# STATISTICAL ANALYSIS PLAN

## ATR-101-202

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

### NCT Number: NCT03669549

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## Signatures

I confirm that this Statistical Analysis Plan accurately describes the planned statistical analyses to the best of my knowledge and was finalized before database lock.

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## Signatures

## Table of Contents

## List of Abbreviations and Key Terms

| | |
|---|---|
| 11-ketoT | 11-ketotestosterone |
| 17-OHP | 17-hydroxyprogesterone |
| A4 | Androstenedione |
| ACTH | Adrenocorticotropic hormone |
| AE | Adverse event |
| aPTT | Activated partial thromboplastin time |
| ATC | Anatomical Therapeutic Chemical classification system of the World Health Organization |
| BID | Bi-daily |
| BMI | Body mass index |
| BSA | Body surface area |
| CAH | Congenital adrenal hyperplasia |
| CI | Confidence interval |
| CP | Clinical protocol |
| CRF | Case Report Form |
| CSR | Clinical study report |
| EoT | End of treatment |
| EoS | End of study |
| GC | Glucocorticoid |
| HCl | Hydrochloride |
| HLT | Highest level term |
| HLGT | Highest level group term |
| ICH | The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| INR | International normalized ratio |
| LLN | Lower limit of normal |
| LLT | Lowest level term |
| MC | Mineralocorticoid |
| max | Maximum |
| MedDRA | Medical Dictionary for Regulatory Activities |
| min | Minimum |
| mITT | modified Intention-to-Treat population |
| N | Number of subjects |
| n | Number of non-missing observations |
| P | Progesterone |
| PK | Pharmacokinetic |
| PKP | Pharmacokinetic population |
| PPP | Per protocol population |

| PT | Preferred term |
|---|---|
| Q1 | First quartile |
| Q3 | Third quartile |
| SAP | Statistical analysis plan |
| SAE | Serious adverse event |
| SAS® | Statistical Analysis System |
| SD | Standard deviation |
| SP | Safety population |
| SOC | System organ class |
| T | Testosterone |
| TEAE | Treatment-emergent adverse event |
| TFLs | Tables / figures / listings |
| ULN | Upper limit of normal |

# 1. Introduction

This statistical analysis plan (SAP) contains a more technical and detailed elaboration of the principal features of the statistical analyses as described in the Study Protocol of the ATR-101-202 study (global protocol amendment 2) dated 31-MAY-2019 and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data. The SAP is finalized and signed prior to final database lock at the end of the study. 17-OHP level cutoffs and targets are adjusted per protocol for menstrual cycle phase for premenopausal women.

# 2. Study Design and Objectives

## 2.1    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, eligible subjects will enter a Baseline and a Treatment Period. During the Treatment Period, subjects will receive nevanimibe HCl twice daily (BID) for 12 or 16 weeks, according to the protocol version (amendment 1 or amendment 2, respectively). Subjects will begin dosing with nevanimibe HCl 1000 mg or 500 mg BID (amendment 1 or amendment 2, respectively). 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. The visit and dosing schedules are schematically depicted for amendments 1 and 2 below (Figure 1 and Figure 2).

**Figure 1:** Visit and dosing schedule, Global Protocol Amendment 1



**Figure 2:** Visit and dosing schedule, Global Protocol Amendment 2



Subjects will be assigned to one of two cohorts in this study: Subjects with a serum 17-OHP ≥ 4x ULN at the initial screening visit (Visit S1) will proceed to the Baseline Visit (Visit B1) and will be assigned to Cohort 1. 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 AND a daily maintenance glucocorticoid dose in the suppressive range (≥ the equivalent of 12 mg hydrocortisone/m² body surface area/day) at the initial screening visit (Visit S1) will be assigned to Cohort 2 and will have their glucocorticoid dose decreased by the equivalent of approximately 5 mg hydrocortisone or 1 mg prednisone or

prednisolone per day. 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.

## 2.2    Treatments

The dose titration scheme for each study visit and telephone visit is shown in Figure 1 (amendment 1) and Figure 2 (amendment 2) and described below.

All subjects enrolled into the treatment period will receive open-label active treatment with nevanimibe HCl orally, starting at a dose of 1000 mg BID (amendment 1) or 500 mg BID (amendment 2). 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 1000 mg BID (amendment 1) or 500 mg BID (amendment 2) 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 1500 mg BID (amendment 1) or 1000 mg BID (amendment 2).

Predose serum 17-OHP levels will be assessed at every visit.  Following Visits T2 and T3 (amendment 1) or Visits T2, T3 and T4 (amendment 2), a post-visit telephone visit will be performed once the serum 17-OHP results from the most recent on-site study visit are available (~10 days after study visits), at which time assessments for dose adjustments will be made based on 17-OHP results.  If the 17-OHP level is ≤2x ULN (primary endpoint met), subjects will have their nevanimibe HCl dose down-titrated to the dose at which they met the primary endpoint

The highest available dose of nevanimibe will increase at each study visit, up to a maximum dose of 2000 mg BID at Visit T3 (amendment 1) or Visit T4 (amendment 2).  Non-responders (i.e., subjects who did not meet the primary endpoint) will continue to undergo dose escalations at each visit. Responders (i.e., subjects who met the primary endpoint) will be treated with the dose at which they most recently met the primary endpoint.  If the 17-OHP level is >2x ULN at a visit after a subject had previously met the primary endpoint, a dose escalation will be performed during the telephone visit, and the subject is now considered a non-responder. Hence, a dose escalation will automatically be performed at the next on-site visit along with the other non-responders. This scenario is a possibility for Visit T3 (amendments 1 and 2) and Visit T4 (amendment 2 only).

