

PROTOCOL NUMBER B23CS ARENA 2 STUDY

A PHASE 3 MULTICENTER, RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED WITHDRAWAL STUDY EVALUATING ADV7103 IN PEDIATRIC AND ADULT SUBJECTS WITH DISTAL RENAL TUBULAR ACIDOSIS

Test Investigational Product: ADV7103 (Potassium Citrate Monohydrate and Potassium Hydrogen Carbonate)

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IND Number: 127465

Date: 30Nov2020
Version: FINAL Version 3.0 (amendment 2.0)



Confidentiality Statement

This document is confidential information of Advicenne SA. It may not be disclosed to parties not associated with the clinical investigation or used for any purpose without the prior written authorization of Advicenne SA.

SIGNATURE PAGE

Protocol Title: A Phase 3 Multicenter, Randomized, Double-blinded, Placebo-controlled Withdrawal Study Evaluating ADV7103 in Pediatric and Adult Subjects With Distal Renal Tubular Acidosis (ARENA 2 Study)

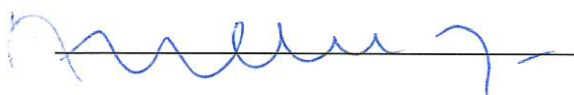
Study Number: B23CS

Protocol Date/ Version: 30Nov2020 (FINAL Version 3.0)

Sponsor's Approval

The protocol has been approved by Advicenne SA.

Sponsor's Authorized Officer:



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Nov. 25, 2020
Date

INVESTIGATOR'S AGREEMENT

I, the undersigned, am responsible for the conduct of the B23CS (ARENA 2) study at my site and agree to the following:

- I understand and will conduct the study in accordance with the approved B23CS (ARENA 2) study protocol (version 3.0) and its attachments, any approved protocol amendments, all statements of confidentiality, Good Clinical Practices, ICH guidelines, local legal and regulatory requirements;
- I will not deviate from the study protocol without prior written permission of the Sponsor or its designee and prior written approval from the Institutional Review Board or Independent Ethics Committee (if applicable), except where necessary to prevent any immediate danger to the subject;
- I have read and understand fully the Investigator's Brochure (edition 07 dated 10Jan2020) and/or any other appropriate document (such as the approved summary of product characteristics and/or sponsor core safety information) concerning ADV7103 and other relevant information concerning the placebo;
- I have sufficient time, an adequate number of qualified staff, and adequate facilities to conduct and complete the study according to the protocol, properly, safely, and within the anticipated timeline;
- I will ensure that all staff at my site who are involved in the study are adequately trained regarding the investigational products (ADV7103 and placebo), the study protocol, and their responsibilities. In case of delegation of any of my study responsibilities, I will ensure that I delegate to qualified staff and this information is captured in a log or some other form of documentation for the study files.

Printed Name of Investigator:

Title of Investigator:

Site Number:

Site Name:

Signature of Investigator

Date

STUDY PERSONNEL CONTACT LIST

Table 1: Contact Information for Key Study Personnel

Role in Study/Purpose	Name/Title/Affiliation	Telephone Number and E-mail Address
SAE reporting	Vigipharme Global Safety and Pharmacovigilance	E-mail: pharmacovigilance@advicenne.com eFax: +33 (0)4 67 10 72 53
Medical Monitor	Anthony Robinson, CRNP VP, Head of Clinical Operations, Advicenne, Inc.	Mobile: +1 484 225 1585 Email: arobinson@advicenne.com
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SUMMARY OF CHANGES TO PROTOCOL B23CS

Version 3.0

In response to the challenges of the COVID-19 Public Health Emergency, Advicenne is amending the protocol for Study B23CS in order to minimize the exposure to COVID-19 by research participants and to minimize the impact on the study data integrity. Changes to the protocol include :

- Period 3 Monitoring changed from in-patient to home or investigational site
- Addition of central lab for safety specimens
- Analysis of total bicarbonate and potassium by point-of-care calibrated iSTAT System (Abbott, Inc.) for use in home by nurses or at sites
- Mobile/ point-of-care cardiac monitoring to include ECG, holter monitor, and/or telemetry.
- Addition of lower limit of potassium for Screening (<3.0 mEq/L).

See Section [17.4](#) for full details of changes made between v. 2.0 and v. 3.0 of this protocol.

1. SYNOPSIS

Name of Sponsor: Advicenne SA
Name of Test Product: ADV7103
Name of Active Ingredients: Potassium citrate monohydrate and potassium hydrogen carbonate
Title of Study: ARENA 2 A Phase 3 Multicenter, Randomized, Double-blinded, Placebo-controlled Withdrawal Study Evaluating ADV7103 in Pediatric and Adult Subjects With Distal Renal Tubular Acidosis
Study Number: B23CS
Clinical Development Phase: 3
Planned Number of Subjects: Approximately 40 to enter the Open-label Lead-in Period, 32 to complete the Withdrawal Period
Study Center(s): Approximately 18 sites in the United States and Canada
Lead Principal Investigator: Laurence Greenbaum, MD
Planned Enrollment Start: October 2018
Planned Enrollment Duration: 20 months
Study Duration: approximately 24 months
Objectives: Primary <ul style="list-style-type: none">• Compare the efficacy of ADV7103 versus placebo in preventing metabolic acidosis, defined as 2 consecutive serum bicarbonate levels < 18 mEq/L for subjects \geq 4 years old and < 17 mEq/L for subjects < 4 years old, during the Withdrawal Period. Secondary <ul style="list-style-type: none">• Compare the proportion of subjects with 2 consecutive serum bicarbonate levels below the lower limit of normal (LLN) for age between the ADV7103 and placebo groups during the Withdrawal Period;• Compare the proportion of subjects who develop new onset hypokalemia (defined as a serum potassium level < 3.5 mEq/L) between the ADV7103 and placebo groups during the Withdrawal Period;• Compare the time to metabolic acidosis, defined by serum bicarbonate levels, between the ADV7103 and placebo groups during the Withdrawal Period;• Compare the time to new onset hypokalemia between the ADV7103 and placebo groups during the Withdrawal Period;

- Compare the proportion of subjects with both metabolic acidosis and new onset hypokalemia between the ADV7103 and placebo groups during the Withdrawal Period;
- Assess the mean urinary calcium/creatinine ratio associated with Visits 1 (SOC) and 2 (ADV7103);
- Compare the change in mean urinary calcium/creatinine ratio during the Withdrawal Period between the ADV7103 and placebo groups;
- Assess the mean urinary citrate/creatinine ratio associated with Visits 1 (SOC) and 2 (ADV7103);
- Compare the change in mean urinary citrate/creatinine ratio during the Withdrawal Period between the ADV7103 and placebo groups;
- Determine the frequency and severity of all study treatment emergent adverse events (TEAEs) by study period and study product assignment;
- Determine the number of treatment emergent adverse events by study period and study product assignment;
- Determine the frequency of suspected unexpected serious adverse reactions (SUSARs) by study period;
- Determine the frequency of new onset hyperkalemia by study period and for each treatment group during the Withdrawal Period;
- Determine the frequency of new onset hypokalemia by study period, and for each treatment group during the Withdrawal Period;
- Assess changes in other serum and urine safety laboratory results from SOC baseline;
- Determine the frequency of urine pH > 8.5 in Periods 1, 2, and 3.

Exploratory

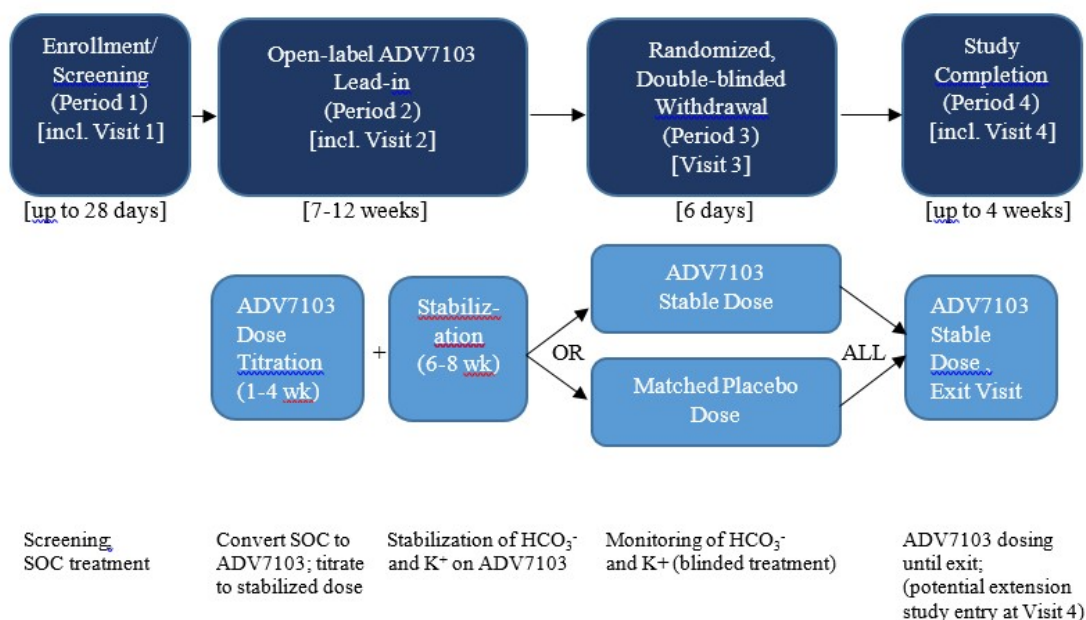
- Compare the gastrointestinal tolerability, measured on an age appropriate scale, of ADV7103 (Visit 2) versus SOC (Visit 1);
- Compare urinary supersaturated (SS) calcium oxalate, SS calcium phosphate, and SS uric acid levels: ADV7103 (Visit 2) versus SOC (Visit 1) and ADV7103 vs. placebo (Period 3);
- Compare age appropriate study product acceptability and satisfaction scores: ADV7103 (Visit 2) versus SOC (Visit 1);
- Compare palatability and ease of administration/swallowing and number of daily product intakes scores: ADV7103 (Visit 2) versus SOC (Visit 1);
- Evaluate quality of life variables through use of questionnaires and semi-structured interviews.

Study Design and Methodology:

This is a phase 3, prospective, multicenter, randomized, double-blinded, placebo-controlled, study product withdrawal study comparing the efficacy of ADV7103 versus placebo in preventing the development of metabolic acidosis defined by serum bicarbonate level in pediatric (6 months to < 18 years of age) and adult (18 to 65 years of age) subjects with primary dRTA.

The study will target enrolling at least 4 subjects in each of the following age groups: 6 months – 23 months; 2-11 years, and ≥ 12 years. Starting with the oldest group (≥ 12 years), each subsequently younger group will be randomized after 4 subjects from the preceding older age group have completed the Withdrawal Period and the unblinded Data Monitoring Committee (uDMC) approves randomization in the next younger group. During uDMC review of data from an age group, enrollment into that age group may continue unless the uDMC recommends cessation of this activity. The uDMC may request additional subjects complete the study in the age group under uDMC review prior to approving randomization of the next younger group. Enrollment of an equal number of subjects in each age group is not required; for pragmatic reasons, enrollment in the youngest age group may be fewer than 4 subjects. After reviewing data from randomized subjects who do not complete the Withdrawal Period, the uDMC may recommend changes to the protocol (including, but not limited to, increasing the total number of subjects enrolled in the study) to ensure a reasonable balance of early withdrawals between treatment groups. Lastly, if laboratory data, clinical symptoms, and cardiac monitoring data warrant, the uDMC may recommend modification of cardiac monitoring.

