Cycle 2, and 97.9 mg/kg/day for Cycles 3-6. Dose down-titrations at Cycle 2 and Cycle 3 were done to ameliorate adverse events of nausea, diarrhea, and anorexia.

An extensive pharmacokinetic dataset also exists from the ACC Phase 1 MTD study and the two healthy volunteer Phase 1 studies (drug-drug interaction and food effects) as detailed in the Investigator's Brochure. Additionally, the previous CAH Phase 2 $AUC_{0\text{-}4\ hr}$ exposures demonstrated step-wise, dose-dependent increases across the 5 nevanimibe doses (Figure 3). Similar, step-wise, dose-dependent exposures are anticipated to occur in this CAH Phase 2b study.

**Figure 3: Previous CAH Phase 2 Study Nevanimibe Exposures**




† n = 9; data do not include AUCs from one subject who received only the 125 and 250 mg BID dose levels due to completing the study early by meeting target 17-OHP levels at the 250 mg BID dose.

In summary, the safety profile of nevanimibe has been extremely well characterized for a drug in the proof-of-concept stage of development. The step-wise systematic approach to dose selection in clinical studies was based on alignment of the known mechanism of action and the disease indication. Thus, higher doses and longer durations of exposure (i.e., greater risk) were used initially only for ACC subjects where the severity of the disease allows for more aggressive dosing but still provides a reasonable benefit:risk. Once this safety profile had been established, use in less aggressive disease states such as CAH and CS could be justified with a reasonable benefit:risk assessment.