In addition to the pre-defined titration scheme, nevanimibe HCl may also be down-titrated by the Investigator, if needed based on safety and tolerability, with approval of the Medical Monitor.

## 2.3    Trial Schedule

A detailed schedule of procedures for the trial can be found in Table 1 (amendment 1) and Table 2 (amendment 2), respectively, and a schematic depiction can be found in Figure 1 and Figure 2. For

more details on the screening procedure used for allocation to Cohort 1 or Cohort 2, refer to section 2.1. For more details on the treatment and titration schedule, refer to section 2.2.

**Table 1:** Schedule of Procedures, Global Protocol Amendment 1

| Study Period: | Screening 2-14 Weeks | | | Baseline 2-8 Weeks | | Treatment 12 Weeks | | | | | | | | | | Follow-up 4 Weeks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Target Study Day:[a] | -56 | -42 | -28 | -14 | -8 | 1 | 15 | 22 | 29 | <43 | 50 | 57 | <71 | 78 | 85 | 113 |
| Study Week:[a] | -8 | -6 | -4 | -2 | -1 | 1 | 3 | 4 | 5 | 7 | 8 | 9 | 11 | 12 | 13 | 17 |
| Visit:[a,b] | S1 | tel | S2[a] | B1 | | T1 | tel | | T2 | tel | | T3 | tel | | T4/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 |
| Physical Examination[d] | X | | | | | X | | | X | | | X | | | X | X |
| 12-lead ECG | X | | | | | | | | | | | | | | X | |
| Hematology & Chemistry | 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 |
| Other Blood Hormones (A4, ACTH, total T, and 11-ketoT)[e] | | | | X | | X | | | X | | | X | | | X | X |
| Salivary 17-OHP, P, and Cortisol[e,f] | | | | X | | X | | | X | | | X | | | X | |
| Salivary 17-OHP Profile[f] | | | | | 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 |
| Start Date of Last Menstrual Period[g,h] | 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 |
| Enrollment | | | | | | X | | | | | | | | | | |
| Dispense and Dose Study Drug[b] | | | | | | X | | | X | | | X | | | X[b] | |
| Dose Titration Assessment[j] | | | | | | | | | | X | | | X | | | |
| Study Drug Compliance | | | | | | | | | X | | | X | | | X | |
| Dose GC and MC at Site[b] | X | | X | X | | X | | | X | | | X | | | X | X |
| Plasma PK and Serum Storage[k] | | | | | | X | | | X | | | X | | | X[b] | |
| Medications and Adverse Events[l] | 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 T4/EoT should undergo an ET visit, which consists of the same procedures as Visit T4/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 T4, 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 T4/EoT. A brief PE will be performed at Visits T2, T3 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. At Visits T1, T2, T3, and T4/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, and 78. 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, and T4, 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/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 T4. 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 12 mg hydrocortisone/m$^2$ body surface area 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 who had not previously met the primary endpoint will undergo an up-titration of study drug dose at Visit T3. 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, and T4/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

**Table 2:** Schedule of Procedures, Global Protocol Amendment 2

| 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 | | | |
| 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 |

<sup>a</sup> 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.

<sup>b</sup> 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.

<sup>c</sup> Height will be assessed at Visit S1 only.

<sup>d</sup> 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.

<sup>e</sup> 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.

<sup>f</sup> 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.

<sup>g</sup> 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.

<sup>h</sup> 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.

<sup>i</sup> 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.

<sup>j</sup> 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.

<sup>k</sup> 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.

<sup>l</sup> 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

## 2.4 Study Objectives

### 2.4.1 Primary Objective

The primary objective of this trial is to evaluate the efficacy and safety of orally administered nevanimibe hydrochloride (HCl) for the treatment of classic congenital adrenal hyperplasia (CAH).

### 2.4.2 Secondary Objectives

The following secondary objectives have been defined for this study:

- Assessment of changes in adrenal cortical steroids and steroid intermediates

- Determination of pharmacokinetic (PK) parameters of nevanimibe and its major metabolite(s)

- Assessment of PK/pharmacodynamic (PD) relationships of nevanimibe and its major metabolite(s).

## 2.5 Study Hypothesis

The hypotheses to be investigated by this study include whether sustained, continuous dosing of nevanimibe HCl will result in greater efficacy than observed in the previous Phase 2 CAH study (ATR-101-201) and whether higher doses are needed. Additionally, it will be evaluated whether the higher doses used in this study still have a sufficient safety profile. The primary efficacy endpoint will be evaluated by means of the percentage of subjects achieving predose serum 17-OHP targets as follows:

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

- Premenopausal women in follicular phase: 17-OHP ≤2x follicular phase ULN

- Premenopausal women in luteal phase: 17-OHP ≤ (2x follicular phase ULN + (luteal phase ULN – follicular phase ULN))

The responder rate (percentage of subjects achieving the predose serum 17-OHP targets) for Cohort $i$ ($i$=1, 2) will be calculated as follows:

$$\text{Responder rate}_{\text{Ci}} = \frac{Number\ of\ responders\ in\ Ci}{N_{Ci}} \times 100\%,$$

with $Ci$ being the corresponding cohort. The responder rate will also be calculated overall.

The study will be considered positive if 40% or more of enrolled subjects in either cohort were classified as responders at any of the four visits T2 (Day 29), T3 (Day 57), T4 (Day 85) or T5 (Day 113; Amendment 2).