The study includes 4 consecutive periods as shown in this schematic:



Study Periods 1, 2, 3, and 4 will involve activities conducted either at the subject's home or at the investigator's office (outpatient) by investigator telehealth visits and/or visiting qualified delegates (home health visiting nurses).

Period 1, Enrollment/Screening:

Subjects are enrolled at the time informed consent is obtained. After obtaining electronic informed consent from the subject or parent/guardian and assent from the subject if indicated, the Screening Visit (Visit 1) will take place on an outpatient basis at the investigational site or within the safety of their home via a home health nurse and as needed, investigator telehealth sessions. Subjects who do not initially meet all eligibility criteria may be re-screened at the Investigator's discretion (in consultation with the Medical Monitor) and enroll in the study if all eligibility criteria are met. During this period, which may involve up to 28 days for each screening attempt (no more than 3 total attempts or 2 re-screens), each subject will remain on her/his SOC alkali regimen and have study baseline assessments performed.

It should be possible to complete nearly all of the required screening/study baseline assessments during the face-to-face Screening Visit (Visit 1). Any remaining activities/assessments (eg, completion of the study baseline 24-hour urine collection, renal ultrasound testing, etc) may be completed via remote interactions (ie, not necessarily face-to-face encounters with study team members at the investigational site).

Period 2, Open-label Lead-in:

This period consists of an ADV7103 **dose titration phase** (from 1 to 4 weeks in duration) and a **stabilization phase** (6-8 weeks in duration; may be lengthened to manage logistics for progression to the Withdrawal Period). Throughout the Open-label Lead-in Period, subjects will be followed by telehealth and phone interactions and undergo in-home, point-of-care blood collection, processing and analysis. A second 24-hour urine collection will be completed at the end of Period 2 (ie, on or before Visit 2). After discussion with the Medical Monitor, the Investigator may elect to transition selected subjects < 5 years of age to ADV7103 in a monitored setting.

Dose Titration Phase:

After eligibility for the study has been confirmed by the Investigator, the subject will be registered into the study and open-label ADV7103 will be provided to the subject during Visit 1 (eg, home visit by a healthcare provider, shipping method/mail delivery, pick up by the subject at the investigational site, etc). The subject will also be given instructions concerning the date and time to stop taking her/his SOC regimen and to begin taking ADV7103 (at the dose specified by the Investigator) prior to the morning meal/snack/feeding on the day after the SOC regimen (including potassium supplementation, if any) is stopped and following confirmation that the 24 hour urine collection is completed (in subjects for whom this is technically feasible). Open-label ADV7103 will be taken approximately every 12 hours (just prior to both the morning and evening meals/snacks/feedings). The initial total daily alkali dose of ADV7103 will approximate the SOC daily alkali dose in mEq.

After ADV7103 dosing is initiated, pre-morning dose (t_0) blood samples will be collected every 2 to 4 days via a home visit by a healthcare provider, or subject visit to an outpatient site to obtain serum bicarbonate and potassium results.

Whole blood samples (0.1 cc) will be gathered and prepared by trained staff, and an electrolyte panel (Cl⁻, K⁺, Na⁺, tCO₂) will be analyzed and reported via the portable point-of-care iSTAT System (Abbott Inc.).

The ADV7103 daily dose will be adjusted as necessary in increments of 8, 16, 24, 32, 40, or 48 mEq based on these results and instructions from the Investigator or her/his designee via phone. The interval between blood collections for this purpose may be extended with permission of the Medical Monitor.

A serum bicarbonate range of 21-27 mEq/L for subjects ≥ 4 years old and a range of 20-26 mEq/L for subjects < 4 years old prior to the morning dose (t_0) will be targeted during titration. ADV7103 dosage will be adjusted until at least the minimum target serum bicarbonate level is reached (ie, 21 or 20 mEq/L) or tolerability issues limit further dose increases. After a dose results in at least 2 consecutive serum bicarbonate levels (2-4 days apart) \geq the lower limit of the targeted range, the investigator will determine that dose titration is complete, and the subject will enter the Stabilization Phase of Period 2. If the serum bicarbonate level is in the targeted range but the serum potassium level is below 3.5 mEq/L, ADV7103 may continue to be uptitrated if ADV7103 continues to be tolerated and serum bicarbonate levels remain in the targeted range and serum potassium levels stay ≤ 5 mEq/L. If a maximum tolerated dose of ADV7103 delivers a serum bicarbonate level in the targeted range and the serum potassium level is ≥ 3.0 mEq/L and < 3.5 mEq/L, an acceptable dose has been identified, if the patient is not symptomatically hypokalemic. If a maximum tolerated dose of ADV7103 delivers a serum bicarbonate level in the targeted range and the serum potassium level is < 3.0 mEq/L, potassium supplementation (potassium hydrochloride) may be considered in consultation with the Medical Monitor and/or Sponsor Medical Representative.

Subjects who are unable to maintain the specified minimum serum bicarbonate level, despite maximum tolerated ADV7103 dose, will be able to enter the open-label extension study or return to their prior SOC at the discretion of the Investigator (in consultation with the Medical Monitor). In either case, these subjects will be discontinued from this study following completion of Visit 4 (early withdrawal) activities.

Stabilization Phase:

Once two consecutive serum bicarbonate levels are 21-27 mEq/L (inclusive) for subjects ≥ 4 years old and 20-26 mEq/L (inclusive) for subjects < 4 years old on the same ADV7103 dose, the subject will remain on this ADV7103 dose for 6-8 weeks (ie, Stabilization Phase of Period 2). During this phase, the subject will be monitored, with serum bicarbonate and potassium levels obtained every 2 weeks (or more often if determined by Investigator in consultation with Medical Monitor). At the end of the Stabilization Phase (ie, after 6-8 weeks post titration), the Stabilization Visit (ie, Visit 2) will take place at the investigational site or in the subject's home and via telehealth with the subject remaining on her/his stable dose of ADV7103. At this time, the Investigator will assess the eligibility of the subject for the Randomized, Double-blinded Withdrawal Period (Period 3).

Subjects eligible for randomization must meet all of the following criteria:

- a stable ADV7103 dose, for a minimum of six weeks;
- serum bicarbonate level within target range and serum potassium level ≥ 3.0 mEq/L, both at Visit 2;

- serum bicarbonate level is maintained in the corresponding age-specific normal range for at least 80% of available results obtained during the Stabilization Phase of Period 2;
- serum potassium level ≥ 3.0 mEq/L for at least 80% of available results obtained during the Stabilization Phase of Period 2;
- acceptable safety and tolerability as determined by the Investigator at the enrolling site.

Period 3, Randomized, Double-blinded Withdrawal:

As soon as practicable following Visit 2, eligible subjects taking their pre-randomization dose of ADV7103 will enter Period 3 (Visit 3) for an adequate period to monitor serum bicarbonate and potassium levels in the context of randomized, double-blinded treatment withdrawal. Period 3 start and randomization may occur in the evening prior to the first dose of blinded study product the next morning or early in the morning prior to the first dose of blinded study product. The duration of this efficacy assessment period (ie, Visit 3) will be approximately 6 days initially. The duration may be adjusted if approved by a blinded Data Monitoring Committee (bDMC) following review of data from a subset of at least 8 subjects to complete Period 3. The final study day of this period may be less than 24 hours in duration with discharge occurring after the evening dose and required data collection.

After baseline evaluations including laboratory tests are completed, subjects will either continue their stabilized ADV7103 dose or switch to a weight-matched identical-appearing placebo dose according to their randomized treatment assignment (without potassium supplementation). In the unexpected situation where these Period 3 baseline evaluations disclose a serum bicarbonate level < 18 mEq/L for subjects ≥ 4 years old and < 17 mEq/L for subjects < 4 years old and/or a serum potassium level < 3.0 mEq/L for all subjects, the subject will not be dosed with blinded study product. Rather, at the Investigator's discretion, the subject may receive open-label ADV7103 or a SOC regimen to address these abnormal laboratory results. When the clinical status of the subject allows, the subject will be discharged from Period 3 with instructions to continue open-label ADV7103 or a SOC regimen and within 4 weeks complete Visit 4 study exit evaluations.

The Investigator and staff (except for the pharmacist) will be blinded to Period 3 study product assignments, but not to laboratory results. The subjects will remain blinded to treatment throughout Period 3. In all subjects, serum bicarbonate and potassium levels will be measured every 24 hours following administration of the first dose of blinded study product (or more frequently if deemed necessary for safe subject management) through the remainder of Visit 3. Potassium will then be supplemented, as needed, for levels falling below 3.0 mEq/L.

If a subject's serum bicarbonate level becomes < 18 mEq/L for subjects ≥ 4 years old or < 17 mEq/L for subjects < 4 years old (study definition of metabolic acidosis), another serum bicarbonate result will be obtained within 2-4 hours or earlier if subject safety requires immediate intervention. If the repeat serum bicarbonate result confirms metabolic acidosis, the subject will have achieved the primary endpoint. If the second level is above the threshold, the subject will continue her/his current study product assignment and resume the regular schedule of blood sample collections. Subjects who develop metabolic acidosis during

the Withdrawal Period will be discontinued from study product in a blinded fashion and begin taking active ADV7103 at the next scheduled dosing time point (unless subject safety requires immediate intervention) at their pre-randomization dose. They will remain under investigator monitoring for approximately 6 days or until the metabolic acidosis (and any accompanying hypokalemia, if applicable) is corrected, whichever is longer. The frequency of laboratory evaluations for subjects who require correction of serum bicarbonate and/or potassium will be determined by the Investigator.

Potassium supplementation initiated during Period 3, if applicable, should be stopped at restoration of ADV7103 dosing.

If restoration of ADV7103 at the pre-randomization dose fails to restore targeted serum bicarbonate levels, the dose of ADV7103 will be increased to achieve this objective as long as it is tolerated. In order to maintain serum potassium levels ≥ 3.0 mEq/L, the dose of ADV7103 may be increased or a potassium supplement may be added to ADV7103 (or the dose of these may be increased if already being taken by the subject), if deemed appropriate by the Investigator. If ADV7103 (with or without a potassium supplement) fails to return serum bicarbonate and potassium levels to pre-randomization levels at the maximally tolerated ADV7103 dose, the Investigator (in consultation with the Medical Monitor and subject/legal guardian) will determine if the subject should continue ADV7103 at a dose that provides acceptable (though not targeted) control of serum bicarbonate and potassium levels in the ARENA 2 extension study, or return to her/his SOC regimen. In either case, the subject will be discontinued from this study after completing Visit 4 activities.