## 2.6    Handling of Screening Failures and Drop-outs

Screening failures will be replaced while subjects who withdraw or are removed from the clinical study after enrollment into the treatment period (i.e., start of dosing with study drug) will be replaced if they do not meet the criteria for being an evaluable subject (8 weeks of continuous dosing with at least one post-baseline serum 17-OHP assessment).

## 2.7    Randomization and Stratification

No randomization or stratification is performed in this trial. Patients will be allocated to one of two cohorts (Cohort 1 or Cohort 2) according to their screening 17-OHP value. Eligible subjects with a 17-OHP value ≥4x ULN at the initial screening visit will be enrolled into Cohort 1, while patients with a 17-OHP value <4x ULN at the initial screening visit will be enrolled into Cohort 2 if their glucocorticoid (GC) dose can be reduced and a subsequent 17-OHP measurement after GC dose reduction indicates an increase in 17-OHP to ≥4x ULN.

## 2.8    Blinding

No blinding is performed in this clinical trial.

## 2.9    Sample Size Calculation

Based on results of the previous Phase 2a study of nevanimibe HCl in classic CAH (ATR-101-201), the sample size of approximately 20-24 subjects is considered to be sufficient for evaluating 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 performed. There are no pre-specified recruitment targets for Cohort 1 and Cohort 2.

## 2.10    Planned Interim or Sequential Analysis

No interim or sequential analysis is planned. However, data for Cohort 1 subjects may be analyzed after completion of the trial by the last Cohort 1 subject, while the analysis of Cohort 2 and overall may be conducted after completion of the trial by the last Cohort 2 subject. This option may be used to account for the longer trial duration of Cohort 2 subjects.

## 2.11 Handling of Changes to the Planned Analyses

Any deviations from planned analyses, the reasons for such deviations, and all alternative or additional statistical analyses that occur before final database lock will be described in amendments to the SAP. All deviations and/or alterations before final database lock or thereafter will be summarized in the clinical study report.

# 3. Technical Aspects and Coding Conventions

All programs will be written using SAS version 9.4 or higher. Tables, listings, and figures will be provided in separate documents with separate table of contents. A minimum font size of 8 points will be used for the tables, corresponding to a line size of 140 characters and a page size of 8.5 x 11 inches. For listings, a standard font size of 8 points with the line size and page size as defined above will be used to produce the output in 8.5 x 11-inch page size.

Courier New will be used as font for all tables and listings. In headings, titles, and listings only the first word will be capitalized. Missing data will be represented on patient listings as blank fields. Listings will be sorted by subject number unless specified otherwise in the mock TFLs attached to this SAP.

## 3.1 Date Coding and Day Numbering

The format for presentation of date variables will be DDMMMYYYY. The format for presentation of time variables will be hh:mm.

If dates needed for calculations are only partially given, they will be completed, if meaningful, as follows below:

For the partial start date of an Adverse Event:

- If only the month and/or year of the start date are known, then the adverse event is assumed to have started at the first day of the month/year

For the partial stop date of an Adverse Event known to not be ongoing:

- If only the month and/or year of the stop date are known, then the adverse event is assumed to have ended at the last day of the month/year

Dates with missing years will only be imputed if the correct year is obvious. Deviations will be documented and explained.

## 3.2    Coding Systems and Conventions

### 3.2.1    Definition of Baseline

In general, all values recorded at Visit T1 (Day 1) prior to the first dose will be regarded as baseline values for this study. In case no predose Visit T1 (Day 1) value was recorded (expected for ECG and for coagulation parameters), the most recent value prior to Visit T1 (Day 1) will be used as baseline value instead.

For serum or plasma 17-OHP, P, cortisol, A4, ACTH, total T, and 11-ketoT, baseline is defined as the mean of the predose value from Visit T1 (Day 1) and the most recent "0-hour" value prior to Visit T1 (Day 1), if the glucocorticoid dose was the same as at Visit T1 (Day 1) (if not the same, then only the predose Visit T1 (Day 1) value will be used).

For on-site salivary 17-OHP, P, and cortisol, baseline is defined as the mean of the predose value from Visit T1 (Day 1) and the most recent "0-hour" value prior to Visit T1, if the glucocorticoid dose was the same as at Visit T1 (if not the same, then only the predose Visit T1 value will be used). Change from baseline will be calculated for salivary 17-OHP values obtained 30 minutes before, as well as 2 hours and 4 hours after intake of the morning dose of nevanimibe HCl. For additional analyses, baseline for on-site salivary 17-OHP is further categorized by the time of sample relative to the time of the morning dose of nevanimibe HCl. Thus, baseline for the predose measurement on visits T2/T3/T4/T5 is defined for the additional analyses as above, while it is defined as the T1 sample taken 2 hours after the morning dose of nevanimibe HCl for the T2/T3/T4/T5 sample taken 2 hours after the morning dose, and defined as the T1 sample taken 4 hours after the morning dose for the T2/T3/T4/T5 sample taken 4 hours after the morning dose.

For home collection salivary 17-OHP profiles, baseline for the 8 AM (08:00), noon (12:00), 4 PM (16:00), 8 PM (20:00), and 10-11 PM (22:00-23:00) time points is defined as the value obtained for the corresponding time point at Day -8.

Except for the above-mentioned case, all values recorded after the first treatment with the study drug will be regarded as post-baseline values.