Period 4, Study Completion:

Subjects who were stabilized on ADV7103 during this study and adherent to the protocol will be offered the opportunity to receive open-label ADV7103 as part of a separate extension study. Subjects may elect to be administered ADV7103 after completing Period 3 (within 4 weeks of Period 3 completion); the subject may complete Visit 4, and the initial extension study visit will take place at the same time as the exit visit (Visit 4) from this study (following informed consent/assent). Subjects declining participation in the extension study can elect to return to their previous SOC regimen after completing Period 3. Within 4 weeks of Period 3 completion, the subject may complete Visit 4 as the exit visit from this study.

Diagnosis and main criteria for inclusion:

Inclusion criteria:

1. Female or male subjects ≥ 6 months of age and ≤ 65 years of age at time of consent;
2. Subject presents with a previous diagnosis of primary dRTA of at least 4 months duration for subjects < 12 years of age, and at least one year for those ≥ 12 years of age, based on documented history of non-anion gap, hyperchloremic, hypokalemic metabolic acidosis;
3. Subject requires ≥ 0.9 mEq/kg/day of alkali therapy to maintain serum bicarbonate levels above the LLN for the laboratory providing results;
4. Urine pH > 5.5 and serum bicarbonate > 18 mEq/L for subjects ≥ 4 years old or > 17 mEq/L for subjects < 4 years old on alkali therapy and potassium

supplementation (if indicated) on at least one occasion for each within 6 months prior to Visit 1;

5. Subject or parent/guardian is willing and able to understand and sign informed consent and willing to comply with protocol instructions; child assent when appropriate; and
6. Heterosexually active female subjects of childbearing potential and non-sterilized males must use at least one of the following acceptable birth control methods from informed consent through 7 days after the last dose of study product:
 - a. Double-barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository)
 - b. Established use of oral, injectable, or implanted hormonal methods of contraception
 - c. Placement of an intrauterine device or intrauterine system
 - d. Abstinence.

Females of childbearing potential are those who have reached the onset of menarche (or 8 years of age, whichever comes first) and are not postmenopausal (≥ 1 year without menses prior to Visit 1)], surgically sterile, or status post hysterectomy (≥ 1 month prior to Visit 1). From informed consent through 7 days after the last dose of study product, female subjects must agree to refrain from egg donation and male subjects must agree to refrain from sperm donation.

Exclusion criteria:

1. Female subject who is pregnant or lactating or has plans for pregnancy during the study;
2. Subject has evidence of proximal tubule dysfunction (eg, hypophosphatemia, low serum uric acid, glycosuria, or amino aciduria);
3. Subject presents with another diagnosed condition as a potential etiology for her/his dRTA (eg, systemic lupus erythematosus, Sjogren's syndrome), in the opinion of the Investigator;
4. Subject requires therapy with potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, trimethoprim, drospirenone and other progestins, nephrotoxic antibiotics, penicillins, tacrolimus, or medications known to delay gastric emptying or otherwise interfere with absorption of study product;
5. Subject has evidence of obstructive uropathy or other findings on renal ultrasound associated with Visit 1 expected to require intervention during the course of the study, in the opinion of the Investigator;
6. Subject has any of the following laboratory abnormalities associated with Visit 1:
 - a. AST and/or ALT > 1.5 x upper limit of normal (ULN)
 - b. Serum potassium > 5.0 mEq/L or < 3.0 mEq/L or hypokalemia accompanied by clinical symptoms (eg, muscle cramps) or significant ECG changes (eg, T wave depression, U wave elevation)
 - c. Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² (according to the updated Schwartz formula for children and Chronic Kidney Disease – Epidemiology Collaboration [CKD-EPI] equation for adults)
 - d. Total bilirubin $> \text{ULN}$, except with known Gilbert's disease.

7. Subject has been hospitalized or had outpatient surgery (other than minor skin and dRTA disease-related procedures or ear tube placement) in the past 6 months or is planning surgery in the next 6 months;
8. In the opinion of the Investigator, the subject has a major medical or psychiatric condition (eg, significant cardiac disease, schizophrenia) or an unstable condition (eg, uncontrolled hypertension, asthma, diabetes, hypercholesterolemia, or cardiac disease) that would potentially interfere with the subject safely completing the study;
9. In the opinion of the Investigator, the subject has a history of difficulty taking oral medication and/or conditions that may hamper absorption of the study drug (eg, any difficulty of swallowing, malabsorption, delayed gastric emptying, esophageal compression, intestinal obstruction, or other chronic gastrointestinal disease);
10. Self-reported or parent/guardian reported alcohol abuse or drug abuse within the past 12 months;
11. Subject is a solid organ or bone marrow transplant recipient;
12. Subject has a history of malignancy within 5 years prior to Visit 1, except for localized skin or cervical carcinoma; or
13. Subject is known to have an allergy or intolerance to any ADV7103 or placebo constituents.

Test study product, dosage and mode of administration:

ADV7103 is a combination of potassium citrate granules (ADV7103-CK) and potassium bicarbonate granules (ADV7103-BK) and has alkalinizing properties.

The ADV7103-CK granules are prepared as 2 mm green coated prolonged-release granules for oral administration containing approximately 67% of potassium citrate monohydrate. The coating allows a release over 2-3 hours.

The ADV7103-BK granules are prepared as 2 mm white coated prolonged-release granules for oral administration containing approximately 66% of anhydrous potassium hydrogen carbonate. The combination of matrix and coating polymer allows approximately zero-order release over 10 to 12 hours.

Each dose of ADV7103 contains a fixed ratio of 1/3 of ADV7103-CK (potassium citrate) and 2/3 of ADV7103-BK (potassium bicarbonate) based on the mass of active substances. The strength is 6.44 ($\pm 10\%$) mEq/g of ADV7103 (alkalinizing power).

Reference study product, dosage and mode of administration:

Placebo is a combination of 2 mm green coated lactose granules and 2 mm white coated lactose granules. Each dose of placebo contains a fixed ratio of 1/3 of green granules and 2/3 of white granules.

Criteria for evaluation:

Efficacy

Primary endpoint:

- Proportion of subjects with metabolic acidosis during the Withdrawal Period. Metabolic acidosis is defined as 2 consecutive serum bicarbonate levels < 18 mEq/L for subjects ≥ 4 years old and < 17 mEq/L for subjects < 4 years old.

Secondary endpoints:

- Proportion of subjects with 2 consecutive serum bicarbonate levels below the LLN for age during the Withdrawal Period;
- Proportion of subjects developing new onset hypokalemia during the Withdrawal Period. Hypokalemia is defined as a serum potassium level < 3.5 mEq/L.
- Time to metabolic acidosis during the Withdrawal Period;
- Time to new onset hypokalemia during the Withdrawal Period;
- Proportion of subjects with both metabolic acidosis and new onset hypokalemia during the Withdrawal Period;
- Mean urinary calcium/creatinine ratio associated with Visit 1, Visit 2;
- Mean change in urinary calcium/creatinine ratio during the Withdrawal Period;
- Mean urinary citrate/creatinine ratio associated with Visit 1, Visit 2;
- Mean change in urinary citrate/creatinine ratio during the Withdrawal Period;
- Frequency and severity of all adverse events (AEs), TEAEs, and all study product-related AEs;
- Frequency of SUSARs;
- Frequency of hyperkalemia;
- Frequency of serum potassium levels < 3.0 mEq/L;
- Frequency of serum potassium levels < 3.5 mEq/L;
- Changes in other serum and urine safety laboratory results from SOC baseline;
- Frequency of urine pH > 8.5 in Periods 1, 2, and 3.

Exploratory endpoints:

- Gastrointestinal tolerability scores, on an age-appropriate scale;
- Urinary SS calcium oxalate, SS calcium phosphate, and SS uric acid levels;
- Study product acceptability and satisfaction scores, with age-appropriate questionnaires;
- Palatability, ease of administration/swallowing, and number of daily product intakes scores, on age-appropriate scales;
- Results from quality of life age-appropriate questionnaires and semi-structured interviews.

Statistical methods:*Number of subjects*

Approximately 40 subjects will enter the Open-label Lead-in Period (Period 2), so that at least 32 complete the Withdrawal Period (Period 3). Sixteen evaluable subjects per arm provides at least 90% power to show superiority of ADV7103 over placebo in the proportion of subjects who develop metabolic acidosis up to Day 6. This calculation assumes that approximately 85% of placebo subjects and 15% of ADV7103 subjects will develop metabolic acidosis. Significance will be assessed at the 2-sided 5% level.

Randomization will be stratified according to the following age categories:

- 6 months – 23 months old
- 2-11 years old
- ≥ 12 years old

Analysis sets

The Intent-to-Treat (ITT) analysis set is defined as all randomized subjects in Period 3. The Modified Intent-to-Treat (mITT) analysis set is defined as all subjects in the ITT Analysis Set who received study product in Period 3 and who have both a baseline and at least one post-baseline efficacy assessment in Period 3. The Per-Protocol (PP) analysis set is defined as all subjects in the mITT analysis set who have no major protocol deviations affecting the assessment of efficacy. Membership of the PP analysis set will be confirmed prior to unblinding the data. The ITT, mITT and PP analysis sets will be analyzed per planned study product assignment.

The Safety analysis set is defined as all subjects who receive at least one dose of study product in any period or phase. The Safety analysis set will be analyzed per actual study product received.

Primary analysis

The primary endpoint is the proportion of subjects with at least one episode of metabolic acidosis up to Day 6 of Period 3. All non-missing serum bicarbonate measurements from first study product dose in Period 3 to Day 6 (≤ 12 hours post-last dose) or early discontinuation will be considered.

The primary analysis will be based on the ITT set. The primary study product comparisons will be made using the two-sided Cochran-Mantel-Haenszel (CMH) test stratified by age category.

Secondary analyses

The proportion of subjects with significant hypokalemia up to Day 6 of Period 3 will be similarly analyzed with a CMH test.

The proportion of subjects who fail to maintain serum bicarbonate levels ≥ 18 mEq/L for subjects ≥ 4 years old or ≥ 17 mEq/L for subjects < 4 years old up to Day 6 (during Period 3) will be compared with the CMH test. Time to first episode of metabolic acidosis and time to first episode of hypokalemia will be compared with a log-rank test. Mean change in serum bicarbonate level, mean change in serum potassium level, mean change in urine calcium/creatinine ratio, and mean change in urinary citrate/creatinine ratio will be compared at a last observation carried forward (LOCF) endpoint with an analysis of covariance model, having study product assignment and age category as factors and baseline as a covariate.

Descriptive summaries will be provided by study product, and overall for the Lead-in Period (Period 2).

Safety data will be summarized in the safety analysis set by study product, and over time, for each period separately and overall.

Multiplicity adjustment strategy

A sequential gatekeeping approach will be used to control the Type I error rate for testing primary and secondary efficacy endpoints.

Additional analyses

The primary and secondary analyses will be repeated on the mITT and PP Sets. Furthermore, selected sensitivity analyses will be performed on the ITT set including multiple imputation, and worst-case methods.

Subgroup analyses

A subgroup analysis of key efficacy and safety data will be performed by age category. Given the expected small sample size, no study product comparison will be made.

Interim analysis

No formal interim analysis of efficacy is planned.

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3. LIST OF ABBREVIATIONS AND TERMS

The following abbreviations and terms are used in this study protocol.

Table 2: Abbreviations and Terms

Abbreviation or Term	Explanation
ACCEPT	Chronic Treatment Acceptance Questionnaire
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
bDMC	Blinded data monitoring committee
BK	Potassium bicarbonate
BL	Baseline
CaOx	Calcium oxalate
CaP	Calcium phosphate
cGMP	Current good manufacturing practices
CK	Potassium citrate
CKD-EPI	Chronic Kidney Disease – Epidemiology Collaboration
CMH	Cochran-Mantel-Haenszel
CRO	Contract research organization
CSR	Clinical study report
dRTA	Distal renal tubular acidosis
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ePRO	Electronic patient reported outcome(s)
EU	European Union
g	Gram(s)
GCP	Good clinical practice
GI	Gastrointestinal
HCO ₃ ⁻	Bicarbonate
IB	Investigator's Brochure
ICH	International Council for Harmonisation

Table 2: Abbreviations and Terms (Continued)

Abbreviation or Term	Explanation
IEC	Independent ethics committee
IND	Investigational new drug
IP	Investigational product
IRB	Institutional review board
ITT	Intent-to-treat
K ⁺	Potassium
KCl	Potassium chloride
kg	Kilogram(s)
L	Liter(s)
LD ₅₀	Lethal dose in 50% of animals
LLN	Lower limit of normal
LOCF	Last observation carried forward
mEq	Milliequivalent(s)
mg	Milligram(s)
mITT	Modified intent-to-treat
mmol	Millimole(s)
NOAEL	No observed adverse effect level
PedsQL	Pediatric Quality of Life Inventory Generic Core Scale
PI	Principal Investigator The Investigator who leads the study conduct at an individual investigational site. Every study center has a Principal Investigator.
PP	Per protocol
RTA	Renal tubular acidosis
SAE	Serious adverse event
SOC	Standard of care
SOP	Standard operating procedure
SP	Study period
SS	Supersaturated
SUSAR	Suspected unexpected serious adverse reaction
t ₀	Prior to the morning dose of study product

Table 2: Abbreviations and Terms (Continued)

Abbreviation or Term	Explanation
TD ₅₀	Tumor-free dose in 50% of animals
TEAE	Treatment emergent adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
uDMC	Unblinded data monitoring committee
ULN	Upper limit of normal
VAS	Visual analog scale

4. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

4.1. Background Information

4.1.1. Investigational Products (Study Products)

The investigational products (IPs) to be administered during the study are the following:

- the test product, ADV7103 prolonged-release granules for oral administration;
- placebo granules for oral administration (product weight and appearance identical to ADV7103).

Presently, standards of care for the treatment of distal renal tubular acidosis (dRTA) are alkalinizing agents prepared as compounded drugs: potassium citrate, potassium bicarbonate, and sodium citrate or sodium bicarbonate, usually as powder prepared in capsules to be swallowed or opened for dilution in a bottle of water ([Chan, 2001](#)).

The test product, ADV7103, is an oral formulation of two alkalinizing salts. It is composed of both 3-hour prolonged-release potassium citrate granules and 10-hour prolonged-release potassium bicarbonate granules which are released successively throughout the gastrointestinal tract.

The exogenous load of alkalinizing salts leads to an increase of blood bicarbonate in order to maintain blood pH at or near 7.4 whenever usual homeostatic mechanisms are disrupted due to disease, as in dRTA. The exogenous load of potassium will lead to an increase in serum potassium as hypokalemia frequently accompanies acidosis in dRTA patients.

4.1.2. Distal Renal Tubular Acidosis

Distal renal tubular acidosis is a condition characterized by a renal defect in hydrogen ion secretion localized in the distal tubules inducing a metabolic acidosis (low blood pH; ie, less than 7.35). In dRTA the same tubular defect that results in metabolic acidosis also induces hyperchloremia, hypokalemia and hypercalciuria, with a relatively high urine pH (> 5.5). Consequences of these changes include osteomalacia in adults, short stature or rickets in children, and nephrocalcinosis or nephrolithiasis which can compromise kidney function. Distal renal tubular acidosis can be an inherited condition or a secondary reflection of a large spectrum of causes. In some genetic forms, deafness is linked to specific mutations.

There is no cure for primary dRTA. The treatment of dRTA is symptomatic and consists of normalization of blood pH using alkali therapy. Correction of metabolic acidosis in dRTA patients improves the clinical spectrum, reducing stone risk and promoting normal or near-normal growth if treatment is instituted early and effectively. Maintenance of stable acid-base parameters with ongoing treatment is necessary to observe clinical improvement, requiring an average alkali dose of 2-4 mEq/kg/day in adults and up to 10 mEq/kg/day in the youngest patients. Alkali therapy appears to have no documented effects (beneficial or otherwise) on hearing abnormalities.

Tripotassium citrate or sodium bicarbonate is the most frequently used treatment. Liver metabolism of citrate to bicarbonate corrects acidosis, and tripotassium citrate is generally better tolerated than sodium bicarbonate (Jungers, 2008; Bouzidi, 2011). Moreover, potassium citrate limits the frequency of hypokalemia and limits renal calcium crystallization through chelation of calcium.

4.1.3. Summary of Preclinical Studies

Potassium citrate and potassium bicarbonate have been administered orally alone or in combination for decades in the following ways:

- active principles (therapeutically effective as short-acting alkalinizing agent to treat acidosis, hypocitraturia, hypokalemia, and crystalluria; citrate also acts as a chelating agent);
- pharmaceutical excipients used for their buffering properties;
- food additives for their anti-oxidative properties, pH control, and flavor enhancement. As food additives, potassium citrate and potassium bicarbonate were evaluated and classified as “generally recognized as safe” substances according to Food and Drug Administration regulations.

Finally, citrate and bicarbonate are natural constituents and common metabolites of plants, animals, and humans. Bicarbonate is the principal form in which carbon dioxide is transported in blood and is a major blood buffer, helping maintain pH of blood within a narrow physiologic range. Carbon dioxide is produced in the mitochondria of all cells, diffusing into the blood and is almost instantaneously converted by carbonic anhydrase to bicarbonate. Citrate is an intermediate metabolite of the Krebs cycle. On average a human produces 2 kg of citrate per day, which is immediately metabolized, as is ingested citrate, to bicarbonate. Also, citrate can be transported out of mitochondria into the cytoplasm and then be involved in fatty acid synthesis.

Potassium is an essential constituent of the body for intracellular osmotic pressure and buffering, cell permeability, acid-base balance, muscle contraction, and nerve function.

Non-clinical data have been submitted to regulatory authorities worldwide by various companies or institutions in the food industry for the purpose of market authorizations. Data concerning toxicology assessment of each of these alkalinizing salts or their associated anions are summarized hereafter. Studies concerning the toxicology profile of the combination potassium citrate and potassium bicarbonate product have not been performed. However, these salts have a multifaceted use history over decades that demonstrates a highly favorable benefit-risk profile in humans.

Since citrate and bicarbonate are well-characterized natural body constituents with a significant history of safe use as therapeutics or food additives, no additional non-clinical studies are planned in the ADV7103 development program.

4.1.3.1. Citrate

In 3 chronic feeding studies using rats, no significant treatment related effects were observed after administration of citric acid. In chronic feeding studies using dogs and rats, no significant treatment related effects were observed after administration of potassium sodium hydrogen

citrate oral doses up to 1.2 g/kg or 3 g/kg. The no observed adverse effect level (NOAEL) for repeated dose toxicity is 1.2 g/kg/day in rats, 1.4 g/kg/day in dogs, and 1.5 g/kg/day in rabbits. In 3 subchronic studies, citric acid did not affect or slightly affected the growth rate of rats. In a subchronic study, daily oral administration of citric acid to dogs did not produce abnormalities. In an acute toxicity study, the lethal dose in 50% of animals (LD₅₀) of citric acid was determined to be approximately 5 g/kg body weight in mice and 12 g/kg body weight in rats. Potassium citrate did not appear to be carcinogenic, mutagenic, or teratogenic (citric acid or potassium sodium hydrogen citrate). No data have been generated concerning the immunotoxicity profile of potassium citrate. Nevertheless, due to the significant body production of citrate and extensive use of potassium citrate, immunotoxicity is not anticipated.

4.1.3.2. Bicarbonate

Potassium bicarbonate is considered slightly toxic with an acute oral LD₅₀ in rats varying between 4220 mg/kg and 2064 mg/kg. In 4 experiments in rats, the carcinogenic potency of potassium bicarbonate was assessed in the urinary bladder. A mean tumor-free dose in half of test animals (TD₅₀) of 13.0 (6.4 and 54.4) g/kg/day was determined and tumors induced were principally transitional-cell papilloma and transitional-cell carcinoma. No data have been generated concerning the mutagenic, teratogenic, immunotoxic profile of potassium bicarbonate because of the high degree of natural exposure (body produces several kilograms of bicarbonate a day).

4.1.3.3. Potassium

Acute oral toxicity of potassium (administered as potassium chloride, KCl) in mammals is low (LD₅₀ = 3020 mg/kg). In humans, acute oral toxicity is rare because large single doses induce nausea and vomiting, and because potassium is rapidly excreted in the absence of any pre-existing kidney damage. For repeated dose toxicity, a NOAEL at 1820 mg/kg/day in rats can be retained. No gene mutations were reported in bacterial tests, with and without metabolic activation. No evidence of treatment-related carcinogenicity was observed in rats administered up to 1820 mg KCl/kg body weight/day through food in a 2-year study. A developmental study revealed no fetotoxic or teratogenic effects of KCl in doses up to 235 mg/kg/day (mice) and 310 mg/kg/day (rats). No fertility studies have been identified in a literature search. However, in the 2-year study in rats, no changes were reported in the absolute and relative organ weights of the testis, seminal vesicle, and prostate.

4.1.4. Summary of Clinical Studies

Study B03CS was a phase 1, double blinded, placebo controlled, 2-period, incomplete crossover study conducted in 16 healthy adult subjects to investigate the safety, tolerability, and pharmacodynamics of ADV7103.

Since the active principles of ADV7103 are endogenous substances and homeostatic mechanisms are fully functional in healthy adult subjects, it was not possible to determine the pharmacokinetic profiles of ADV7103 constituents and to evaluate their effects in the blood. Therefore, the main objective was to assess pharmacodynamic effects on urine pH of oral doses of ADV7103 after 5 days of treatment. It has been demonstrated that ADV7103 produces alkalization of the urine over at least 8 hours, which supports a dosing frequency limited to

2 times a day. The observed safety profile of ADV7103 was favorable: only 4 adverse events that may be attributed to the IP were observed (2 headache, 1 vertigo, and 1 nausea), and no serious adverse event occurred during the study. Contrary to current alkalinizing agents that are associated with frequent gastrointestinal side effects, only one episode of nausea of mild intensity was observed after administration of the highest dose of ADV7103 (50/100 mg/kg of ADV7103 (ie, approximately 100 mEq of alkali load) for a total of 240 doses without meals. Moreover, no hyperkalemia was observed when blood samples were obtained 2 hours after ADV7103 intake.