### 3.2.2    Coding of Adverse Events and Medical History

Adverse event (AE) and medical history terms will be assigned a lower level term (LLT) and will be classified by preferred term (PT), high level term (HLT), high level group term (HLGT) and system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at the time the database is closed.

### 3.2.3    Coding of Medications

Frequencies of previous and concomitant medication terms will be given based on Anatomical Therapeutic Chemical Classification (ATC) code levels 1 through 5 according to the Anatomical

Therapeutic Chemical classification system in effect at the time the database is closed. Non-drug treatments will not be coded.

### 3.2.4    Identification of Prior and Concomitant Medications

Identification of prior and concomitant medications will be done by comparison of the start and stop dates of the medication with the date of first dose of study drug.

- **Prior medications:** If the start date is before date of first dose of study drug, the medication is considered to be a prior medication. If the start date is partially given and unambiguously before start of treatment, the medication is also considered to be a prior medication.

- **Concomitant medications:** If the stop date is the same as or after the date of first dose of study drug or the medication is ongoing, the medication is considered to be a concomitant medication. If the stop date is partially given and not unambiguously before the date of first dose of study drug, the medication is considered to be a concomitant medication. If the stop date is missing and the medication is not known to be ongoing, the medication is considered to be a concomitant medication.

## 4. Analysis Populations and Subgroups

### 4.1    Analysis Populations

The statistical analysis is based on the following analysis sets:

**All Screened (AS) population:** The AS population includes all patients who attended at least one screening visit. The AS population will be used to assess reasons for screening failures and changes in the glucocorticoid dose over time.

**Modified Intent-to-Treat (mITT) population**: The mITT population includes all subjects who received at least one dose of study drug and had at least one post-baseline serum 17-OHP assessment. The mITT population will be used for all efficacy summarizations.

**Per Protocol Population (PPP)**: The PPP is a subpopulation of the mITT population that includes all subjects who received at least one dose of study drug, had at least one post-baseline serum 17-OHP assessment, were in the treatment period of the study for at least 56 days, were compliant with study drug administration (defined as having taken 80-120% of the assigned study drug dose for at least 8 consecutive weeks (evaluable subjects), and did not have any major protocol deviations that would compromise assessment of efficacy. The PPP will be used to repeat the summarizations of the primary endpoint to assess the impact of compliance with study drug and of major protocol deviations on the obtained data.

**Safety Population (SP)**: The SP includes all subjects who received at least one dose of study drug. The SP will be used for evaluation of all safety parameters.

**Pharmacokinetic Population (PKP)**: The PKP includes all subjects with measurable study drug concentrations.

## 4.2      Subgroups

Two cohorts (Cohort 1 and Cohort 2) are included in this trial. Eligible subjects are assigned to Cohort 1 if their serum 17-OHP is ≥4x ULN at the initial screening visit. If this is not the case, subjects may undergo a reduction in glucocorticoid dose and will be reassessed for their serum 17-OHP value. If the serum 17-OHP level is ≥4x ULN after reassessment, the subject can be enrolled into Cohort 2. No formal group sizes have been appointed for Cohort 1 and 2. All efficacy and PK analyses will be performed overall and by cohort.

Additionally, levels of androstenedione, testosterone and 11-ketotestosterone will be summarized by sex (male, female).

To assess the possible impact of protocol amendment 2 on the safety profile, the analysis of adverse events will be repeated for the subgroup of subjects enrolled according to global amendment 1 and global amendment 2.

## 4.3      Stratification

While subjects will be enrolled into Cohort 1 or Cohort 2 based on the 17-OHP value at the initial screening visit as described above, no formal stratification of subjects will be performed and no prespecified enrollment targets have been set for either of the cohorts.

# 5. Data Handling

## 5.1      Handling of Missing Data and Outliers

Data will only be used as available (i.e., observed case data only will be used) and missing data will not be imputed unless specified otherwise.

During data recording and manual data checks, queries may be raised regarding implausible data. All queries will be closed prior to final database lock. The investigator will either confirm or correct the value. Subsequently, the corrected or confirmed value will be used for the analysis.

## 5.2     Handling of Withdrawals and Drop-outs

Subjects who terminate the study and are not considered evaluable (at least 8 weeks of continuous dosing and at least one post-baseline serum 17-OHP assessment) will be replaced. Data of subjects who prematurely terminated the study will be used as available.

## 5.3     Handling of Multiple Comparisons and Multiple Primary Variables

Not applicable.

## 5.4     Data Review

There will be a Data Review Meeting (DRM) using a database snapshot after the majority of sites have opened and there are sufficient data (e.g., at least 4-5 subjects  with a minimum of 8 weeks on study drug). Additionally, there will be two DRMs, one after database soft lock for Cohort 1 and one after database soft lock for Cohort 2 and prior to hard lock of the database. All open queries and issues will be resolved prior to final database lock at the end of the study. All open questions/discrepancies for a subject that cannot be solved (even after consultation of the corresponding investigator (if applicable)), will be provided in a list to the sponsor for a case-by-case evaluation before final database lock. The definite classification of protocol deviations and the exclusion of subjects from the analysis set are reserved for the sponsor. It is important to note that, for the purpose of maintaining oversight over critical shortcomings, COVID-19-related protocol deviations are not marked as protocol deviations during the ongoing trial. They will, however, be recorded and a classification of COVID-19-related protocol deviations will be performed during the Data Review Meetings for Cohort 1 or Cohort 2.