Thus, this phase 1 study demonstrated a favorable safety and tolerability profile for ADV7103 with urine alkalinizing effects of a duration that supports twice daily dosing. Improved gastrointestinal tolerability relative to other alkalinizing agents was apparent. Additional details are presented in the ADV7103 investigator's brochure (IB).

A phase II/III multicenter, open-label, non-inferiority, sequential study (B21CS) was conducted in order to evaluate the efficacy, safety, tolerability and acceptability of ADV7103 compared to the standard of care (SOC) in pediatric and adult subjects with dRTA.

Thirty-two (32) subjects have completed the study, including 7 adults, 8 adolescents (12-17 years old), 14 children (4-11 years old) and 3 infants (0.5-3 years old). Thirty (30) of them have been fully evaluable.

The subjects participated in three consecutive study periods:

- First Study Period (SP I) of 5 days: the subjects receive their current alkali treatment so called Standard of Care (SOC);
- Second Study Period (SP II) of 3 to 30 days: switch from SOC to ADV7103 twice a day for a titration phase up to the optimal dose;
- Third Study Period (SP III) of 5 days: maintenance of treatment with ADV7103 twice a day at the fixed optimal dose.

The primary objective of Study B21CS was to evaluate the relative efficacy of ADV7103 and SOC on correcting metabolic acidosis as measured on pre-morning dose blood bicarbonate levels after 4 days of treatment at steady state (comparison of residual blood concentration of bicarbonate on SPIII Day 2 t0, Day 3 t0, Day 4 t0 to residual blood concentration of bicarbonate on SPI Day 2 t0, Day 3 t0, Day 4 t0).

Preliminary data revealed that blood bicarbonate levels were lower after SOC than after ADV7103 administration. Using a target therapeutic level of blood bicarbonate concentration of 22 mmol/L, SOC therapy provided suboptimal correction of acidosis for the pediatric subjects, with high variability observed in the adult subjects. When switched to ADV7103 twice daily, the blood bicarbonate concentrations increased overall indicating good control of the metabolic acidosis, with twice daily administration of ADV7103 at least as effective as SOC therapy.

The doses of ADV7103 taken in this study ranged from 0.75 mEq/kg/day to 8.45 mEq/kg/day, for periods from 15 to 43 days. The maximal dose provided was for a child who needed 6 mEq/kg/day, or 334 mEq/day. The doses of alkalizing agents used across the age groups of subjects indicated that, while the total daily dose of alkalizing agent was similar with SOC and ADV7103 for adults and adolescents, it increased in younger children and infants. However, the

doses of ADV7103 are in accordance with the doses of alkalinating agents reported in the literature regardless of age.

These preliminary data, in combination with clinical experience, indicate that the alkali dose was not optimized with the SOC treatment, particularly in these younger age groups. From the investigator's point of view, the SOC dosing may be limited by gastrointestinal issues, whereas ADV7103, better tolerated by subjects, may facilitate more appropriate dosing. Additionally, SOC typically requires administration several times a day, which leads to adherence issues; alternatively, twice daily administration of ADV7103 (morning and evening), may promote better adherence.

A secondary objective of Study B21CS was to evaluate the relative efficacy of ADV7103 and SOC in correcting hypokalemia. Blood potassium concentrations were restored with potassium salts as part of SOC or as add-on potassium supplements (when not directly included in SOC preparations) and with ADV7103 in most subjects. Nevertheless, the cases of hypokalemia were significantly different after SOC therapy and after ADV7103 therapy, 9 cases versus 1 case, respectively.

During the phase II/III study (B21CS), the SOC dose of the subject was taken at the optimal dose for a first study period (SPI) of 5 days, then switched to ADV7103 with a second period of titration (SPII of 30 days maximum) followed by a third period (SPIII) of 5 days at the optimal dose.

There was a lower proportion of subjects who reported TEAEs during the comparable 5-day steady state SPs. A total of 10.8 % of subjects reported at least one TEAE whilst receiving their SOC during SP I compared to 3.1 % of subjects during SP III. During SPII, 26.5 % of the subjects reported at least one TEAE for ADV7103 doses below or equal to the doses received in SPIII.

All TEAEs in SPII were gastro-intestinal disorders. A further evaluation of the reported gastrointestinal events demonstrated that of the 5 subjects who reported such events when receiving SOC, 2 reported moderate events and 3 reported mild events. None of the 4 subjects who continued into SP III (Subject 005-003 did not continue) reported gastrointestinal events while receiving ADV7103 during this period). Only one subject reported a mild gastrointestinal TEAE following treatment with ADV7103 in SP III.

During the currently ongoing B22CS Study, the preliminary data at 6 months show that only 2 subjects reported each 2 TEAEs, all of mild intensity, 3 possibly and 1 probably related to the study product (3 gastro-intestinal AEs (diarrhea, gastro-intestinal pain and dyspepsia) and alopecia. The sole SAE in B22CS, (pain in the area of the left kidney requiring hospitalization was reported in a 10-year old subject following 14 months of ADV7103 treatment) was considered as a suspected unexpected serious adverse reaction (SUSAR) as it was unlisted at the time in the Investigator Brochure. This SAE was stated unlikely related to the study product, but rather related to a complication of the disease, however the relation to the study product cannot be totally excluded.

The efficacy and safety of potassium bicarbonate and potassium citrate salts are well known both in adults and in children. These active principles have been used for decades singly or together as alkalinizing treatment and are also endogenous substrates. Potassium is used alone for

prophylaxis or treatment of hypokalemia; as a nutrient, dietary supplement, and food additive; and is an essential constituent of the body for intracellular osmotic pressure and buffering, cell permeability, acid-base balance, muscle contraction, and nerve function.

4.2. Rationale for the Current Clinical Study

4.2.1. Rationale for the Study Design and Objectives

This is a phase 3, prospective, multicenter, randomized, double-blinded, placebo-controlled, study product withdrawal study comparing the efficacy of ADV7103 versus placebo in preventing the development of metabolic acidosis defined by serum bicarbonate level in pediatric (6 months to <18 years of age) and adult (18 to 65 years of age) subjects with primary dRTA.

This study involves 4 study periods. Periods 1 and 2 are performed at the enrolling investigational site on an outpatient basis. During Period 1, subject eligibility is ascertained and baseline information is collected while the subject continues to take her/his SOC regimen. This period ensures that subjects representative of the primary dRTA population with appropriate disease severity are enrolled.

Period 2 involves switching from a stable SOC regimen to open-label ADV7103. The initial ADV7103 alkali daily dose will be similar to the SOC alkali daily dose in mEq. The ADV7103 daily dose will be titrated to achieve a serum bicarbonate range of 21-27 mEq/L for subjects ≥ 4 years old and a range of 20-26 mEq/L for subjects < 4 years old prior to the morning dose (t_0). Dose titration is accomplished to ensure that ADV7103 results in a desired serum bicarbonate level prior to the morning dose. Dose titration is followed by a 6-8 week period of continuing to monitor serum bicarbonate and potassium levels in order to monitor the safety, efficacy, and tolerability of ADV7103 over a protracted period and ensure that the subject is clinically stable on ADV7103. At the end of this period, the enrolling site Investigator will assess the eligibility of the subject for the Randomized, Double-blinded Withdrawal Period (Period 3).

Subjects eligible for randomization must meet all of the following criteria:

- a stable ADV7103 dose, for a minimum of six weeks;
- serum bicarbonate within level target range and serum potassium level ≥ 3.0 mEq/L, both at Visit 2;
- serum bicarbonate level is maintained in the corresponding age-specific normal range for at least 80% of available results obtained during the Stabilization Phase of Period 2;
- serum potassium level ≥ 3.0 mEq/L for at least 80% of available results obtained during the Stabilization Phase of Period 2;
- acceptable safety and tolerability as determined by the Investigator at the enrolling site.

Serum bicarbonate and potassium levels should be checked at least every 4 weeks between Visit 2 and admission to Period 3 if the time between these encounters becomes protracted.

Randomization will be completed after informed consent (and assent, when appropriate) for Period 3 is obtained and prior to blinded study product administration. It is expected that subjects

will consent (or assent, when applicable) to participation in Periods 1 through 4 during the Screening Visit. Obtaining a separate informed consent/assent for Period 3 will be at the discretion of the IRBs providing oversight to the investigational sites selected for Period 3.

Subjects meeting all criteria for continuation will be admitted into Period 3. Period 3 involves administration of blinded ADV7103 or placebo to demonstrate the efficacy of ADV7103 in preventing metabolic acidosis. Randomization and blinding limits various sources of bias in the assessment of study subjects. Although the Investigator and all site staff (except for the pharmacist) will be blinded to study product, they will have full access to test results and other clinical information required to care for the subject. The planned 6-day duration of Period 3 is estimated to be an adequate length time to observe potential decreases in serum bicarbonate that are associated with administration of placebo; however, a blinded Data Monitoring Committee (bDMC; independent of the unblinded Data Monitoring Committee, or uDMC) will review data from at least 8 subjects completing Period 3 and determine whether Period 3 duration may be adjusted.

Period 4 consists of the time following discharge from Period 3 to the study exit visit (ie, Visit 4). Subjects will return within 4 weeks of discharge for study completion activities. Visit 4 may be completed following discharge activities on the same day.

Most study objectives are associated with characterizing the pharmacodynamic effects of ADV7103 on serum bicarbonate and potassium levels and its safety/tolerability profile including potentially improved gastrointestinal tolerability. This study design enables achievement of these objectives while providing for the safety of study subjects. Although comparisons with SOC are across study periods, they should be informative. Duration of study participation is relatively short, limiting potential impact of period effects.

Additional objectives are intended to enhance understanding of other characteristics of ADV7103 including an improved product acceptability profile and effects on urinary calcium excretion.

4.2.2. Rationale for the Study Population

The study population is composed of subjects who have a diagnosis of primary, hypokalemic (classic, Type 1) dRTA without evidence of another cause or proximal tubular dysfunction. Eligibility criteria were chosen to facilitate enrollment of dRTA subjects representative of the broader primary dRTA population (including adults, adolescents, children, and infants ≥ 6 months old) without conferring an unacceptable degree of risk to study subjects, particularly pediatric subjects. These criteria should enable informative efficacy, acceptability, and safety assessments of ADV7103 without undue influence from potentially confounding factors (eg, difficulty swallowing, gastrointestinal signs and symptoms, hepatic or renal impairment, respiratory or cardiac disease). Since ADV7103 is composed of potassium salts, subjects who are prone to hyperkalemia (Type IV dRTA) and/or have severe renal impairment will be excluded from the study.