# 6. Variables for Analysis

## 6.1     Demographics and Baseline Characteristics

The following variables are demographic and baseline characteristics:

-Demographics (Age, Sex (male, female (premenopausal woman, postmenopausal woman)), Ethnicity, Race)

-Other baseline characteristics (weight, height, BMI, BSA, baseline glucocorticoid (i.e., hydrocortisone, prednisone, prednisolone, dexamethasone, or other), baseline glucocorticoid dose in equivalent mg of hydrocortisone/day, daily glucocorticoid dose in equivalent mg of hydrocortisone/body surface area (mg/m²), proportion of subjects with baseline glucocorticoid dose $\geq 12$ mg/m$^2$/day, baseline mineralocorticoid, baseline mineralocorticoid dose)

-Medical history

-Prior and concomitant medications

## 6.2    Primary Efficacy Endpoint

The primary efficacy endpoint is the overall response rate within each cohort, defined as the percentage of subjects achieving predose serum 17-OHP targets at Visit T2 (Day 29), Visit T3 (Day 57), Visit T4 (Day 85) or Visit T5 (Day 113; Amendment 2).

## 6.3    Secondary Efficacy Endpoints

The following are secondary efficacy endpoints:

-Androstenedione, progesterone, total testosterone, and 11-ketotestosterone levels as measured at Baseline, Visit T2 (Day 29), Visit T3 (Day 57), Visit T4 (Day 85), Visit T5 (Day 113; Amendment 2) and Follow-up Visit (Day 113 (Amendment 1) or Day 141 (Amendment 2)); and change from Baseline to Visit T2 (Day 29), Visit T3 (Day 57), Visit T4 (Day 85), Visit T5 (Day 113; Amendment 2) and Follow-up Visit (Day 113 (Amendment 1) or Day 141 (Amendment 2)).

-Serum 17-OHP levels as measured at Visit T1 (Day 1), Visit T2 (Day 29), Visit T3 (Day 57), Visit T4 (Day 85), and Visit T5 (Day 113; Amendment 2) at h0, h1, h2, h3 and h4 (predose and 1-4 hours after administration of the morning replacement glucocorticoid, mineralocorticoid (if applicable), and/or study drug (if applicable) doses); and change from baseline (Visit T1 (Day 1)) to Visit T2 (Day 29), Visit T3 (Day 57), Visit T4 (Day 85), Visit T5 (Day 113; Amendment 2).

-Salivary 17-OHP levels as measured at Visit T1 (Day 1), Visit T2 (Day 29), Visit T3 (Day 57), Visit T4 (Day 85), and Visit T5 (Day 113; Amendment 2) (at time points h0, h2 and h4 (just before, 2 hours after, and 4 hours after (respectively) administration of the morning replacement glucocorticoid (if applicable), mineralocorticoid (if applicable) and/or study drug (if applicable) doses)) and change from Baseline (Visit T1 (Day 1)) to Visit T2 (Day 29), Visit T3 (Day 57), Visit T4 (Day 85), and Visit T5 (Day 113; Amendment 2).

## 6.4    Safety Endpoints

The following are safety endpoints:

-Incidence of (serious) adverse events

-Serum and urine pregnancy test results

-Vital signs (weight, blood pressure (systolic, diastolic), pulse rate, respiratory rate, body temperature); and change from baseline in vital signs

-Physical examination (interpretation)

-Electrocardiogram parameters (heart rate, P-R interval, QRS interval, Q-T interval, QTcF interval, R-R interval, overall interpretation); and change from baseline in ECG parameters

-Laboratory values and change from baseline in laboratory values, including:

-Hematology (hematocrit, hemoglobin, platelets, red blood cells, white blood cells, neutrophils, eosinophils, basophils, lymphocytes, monocytes)

-Clinical chemistry (serum albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), blood urea nitrogen, calcium, creatinine, plasma glucose, total bilirubin, total serum protein, magnesium, sodium, potassium, chloride, bicarbonate)

-Coagulation parameters (prothrombin time (PT), aPTT, INR)

-Blood hormones (ACTH and cortisol)

-Saliva hormones (progesterone (premenopausal women only), cortisol)

-Urinalysis (bilirubin, glucose, ketones, white blood cells, nitrite, blood, pH, protein, specific gravity, urobilinogen)

-Urine microscopy (clarity, color, RBC, WBC, bacterial count, squamous epithelial cells, renal tubular cells, transitional cells, hyaline casts, granular casts, RBC casts, WBC casts, triple phosphate crystals, calcium carbonate crystals, calcium oxalate crystals, urate salts, uric acid crystals, yeast cells, molds, mucus, amorphous phosphates)

## 6.5　　Pharmacokinetic Variables

Pharmacokinetic and pharmacodynamic parameters will be determined based on the concentrations of nevanimibe HCl and its major metabolite(s). A list of pharmacokinetic and pharmacodynamic parameters of interest can be found in section 7.8.

## 6.6　　Other Variables

The following additional variables are related to exposure and compliance:

-Duration of treatment (number of patient years per dose)

-Duration of exposure (average number of days of treatment per subject)

-Compliance (percentage of expected study drug taken)

# 7. Statistical Analysis Methods

All summarizations will be performed in an exploratory manner only. Where applicable and meaningful, analyses will be performed by cohort, nevanimibe HCl dose or study visit, and overall.

## 7.1    Descriptive Statistics

The default summary statistics for quantitative variables will be the number of non-missing observations (n), mean (arithmetic or geometric (if applicable for pharmacokinetic data)) and/or median, standard deviation (SD) and/or quartiles (Q1 and Q3), minimum (min) and maximum (max) for those patients with data available.