In order to minimize risks and constraints for the most vulnerable age groups and account for differences in renal maturation among these age groups, a staggered enrollment approach will be implemented. Starting with the oldest group (≥ 12 years), each subsequently younger group will be randomized after 4 subjects from the preceding older age group have completed the

Withdrawal Period and the uDMC approves randomization in the next younger group. During uDMC review of data from each age group, enrollment into that age group may continue unless the uDMC recommends cessation of this activity. The uDMC may request additional subjects complete the study in the age group under uDMC review prior to approving randomization of the next younger group. Enrollment of an equal number of subjects in each age group will not be required; for pragmatic reasons, enrollment in the youngest age group may be fewer than 4 subjects. After reviewing data from randomized subjects who do not complete the Withdrawal Period, the uDMC may recommend changes to the protocol (including, but not limited to, increasing the total number of subjects enrolled in the study) to ensure a reasonable balance of early withdrawals between treatment groups. Lastly, if laboratory data, clinical symptoms, and cardiac monitoring data warrant, the uDMC may recommend modification of cardiac monitoring in this study.

A bDMC (independent of the uDMC) will review data from a subset of at least 8 subjects to complete the Withdrawal Period to determine if the duration of inpatient confinement may be adjusted.

4.2.3. Dosing Rationale

Doses of ADV7103 and SOC regimens will vary from subject to subject based on a variety of factors including age, diet, and disease severity. In an effort to maintain a stable blood pH in subjects, the initial dose of ADV7103 in Period 2 will approximate the SOC dose in mEq of alkali administered.

The ADV7103 daily dose will be adjusted by the Investigator to achieve serum bicarbonate level in the range of 21 - 27 mEq/L for subjects ≥ 4 years old and a range of 20 - 26 mEq/L for subjects < 4 years old prior to a morning dose. In order to achieve a given alkalinizing effect, higher doses of ADV7103 (a prolonged-release formulation) may be needed compared to the immediate release formulations of other products. These doses have been shown to be safe in subjects including infants ([Chan, 2001](#); [Rodriguez-Soriano, 1982](#); [Kossoy, 1986](#); data on file at Advicenne).

It is anticipated that serum potassium levels within an acceptable range will accompany a stable ADV7103 dose that achieves the target serum bicarbonate level.

4.3. Overall Risks and Benefits

Potassium citrate and potassium bicarbonate are well-characterized substances. The safety profiles of these drugs are described in the ADV7103 IB.

4.3.1. Known and Potential Risks

The risks related to potassium citrate and potassium bicarbonate are primarily gastrointestinal (GI) adverse events (AEs) and hyperkalemia with potential cardiac consequences. The proposed prolonged-release formulation (ADV7103) should allow avoiding both GI intolerance and significant hyperkalemia, as already demonstrated during the Phase I B03CS study in healthy subjects. Data from the B21CS and B22CS studies do not indicate major risks related to hyperkalemia.

The required doses of ADV7103 in this study are anticipated to be lower than the maximal recommended intake of potassium per day (Mandal, 1997; EFSA, 2006). Electrolyte balance is tightly regulated and adaptive to exogenous intake via homeostatic mechanisms. The renal elimination of potassium increases and reabsorption decreases with increased potassium intake in healthy kidneys (Hannedouche, 2007). Patients with hypokalemic dRTA typically require potassium supplementation in addition to alkalizing therapy. Subjects with severe renal impairment are excluded from this study.

Females of childbearing potential can be enrolled in the study. The reproductive toxicity studies show no teratogenic or embryotoxic/fetotoxic effects of various forms of citrate (refer to ADV7103 IB). In a clinical study, 46 pregnant cystinuric subjects treated with sodium bicarbonate and potassium citrate continued treatment throughout pregnancy with no effect on the fetus (Gregory, 1983).

Risks associated with dRTA subjects receiving placebo (representing withdrawal of alkalinizing agent and potassium supplement) include development of metabolic acidosis and its associated clinical manifestations, hypokalemia, as well as allergy or intolerance to components of the placebo formulation. All subjects in the Withdrawal period will be closely monitored, with frequent monitoring of serum bicarbonate and potassium levels to minimize potential risks of acidosis and hypokalemia.

4.3.2. Known and Potential Benefits

Some direct benefits of ADV7103 relative to SOC regimens are anticipated for subjects participating in this study:

- improved gastrointestinal tolerability as a result of slow release of the alkalinizing agents throughout the GI tract;
- decreased reluctance to take the medication since it is tasteless;
- decreased frequency of administration (twice daily) due to the protracted effect of ADV7103 which may limit the risk of metabolic acidosis in the overnight period; and
- potential reduction of some disease consequences (eg, osteomalacia, short stature) which reflect erratic control of acidosis.

5. STUDY OBJECTIVES

5.1. Primary Objective

- Compare the efficacy of ADV7103 versus placebo in preventing metabolic acidosis, defined as 2 consecutive serum bicarbonate levels < 18 mEq/L for subjects ≥ 4 years old and < 17 mEq/L for subjects < 4 years old, during the Withdrawal Period.

5.2. Secondary Objectives

- Compare the proportion of subjects with 2 consecutive serum bicarbonate levels below the lower limit of normal (LLN) for age between the ADV7103 and placebo groups during the Withdrawal Period;
- Compare the proportion of subjects who develop new onset hypokalemia (defined as a serum potassium level < 3.5 mEq/L) between the ADV7103 and placebo groups during the Withdrawal Period.
- Compare the time to metabolic acidosis, defined by serum bicarbonate levels, between the ADV7103 and placebo groups during the Withdrawal Period;
- Compare the time to new onset hypokalemia between the ADV7103 and placebo groups during the Withdrawal Period;
- Compare the proportion of subjects with both metabolic acidosis and new onset hypokalemia between the ADV7103 and placebo groups during the Withdrawal Period;
- Assess the mean urinary calcium/creatinine ratio associated with Visits 1 (SOC) and 2 (ADV7103);
- Compare the change in mean urinary calcium/creatinine ratio during the Withdrawal Period between the ADV7103 and placebo groups;
- Assess the mean urinary citrate/creatinine ratio associated with Visits 1 (SOC) and 2 (ADV7103);
- Compare the change in mean urinary citrate/creatinine ratio during the Withdrawal Period between the ADV7103 and placebo groups;
- Determine the frequency and severity of all study treatment emergent adverse events (TEAEs) by study period and study product assignment;
- Determine the number of treatment emergent adverse events by study period and study product assignment;
- Determine the frequency of suspected unexpected serious adverse reactions (SUSARs) by study period;
- Determine the frequency of new onset hyperkalemia by study period and for each treatment group during the Withdrawal Period;

- Determine the frequency of new onset hypokalemia by study period, and for each treatment group during the Withdrawal Period;
- Assess changes in other serum and urine safety laboratory results from SOC baseline;
- Determine the frequency of urine pH > 8.5 in Periods 1, 2, and 3.

5.3. Exploratory Objectives

- Compare the gastrointestinal tolerability, measured on an age appropriate scale, of ADV7103 (Visit 2) versus SOC (Visit 1);
- Compare urinary supersaturated (SS) calcium oxalate, SS calcium phosphate, and SS uric acid levels: ADV7103 (Visit 2) versus SOC (Visit 1) and ADV7103 vs. placebo (Period 3);
- Compare age appropriate study product acceptability and satisfaction scores: ADV7103 (Visit 2) versus SOC (Visit 1);
- Compare palatability and ease of administration/swallowing and number of daily product intakes scores: ADV7103 (Visit 2) versus SOC (Visit 1);
- Evaluate quality of life variables through use of questionnaires and semi-structured interviews.

6. INVESTIGATIONAL PLAN

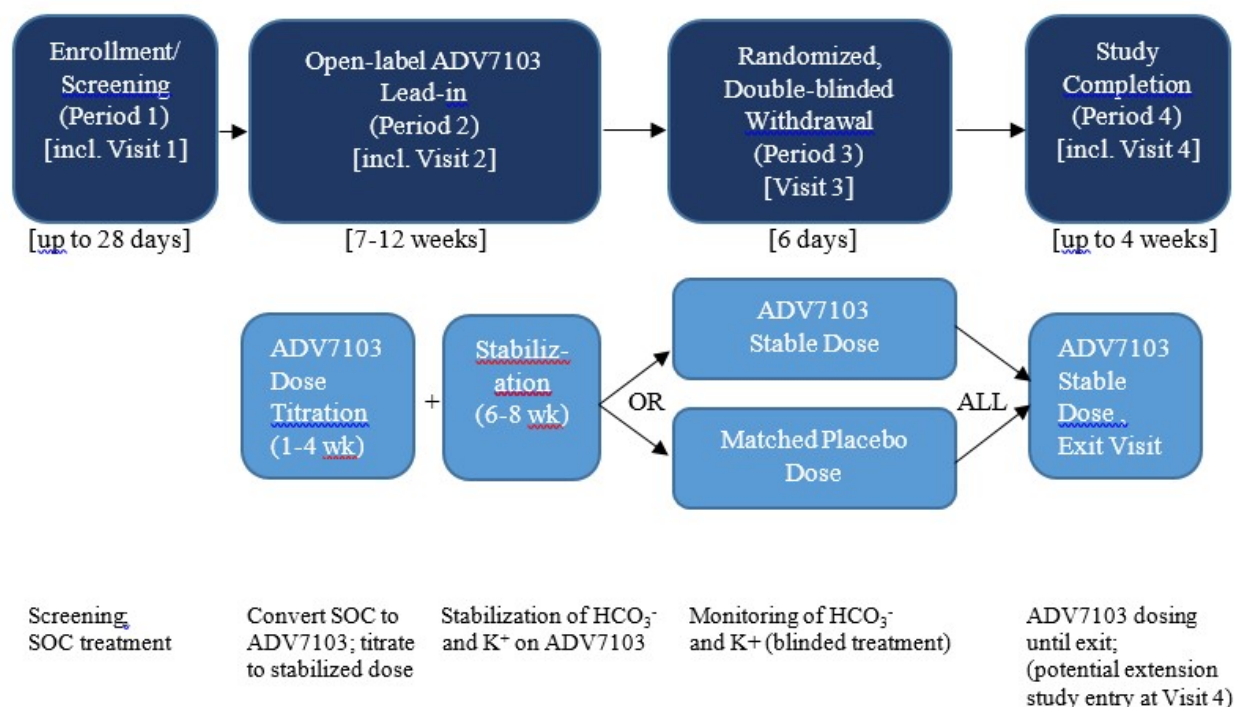
6.1. Overall Study Design

This is a phase 3, prospective, multicenter, randomized, double-blinded, placebo-controlled, study product withdrawal study comparing the efficacy of ADV7103 versus placebo in preventing the development of metabolic acidosis defined by serum bicarbonate level in pediatric (6 months to <18 years of age) and adult (18 to 65 years of age) subjects with primary dRTA.

The study will target at least 4 subjects in each of the following age groups: 6 months – 23 months; 2-11 years, and ≥ 12 years. Starting with the oldest group (≥ 12 years), each subsequently younger group will be randomized after 4 subjects from the preceding older age group have completed the Withdrawal Period and the uDMC approves randomization in the next younger group. During uDMC review of data from an age group, enrollment into that age group may continue unless the uDMC recommends cessation of this activity. The uDMC may request additional subjects complete the study in the age group under uDMC review prior to approving randomization of the next younger group. Enrollment of an equal number of subjects in each age group is not required; for pragmatic reasons, enrollment in the youngest age group may be fewer than 4 subjects. After reviewing data from randomized subjects who do not complete the Withdrawal Period, the uDMC may recommend changes to the protocol (including, but not limited to, increasing the total number of subjects enrolled in the study) to ensure a reasonable balance of early withdrawals between treatment groups. Lastly, if laboratory data, clinical symptoms, and cardiac monitoring data warrant, the uDMC may recommend modification of cardiac monitoring in this study.

The study includes 4 consecutive periods as shown in [Figure 1](#):

Figure 1: B23CS (ARENA 2) Study Schematic



6.2. Study Periods

6.2.1. Period 1 (Enrollment/Screening)

Subjects are enrolled at the time informed consent is obtained. After obtaining electronic informed consent from the subject or parent/guardian and assent from the subject if indicated, the Screening Visit (Visit 1) will take place on an outpatient basis at the investigational site or within the safety of their home via a home health nurse and as needed, investigator telehealth sessions. Subjects who do not initially meet all eligibility criteria may be re-screened at the Investigator's discretion (in consultation with the Medical Monitor) and enroll in the study if all eligibility criteria are met. During this period, which may involve up to 28 days for each screening attempt (no more than 3 total attempts or 2 re-screens), each subject will remain on her/his SOC alkali regimen and have study baseline assessments performed.

It should be possible to complete nearly all of the required screening/study baseline assessments during the face-to-face Screening Visit (Visit 1). Any remaining activities/assessments (eg, completion of the study baseline 24-hour urine collection, renal ultrasound testing, etc) may be completed via remote interactions (ie, not necessarily face-to-face encounters with study team members at the investigational site).

6.2.2. Period 2 (Open-label Lead-in)

This period consists of an ADV7103 **dose titration phase** (from 1 to 4 weeks in duration) and a **stabilization phase** (6-8 weeks in duration; may be lengthened to manage logistics for progression to the Withdrawal Period).

Throughout the Open-label Lead-in Period, subjects will be followed by telehealth and phone interactions and undergo in-home, point-of-care blood collection, processing and analysis. A second 24-hour urine collection will be completed at the end of Period 2 (ie, on or before Visit 2). After discussion with the Medical Monitor, the Investigator may elect to transition selected subjects < 5 years of age to ADV7103 in a monitored setting.

6.2.2.1. Period 2 - Dose Titration Phase

After eligibility for the study has been confirmed by the Investigator, the subject will be registered into the study and open-label ADV7103 will be provided to the subject during Visit 1 (eg, home visit by a healthcare provider, shipping method/mail delivery, pick up by the subject at the investigational site, etc). The subject will also be given instructions concerning the date and time to stop taking her/his SOC regimen and to begin taking ADV7103 (at the dose specified by the Investigator) prior to the morning meal/snack/feeding on the day after the SOC regimen (including potassium supplementation, if any) is stopped and following confirmation that the 24 hour urine collection is completed (in subjects for whom this is technically feasible). Open-label ADV7103 will be taken approximately every 12 hours (just prior to both the morning and evening meals/snacks/feedings). The initial total daily alkali dose of ADV7103 will approximate the SOC daily alkali dose in mEq.

After ADV7103 dosing is initiated, pre-morning dose (t_0) blood samples will be collected every 2 to 4 days via a home visit by a healthcare provider, or subject visit an outpatient site to obtain serum bicarbonate and potassium results.

Whole blood samples (0.1 cc) will be gathered and prepared by trained staff, and an electrolyte panel (Cl⁻, K⁺, Na⁺, tCO₂) will be analyzed and reported via the portable point-of-care iSTAT System (Abbott Inc.).

The ADV7103 daily dose will be adjusted as necessary in increments of 8, 16, 24, 32, 40, or 48 mEq based on these results and instructions from the Investigator or her/his designee via phone. The interval between blood collections for this purpose may be extended with permission of the Medical Monitor.

A serum bicarbonate range of 21-27 mEq/L for subjects ≥ 4 years old and a range of 20-26 mEq/L for subjects < 4 years old prior to the morning dose (t_0) will be targeted during titration. The ADV7103 dosage will be adjusted until at least the minimum target serum bicarbonate level is reached (ie, 21 or 20 mEq/L) or tolerability issues limit further dose increases. After a dose results in at least 2 consecutive serum bicarbonate levels (2-4 days apart) \geq the lower limit of the targeted range, the investigator will determine that dose titration is complete, and the subject will enter the Stabilization Phase of Period 2. If the serum bicarbonate level is in the targeted range but the serum potassium level is below 3.5 mEq/L, ADV7103 may continue to be uptitrated if ADV7103 continues to be tolerated and serum bicarbonate levels remain in the targeted range and serum potassium levels stay ≤ 5.0 mEq/L. If a maximum tolerated dose of ADV7103 delivers a serum bicarbonate level in the targeted range and the serum potassium level is ≥ 3.0 mEq/L and < 3.5 mEq/L, an acceptable dose has been identified, if the patient is not symptomatically hypokalemic. If a maximum tolerated dose of ADV7103 delivers a serum bicarbonate level in the targeted range and the serum potassium level is

< 3.0 mEq/L, potassium supplementation (potassium hydrochloride) may be considered in consultation with the Medical Monitor and/or Sponsor Medical Representative.

Subjects who are unable to maintain the specified minimum serum bicarbonate level, despite maximum tolerated ADV7103 dose, will be able to enter the open-label extension study or return to their prior SOC at the discretion of the Investigator (in consultation with the Medical Monitor). In either case, these subjects will be discontinued from this study following Visit 4 (early withdrawal) activities.

6.2.2.2. Period 2 - Stabilization Phase

Once two consecutive serum bicarbonate levels are 21-27 mEq/L (inclusive) for subjects ≥ 4 years old and 20-26 mEq/L (inclusive) for subjects < 4 years old on the same ADV7103 dose, the subject will remain on this ADV7103 dose for 6-8 weeks (ie, Stabilization Phase of Period 2). During this phase, the subject will be monitored, with serum bicarbonate and potassium levels obtained every 2 weeks (or more often if determined by the Investigator in consultation with Medical Monitor). At the end of the Stabilization Phase (ie, after 6-8 weeks post titration), the Stabilization Visit (ie, Visit 2) will take place at the investigational site or in the subject's home and via telehealth, with the subject remaining on her/his stable dose of ADV7103. At this time, the Investigator will assess the eligibility of the subject for the Randomized, Double-blinded Withdrawal Period (Period 3).

Subjects eligible for randomization must meet all of the following criteria:

- a stable ADV7103 dose, for a minimum of six weeks;
- serum bicarbonate level within target range and serum potassium level ≥ 3.0 mEq/L, both at Visit 2;
- serum bicarbonate level is maintained in the corresponding age-specific normal range for at least 80% of available results obtained during the Stabilization Phase of Period 2;
- serum potassium level ≥ 3.0 mEq/L for at least 80% of available results obtained during the Stabilization Phase of Period 2;
- acceptable safety and tolerability as determined by the Investigator at the enrolling site.

6.2.3. Period 3 (Randomized, Double-blinded Withdrawal)

As soon as practicable following Visit 2, eligible subjects taking their pre-randomization dose of ADV7103 will enter Period 3 (Visit 3) randomization for an adequate period to monitor serum bicarbonate and potassium levels in the context of randomized, double-blinded treatment withdrawal. Period 3 start and randomization may occur in the evening prior to the first dose of blinded study product the next morning or early in the morning prior to the first dose of blinded study product. The duration of this efficacy assessment period (ie, Visit 3) will be approximately 6 days initially. The duration may be adjusted if approved by a bDMC following review of data from a subset of at least 8 subjects to complete Period 3 (see details in [Section 11.8.2](#)). The final

study day of this period may be less than 24 hours in duration with discharge occurring after the evening dose and required data collection.

After baseline evaluations including laboratory tests are completed, subjects will either continue their stabilized ADV7103 dose or switch to a weight-matched identical-appearing placebo dose according to their randomized treatment assignment (without potassium supplementation). In the unexpected situation where these Period 3 baseline evaluations disclose a serum bicarbonate level < 18 mEq/L for subjects ≥ 4 years old and < 17 mEq/L for subjects < 4 years old and/or a serum potassium level < 3.0 mEq/L for all subjects, the subject will not be dosed with blinded study product. Rather, at the Investigator's discretion, the subject may receive open-label ADV7103 or a SOC regimen to address these abnormal laboratory results. When the clinical status of the subject allows, the subject will be discharged from Period 3 with instructions to continue open-label ADV7103 or a SOC regimen and within 4 weeks to complete Visit 4 study exit evaluations.

The Investigator and staff (except for the pharmacist) will be blinded to Period 3 study product assignments, but not to laboratory results. The subjects will remain blinded to treatment throughout Period 3. In all subjects, serum bicarbonate and potassium levels will be measured every 24 hours following administration of the first dose of blinded study product (or more frequently if deemed necessary for safe subject management) through the remainder of Visit 3.

To ensure maximum safety for the subjects who may experience a decline in serum potassium, repeat serum potassium measurements should be performed 2-4hrs (and not 24hrs) after the first measurement if serum potassium is found to be below 3.5 mEq/L or to have decreased by more than 15 percent since the last measurement. Potassium (potassium hydrochloride) will be supplemented, as needed, for levels falling below 3.0 mEq/L.

If a subject's serum bicarbonate level becomes < 18 mEq/L for subjects ≥ 4 years old or < 17 mEq/L for subjects < 4 years old (study definition of metabolic acidosis), another serum bicarbonate result will be obtained within 2-4 hours or earlier if subject safety requires immediate intervention. If the repeat serum bicarbonate result confirms metabolic acidosis, the subject will have achieved the primary endpoint. If the second level is above the threshold, the subject will continue her/his current study product assignment and resume the regular schedule of blood sample collections. Subjects who develop metabolic acidosis during the Withdrawal Period will be discontinued from study product in a blinded fashion and begin taking active ADV7103 at the next scheduled dosing time point (unless subject safety requires immediate intervention) at their pre-randomization dose.

They will remain under investigator monitoring for approximately 6 days or until the metabolic acidosis (and any accompanying hypokalemia, if applicable) is corrected, whichever is longer. The frequency of laboratory evaluations for subjects who require correction of serum bicarbonate and/or potassium will be determined by the Investigator.

Potassium supplementation initiated during Period 3, if applicable, should be stopped at restoration of ADV7103 dosing..

If restoration of ADV7103 at the pre randomization dose fails to restore targeted serum bicarbonate levels, the dose of ADV7103 will be increased to achieve this objective as long as it is tolerated. In order to maintain serum potassium levels ≥ 3.0 mEq/L, the dose of ADV7103

may be increased or a potassium supplement may be added to ADV7103 (or the dose of these may be increased if already being taken by the subject), if deemed appropriate by the Investigator. If ADV7103 (with or without a potassium supplement) fails to return serum bicarbonate and potassium levels to pre randomization levels at the maximally tolerated ADV7103 dose, the Investigator (in consultation with the Medical Monitor and subject/legal guardian) will determine if the subject should continue ADV7103 at a dose that provides acceptable (though not targeted) control of serum bicarbonate and potassium levels in the ARENA 2 extension study, or return to her/his SOC regimen. In either case, the subject will be discontinued from this study after completing Visit 4 activities.