For qualitative variables, the number (n) and percentage (%) of patients with non-missing data per category will be the default summary presentation, and where appropriate and present, the number of missing values as a "Missing" category. Percentages will be calculated using a denominator of all patients in a specified population or treatment group. The denominator will be specified in a footnote to the tables for clarification if necessary.

## 7.2    Rounding Rules

### 7.2.1    Estimates of the Mean and Standard Deviation

When using raw data, the mean will be presented to 1 more decimal place and standard deviation will be presented to 2 more decimal places than the raw data. Consequently, these parameters will be calculated to at least 1 more decimal place than will be presented, and the result will be rounded to obtain the presented value.

### 7.2.2    Other Data

Quartiles, confidence intervals (CIs) and median will be presented with the same number of decimal places as the mean. Minimum and maximum will be presented with the same number of decimal places as the data used. For estimates of proportions, the result will be rounded to 3 decimal places. If proportions are displayed as percentages, 1 decimal place will be displayed. For example, a proportion of 0.655 will be presented in percentage form as 65.5%.

## 7.3    Calculation of Study Days and Durations

Study days and, if applicable and meaningful, durations will be determined by comparing the respective date to the date of first dose of study drug.

- If the respective date is on or after date of first dose of study drug:

  Study day/Duration = (Date (e.g., date of visit) - Date of first dose of study drug) + 1

- If the respective date precedes the date of first dose of study drug:

Study day/Duration = Date (e.g., date of medical history event) - Date of first dose of study drug

Time to onset and duration of adverse events will be calculated as follows:

- Time to onset = start date of AE - date of first dose of study drug [+1 for AE starting on or after date of first dose of study drug]

- Duration of adverse event = (stop date – start date) + 1

## 7.4 Evaluation of Demographics and Baseline Characteristics

### 7.4.1 Disposition of Patients

Subject disposition will be tabulated including the numbers of screened subjects, subjects completing the study, subjects withdrawing from the study, and subjects in the mITT population, PPP, SP and PKP. Subjects withdrawn from the study will be listed along with the primary reason for withdrawal. COVID-19 relatedness of early study terminations will be tabulated separately. In addition, the primary reason for withdrawal will be tabulated. Exclusion from analysis sets as well as the reason(s) for exclusion will be listed.

### 7.4.2 Demographics

Demographic information (age, sex (including information on menopause), ethnicity, race) will be summarized using summary statistics (N, mean, SD, median, minimum, maximum, upper and lower quartile) for continuous variables (age) or absolute and relative frequencies (n, %) for categorical variables (sex, ethnicity, race). Results will be presented for each analysis population (mITT, PPP, SP, PKP), by cohort and overall. Additionally, baseline characteristics will be presented for the SP population for the male and female subgroups.

### 7.4.3 Baseline Characteristics

Baseline characteristics (height, weight, BMI, BSA, type of baseline glucocorticoid (i.e., hydrocortisone, prednisone, prednisolone, dexamethasone, or other), baseline daily glucocorticoid dose in equivalent mg of hydrocortisone/day, baseline daily glucocorticoid dose in equivalent mg of hydrocortisone/body surface area (mg/m²), proportion of subjects with baseline glucocorticoid dose $\geq$ 12 mg/m²/day, baseline mineralocorticoid, baseline mineralocorticoid dose in µg of fludrocortisone, and baseline fold-ULN for 17-OHP) will be summarized using summary statistics for continuous variables and absolute and relative frequencies (n, %) for categorical variables. Results will be presented for the mITT population and the SP, by cohort and overall. Additionally, they will be presented for the SP population on the male and female subgroups.

Conversion of glucocorticoid dose to equivalent mg of hydrocortisone will be performed using conversion factors listed below (updated with global amendment 2 for all data analyses):

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

Conversion of mineralocorticoids into µg of fludrocortisone will be performed using conversion factors listed below:

| Mineralocorticoid | Equivalent Doses Mineralocorticoid Activity (mg) | Conversion Factor | Equivalent µg Fludrocortisone |
|---|---|---|---|
| Hydrocortisone | 20 | 0.005 | 100 |
| Prednisone | 50 | 0.002 | 100 |
| Prednisolone | 50 | 0.002 | 100 |
| Dexamethasone | - | 0 | 0 |
| Cortisone acetate | 25 | 0.004 | 100 |
| Fludrocortisone | 0.1 | 1 | 100 |

BMI will be calculated using the following formula:

$$BMI = \frac{weight\ [kg]}{height^2 [m^2]}$$

BSA will be calculated according to Dubois and Dubois using the following formula:

$$BSA = 0.007184 \times (height\ [cm])^{0.725} \times (weight\ [kg])^{0.425}$$

In addition, for Cohort 2, the type of glucocorticoid, daily glucocorticoid dose in equivalent mg of hydrocortisone/day, daily glucocorticoid dose in equivalent mg of hydrocortisone/body surface area (mg/m²), and the proportion of subjects with glucocorticoid dose $\geq 12$ mg/m$^2$/day will be summarized for Visit S1 (the initial screening visit ), Visit S2, Visit B1, and Visit T1.

### 7.4.4 Medical History and Prior and Concomitant Medication

Absolute and relative frequencies (n, %) of medical history will be described based on MedDRA system organ class (SOC) and preferred term (PT) levels for the SP, overall.

Absolute and relative frequencies (n, %) of prior and concomitant medications (separately) will be provided based on Anatomical Therapeutic Chemical (ATC) Classification code levels 1 through 5 for the SP, overall.

## 7.5 Evaluation of the Primary Efficacy Endpoint

The primary efficacy endpoint, the percentage of subjects achieving predose serum 17-OHP targets at Visit T2 (Day 29), Visit T3 (Day 57), Visit T4 (Day 85), or Visit T5 (Day 113; Amendment 2), will be evaluated for the mITT population and repeated for the PPP. Achievement of the serum 17-OHP targets will be determined 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))

Each subject who falls below the applicable 17-OHP target for at least one visit will be counted as a responder to treatment with nevanimibe HCl. Any subjects who prematurely terminates the study and was not categorized as responder before termination will be counted as a non-responder. The responder rate will be calculated overall and for each cohort (Cohort 1 and Cohort 2), by nevanimibe dose and overall. The clinical trial will be regarded as successful if a responder rate of at least 40% was observed for either of the two cohorts.

The 90% exact binomial confidence interval will be calculated for the responder rates. A variation of the following SAS code will be used for calculation of the confidence limits:

```
proc freq data = input-dataset;
        tables responder / binomial(level='Yes' wilson) alpha=.1;
        by visit;
        exact binomial;
        ods output BinomialCLs = output-dataset;
run;
```

Additional summary statistics will be prepared, including summaries relative to the upper limit of normal (x ULN) and absolute as well as relative change from baseline. The dose-response relationship may additionally be displayed graphically.

## 7.6 Evaluation of Secondary Efficacy Endpoints

All secondary variables will be evaluated for the mITT population and the PPP.

Absolute values as well as change and percentage change from baseline in androstenedione, progesterone, total testosterone, and 11-ketotestosterone (as available) as measured at Visit T2 (Day 29), Visit T3 (Day 57), Visit T4 (Day 85), Follow-up Visit (Day 113; Amendment 1) or Visit T5 (Day 113; Amendment 2) and Follow-up Visit (Day 141; Amendment 2) will be assessed descriptively using summary statistics for continuous variables. Percentage change from baseline at Day x will be calculated as (measurement at Day x - measurement at baseline) / (measurement at baseline). Results will be presented overall and by cohort. Levels of androstenedione, testosterone and 11-ketotestosterone will additionally be summarized by sex (male, female) and cohort (cohort 1, cohort 2).

Absolute values as well as change and percentage change from baseline in serum 17-OHP levels at Visit T1 (Day 29), Visit T2 (Day 57), Visit T3 (Day 85), Visit T5 (Day 113; Amendment 2) and Follow-up Visit (Day 113 (Amendment 1) or Day 141 (Amendment 2)) will be evaluated by cohort, nevanimibe dose and overall. For each study visit, up to five (5) samples are collected per subject at specified pre/postdose timepoints. For each study day, the sum of all values from the time series (i.e., samples at specified pre/post-dose time points) will be calculated and used for comparison with data from Visit T1. Percentage change from baseline at Day x will be calculated as (measurement at Day x – measurement at baseline) / (measurement at baseline). For those samples with a 17-OHP value >30 µg/L, the undiluted value received after transformation of the measurement after appropriate dilation will be used. A footnote detailing the number of samples that exceeded the measurement limit of 30 µg/L will be included.

Results will be described using summary statistics for continuous variables. 90% confidence limits will be calculated for each of the visits.

Change and percentage change from Baseline (Visit T1 (Day 1)) in salivary 17-OHP levels (samples collected on-site) at Visit T2 (Day 29), Visit T3 (Day 57), Visit T4 (Day 85), and Visit T5 (Day 113; Amendment 2) will be evaluated by cohort, nevanimibe dose and overall. For each sampling day, up to five (5) different time points are collected per subject. Summary statistics for each time point will be calculated for each sampling day and used for comparison with data from Visit T1. In addition, for the five (5) on-site salivary samplings, the sum of the h0, h1, h2, h3 and h4 values per subject per study day will be evaluated by cohort, nevanimibe dose and overall, for all subjects with data available at all five timepoints for the respective on-site sampling day. Availability of data for imputation of the missing values will be assessed during the final DRM meeting prior to data analysis, and changes may be made to the described analysis to utilize all available data more effectively. Results will be described using summary statistics for continuous variables.

## 7.7    Evaluation of Safety Endpoints

All safety variables will be evaluated for the safety population (SP). The analyses of treatment-emergent adverse events (TEAEs) will be performed overall and for subjects enrolled under global

amendment 1 and global amendment 2 separately. The analysis on the SOC and PT level will be repeated for the All Screened population to cover all AEs, also those recorded prior to first treatment with the study drug.

Treatment-emergent adverse events (TEAEs) will be summarized overall and by causal relationship and severity. TEAEs will be coded using the latest MedDRA version at the time of database close. Incidences and percentages will be provided on the subject-level (n), overall as well as on the system organ class (SOC) level and on the preferred term (PT) level for all subjects and by nevanimibe dose category. Results will additionally be prepared by time range. The suitable time ranges will be selected during the DRM for Cohort 1. A subject with more than one AE overall or assigned to one SOC or assigned to one PT will be counted once for the worst category (causal relationship or severity) on the subject level. For the summarization by relationship to study drug, the relationship will be categorized as "related" and "not related," where related AEs are those with at least a possible relationship to the study treatment. For the summarization by nevanimibe dose, subjects with more than one AE overall or assigned to one SOC or assigned to one PT will be counted once on the subject level at the lowest nevanimibe dose category on which they experience the AE (i.e., a subject with two AEs, one when treated with 1000 mg BID and one when treated with 1500 mg BID, will be counted once at the 1000 mg BID dose). Additionally, the number of AEs per patient-year of treatment will be calculated by nevanimibe dose as (sum of number of AEs of subjects at the respective nevanimibe dose) / (patient-years of treatment at the respective nevanimibe dose).

The mean time to onset of AEs (including worsening of preexisting conditions) will additionally be presented using summary statistics for continuous variables, overall and by SOC and PT. Time to first treatment-related TEAE and/or onset of selected TEAEs/groups of TEAE, may further be displayed in a Kaplan-Meier curve(s), by dose and/or in total, and by cohort and in total, where the time reflects the number of days since first being treated with the corresponding dose and changes to the dose will be included as censored information. If a subject is treated at a certain dose, then the dose is changed and at a later point, the subject is treated with the same dose again, then the duration of treatment with said dose will be added to the initial treatment period. Serious adverse events (SAEs) as well as AEs leading to death or discontinuation will be listed. Additionally, SAEs will be summarized overall and by nevanimibe dose.

Laboratory assessments, physical examinations, ECG and vital signs will be evaluated as continuous or categorical variables according to standard summary statistics for each visit, overall. Changes from baseline will be calculated for continuous variables and shift tables depicting the change from baseline will be produced for categorical variables where applicable and meaningful.

## 7.8    Evaluation of Pharmacokinetic Variables

Pharmacokinetic parameters ($C_{last}$, $C_{max}$, $C_{max}/D$, $T_{max}$, $AUC_{0-4}$, $AUC_{0-4}/D$, $AUC_{0-t}$, $\lambda_z$, $t\frac{1}{2}$, $AUC_{0-\infty}$, $AUC_{\%extrap}$, CL/F) for nevanimibe and its major metabolite(s) will be computed as data permit and as appropriate

using non-compartmental methods employing WinNonlin® Phoenix version 6.3 or later (Pharsight Corp., Mountain View, CA). PK parameters may also be estimated for replacement glucocorticoids and/or mineralocorticoids as appropriate.

The pharmacokinetic analyses will be described in detail in a separate PK Analysis Plan by Certara USA, Inc. (Princeton, New Jersey, USA) as it will be conducted separately from the analyses described in this document.

## 7.9    Evaluation of Other Variables

Study drug compliance will be evaluated for the safety population according to the counts of number of tablets dispensed and number of tablets returned, along with the assigned doses of study drug, as recorded in the eCRF. The compliance will be calculated for Visit T1 (Day 1) – Visit T2 (Day 29), Visit T2 (Day 29) – Visit T3 (Day 57), Visit T3 (Day 57) – Visit T4 (Day 85), Visit T4 (Day 85) – Visit T5 (Day 113) and overall (Visit T1 (Day 1) – Visit T4/T5 (Day 85/113)(or early termination date)) as follows:

$\Delta$ = (Number of tablets the subject should have taken (based on assigned dose level(s)) - Number of tablets taken)

$$\text{Compliance} = \left(1 - \frac{\Delta}{\text{Number of tablets the subject should have taken}}\right) x \ 100\%$$

Overall compliance for amendment 1 patients will be calculated from Visit T1 to Visit T4 or early study termination date, while compliance for amendment 2 patients will be calculated from Visit T1 to Visit T5 or early study termination date.

The duration of exposure will be calculated as follows:

Duration = (Date of last dose of study drug – date of first dose of study drug) + 1

The mean duration of exposure will be calculated overall, by amendment and by cohort.

The duration of treatment in subject-years will be calculated by cohort and by nevanimibe dose as the sum of the duration of exposure of all subjects, overall or in the respective cohort or nevanimibe dose.

All information recorded in the eDiary, including the usage of glucocorticoids and mineralocorticoids, will be listed only.

## 7.10    Special Analytical Issues

Data from unscheduled visits will only be listed except for data regarding AEs, concomitant medications and medical history.

Subject doses will be allocated unambiguously into the following categories for the analysis by dose:

- <500 mg BID

- 500 mg BID to <1000 mg BID

- 1000 mg BID to <1500 mg BID

- 1500 mg BID to <2000 mg BID

- 2000 mg BID

### 7.10.1  Interim Analysis

No Interim analysis will be performed.

# 8.  Changes in the Planned Analyses

Changes made to the planned analyses in the clinical study protocol as of the finalization of this SAP (version 1.0) are as follows:

- The PPP definition has been updated to additionally stipulate that the subjects were in the treatment period of the study for at least 56 days and were compliant with study drug administration.

Any additional changes to the planned analyses in the clinical study protocol or the SAP decided before final database lock at the end of the study and the reasoning will be described in amendments to the clinical study protocol and/or the SAP and will be detailed in the clinical study report (CSR). Any exploratory analyses conducted in addition to the analyses described in the SAP after final database lock at the end of the study and the reasoning will be clearly highlighted and discussed in the clinical study report.

## 9. APPENDIX 1

The following lists give an overview of the required tables, figures and listings. Numbering and titles are not obligatory, and changes may occur after agreement of the sponsor. The changes, however, should not contradict the planned analyses described in this SAP. Any post-hoc analyses not defined in the final version of the study protocol/amendment or the SAP may be implemented as exploratory analyses and will be clearly identified as not planned in advance.

For additional information on the layout of the tables and listings, refer to the mock tables or mock listings documents.

**Tables**

**Listings**

**Figures**