6.2.4. Period 4 (Study Completion)

Subjects who were stabilized on ADV7103 during this study and adherent to the protocol will be offered the opportunity to receive open-label ADV7103 as part of a separate extension study. Subjects may elect to be administered ADV7103 after completing Period 3 (within 4 weeks of Period 3 completion); the subject may complete Visit 4 and the initial extension study visit will take place at the same time as the exit visit (Visit 4) from this study (following informed consent/assent). Subjects declining participation in the extension study can elect to return to their previous SOC regimen after completing Period 3 (within 4 weeks of Period 3 completion) the subject may complete Visit 4 as the exit visit from this study.

6.3. Study Endpoints

6.3.1. Primary Endpoint

- Proportion of subjects with metabolic acidosis during the Withdrawal Period. Metabolic acidosis is defined as 2 consecutive serum bicarbonate levels < 18 mEq/L for subjects ≥ 4 years old and < 17 mEq/L for subjects < 4 years old.

6.3.2. Secondary Endpoints

- Proportion of subjects with 2 consecutive serum bicarbonate levels below the LLN for age during the Withdrawal Period;
- Proportion of subjects developing new onset hypokalemia during the Withdrawal Period. Hypokalemia is defined as a serum potassium level < 3.5 mEq/L.
- Time to metabolic acidosis during the Withdrawal Period;
- Time to new onset hypokalemia during the Withdrawal Period;
- Proportion of subjects with both metabolic acidosis and new onset hypokalemia during the Withdrawal Period;
- Mean urinary calcium/creatinine ratio associated with Visit 1, Visit 2;
- Mean change in urinary calcium/creatinine ratio during the Withdrawal Period;
- Mean urinary citrate/creatinine ratio associated with Visit 1, Visit 2;
- Mean change in urinary citrate/creatinine ratio during the Withdrawal Period;

- Frequency and severity of all adverse events (AEs), TEAEs, and all study product-related AEs;
- Frequency of SUSARs;
- Frequency of hyperkalemia;
- Frequency of serum potassium levels < 3.0 mEq/L;
- Frequency of serum potassium levels < 3.5 mEq/L;
- Changes in other serum and urine safety laboratory results from SOC baseline;
- Frequency of urine pH > 8.5 in Periods 1, 2, and 3.

6.3.3. Exploratory Endpoints

- Gastrointestinal tolerability scores, on an age-appropriate scale;
- Urinary SS calcium oxalate, SS calcium phosphate, and SS uric acid levels; comparison between Visit 1 and Visit 2 levels, and between treatment and placebo levels;
- Study product acceptability and satisfaction scores, with age-appropriate questionnaires;
- Palatability, ease of administration/swallowing, and number of daily product intakes scores, on age-appropriate scales;
- Results from quality of life age-appropriate questionnaires and semi-structured interviews.

6.4. Number of Subjects

Approximately 40 subjects are planned to enter Period 2 and begin taking ADV7103 instead of a SOC regimen. Of these, at least 32 subjects should complete Period 3 (Withdrawal Period).

6.5. Treatment Assignment

During Period 1, subjects will continue to take their SOC alkali regimens. If Period 2 begins the day following Visit 1, subjects will discontinue their SOC alkali regimens after taking the last scheduled SOC dose on the day of Visit 1.

As described in Section 6.2.2, subjects entering Period 2 will be switched from their SOC regimens and any potassium supplementation to open-label ADV7103 twice daily. The initial ADV7103 alkali daily dose will approximate the SOC alkali daily dose in mEq. After informed consent (and assent, when appropriate) for Period 3 is obtained (if separate consent/assent is needed by a Period 3 site) and prior to blinded study product administration, subjects will be randomized to either continue their stabilized ADV7103 dose or switch to a weight-matched identical-appearing placebo in Period 3. During Period 3, blinded study products will be administered twice daily, as described in Section 6.2.3.

6.6. Initial ADV7103 Dose and Dose Adjustment

The initial dose of open-label ADV7103 for a subject entering Period 2 will be determined by the Investigator based on the current SOC alkali dose in mEq/day. The following factors should be taken into consideration when selecting the initial ADV7103 dose:

- SOC potassium supplementation taken by the subject (if any);
- Visit 1 (or most recent) serum bicarbonate level; and
- Visit 1 (or most recent) serum potassium level.

The ADV7103 dose will be adjusted by the Investigator based primarily on serum bicarbonate levels. A serum bicarbonate range of 21-27 mEq/L for subjects ≥ 4 years old and a range of 20-26 mEq/L for subjects < 4 years old prior to the morning dose (t_0) will be targeted during titration. ADV7103 dosage will be adjusted until at least the minimum target serum bicarbonate level is reached (ie, 21 or 20 mEq/L) and potassium ≥ 3.0 mEq/L, or tolerability issues limit further dose increases. After a dose results in at least 2 consecutive serum bicarbonate levels (2-4 days apart) \geq the lower limit of the targeted range, the investigator will determine that dose titration is complete, and the subject will enter the Stabilization Phase of Period 2. If the serum bicarbonate level is in the targeted range but the serum potassium level is below 3.5 mEq/L, ADV7103 may continue to be uptitrated if ADV7103 continues to be tolerated and serum bicarbonate levels remain in the targeted range and serum potassium levels stay ≤ 5.0 mEq/L. If a maximum tolerated dose of ADV7103 delivers a serum bicarbonate level in the targeted range and the serum potassium level is ≥ 3.0 mEq/L and < 3.5 mEq/L, an acceptable dose has been identified, if the patient is not symptomatically hypokalemic. If a maximum tolerated dose of ADV7103 delivers a serum bicarbonate level in the targeted range and the serum potassium level is < 3.0 mEq/L, potassium supplementation (potassium hydrochloride) may be considered in consultation with the Medical Monitor and Sponsor Medical Representative.

Subjects who are unable to maintain the specified minimum serum bicarbonate level, despite maximum tolerated ADV7103 dose, will be able to enter the open-label ARENA 2 extension study or return to their prior SOC at the discretion of the Investigator (in consultation with the Medical Monitor). In either case, these subjects will be discontinued from this study following completion of Visit 4 activities.

6.7. Reasons for Study Suspension or Termination

Advicenne Pharma may suspend or prematurely terminate either the clinical study at an individual investigational site or the entire clinical study for significant and documented reasons.

A Principal Investigator (PI), institutional review board (IRB), or regulatory authority may suspend or prematurely terminate participation in a clinical study at the investigational sites for which they are responsible.

The uDMC may recommend modification of the study protocol, suspension of enrollment, or termination of the study for safety or other reasons. Advicenne Pharma will consider all recommendations from the uDMC. All decisions that directly impact study subjects will be communicated promptly and thoroughly to them with detailed instructions for discontinuation of ADV7103 and conversion to a SOC regimen (with or without potassium supplementation).

If suspicion of an unacceptable risk to subjects arises during the clinical study, or when so requested by the IRB or regulatory authorities, Advicenne Pharma will suspend the clinical study while the risk is assessed. Advicenne Pharma will terminate the clinical study if an unacceptable risk is confirmed.

Advicenne Pharma will consider terminating or suspending the participation of a particular investigational site or Investigator if monitoring or auditing identifies serious or repeated deviations on the part of an Investigator.

If suspension or premature termination occurs, the terminating party shall justify its decision in writing and promptly inform the other parties with whom they are in direct communication.

If, for any reason, Advicenne Pharma suspends or prematurely terminates the study at an individual investigational site, Advicenne Pharma or its designee will inform the responsible regulatory authority if required and ensure that the IRB is notified. If the suspension or premature termination was due to a safety-related reason, Advicenne Pharma will inform all other PIs.

If suspension or premature termination occurs,

- Advicenne Pharma will remain responsible for providing resources to fulfill the obligations from the protocol and existing agreements for following up the subjects enrolled in the clinical study; and
- the PI or authorized designee will promptly inform the enrolled subjects at her/his investigational site, if appropriate.

In the event that the study is discontinued, the reasons for discontinuation will be explained to the investigators and may be disclosed to the study subjects. Advicenne Pharma will provide all information needed by the Investigator to ensure the safety and well-being of the study subjects.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

Subjects must meet all of the following criteria to be registered into this study:

1. Female or male subjects ≥ 6 months of age and ≤ 65 years of age at time of consent;
2. Subject presents with a previous diagnosis of primary dRTA of at least 4 months duration for subjects < 12 years of age, and at least one year for those ≥ 12 years of age, based on documented history of non-anion gap, hyperchloremic, hypokalemic metabolic acidosis;
3. Subject requires ≥ 0.9 mEq/kg/day of alkali therapy to maintain serum bicarbonate levels above the LLN for the laboratory providing results;
4. Urine pH > 5.5 and serum bicarbonate > 18 mEq/L for subjects ≥ 4 years old or > 17 mEq/L for subjects < 4 years old on alkali therapy and potassium supplementation (if indicated) on at least one occasion for each within 6 months prior to Visit 1;
5. Subject or parent/guardian is willing and able to understand and sign informed consent and willing to comply with protocol instructions; child assent when appropriate; and

6. Heterosexually active female subjects of childbearing potential and non-sterilized males must use at least one of the following acceptable birth control methods from informed consent through 7 days after the last dose of study product:
 - a. Double-barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository)
 - b. Established use of oral, injectable, or implanted hormonal methods of contraception
 - c. Placement of an intrauterine device or intrauterine system
 - d. Abstinence.

Females of childbearing potential are those who have reached the onset of menarche (or 8 years of age, whichever comes first) and are not postmenopausal (≥ 1 year without menses prior to Visit 1)], surgically sterile, or status post hysterectomy (≥ 1 month prior to Visit 1). From informed consent through 7 days after the last dose of study product, female subjects must agree to refrain from egg donation and male subjects must agree to refrain from sperm donation.

7.2. Subject Exclusion Criteria

Subjects meeting any of the following criteria will be considered ineligible for registration into this study:

1. Female subject who is pregnant or lactating or has plans for pregnancy during the study;
2. Subject has evidence of proximal tubule dysfunction (eg, hypophosphatemia, low serum uric acid, glycosuria, or amino aciduria);
3. Subject presents with another diagnosed condition as a potential etiology for her/his dRTA (eg, systemic lupus erythematosus, Sjogren's syndrome), in the opinion of the Investigator;
4. Subject requires therapy with potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, trimethoprim, drospirenone and other progestins, nephrotoxic antibiotics, penicillins, tacrolimus, or medications known to delay gastric emptying or otherwise interfere with absorption of study product;
5. Subject has evidence of obstructive uropathy or other findings on renal ultrasound associated with Visit 1 expected to require intervention during the course of the study, in the opinion of the Investigator;

6. Subject has any of the following laboratory abnormalities associated with Visit 1:
 - a. AST and/or ALT > 1.5x upper limit of normal (ULN)
 - b. Serum potassium > 5.0 mEq/L or <3.0 mEq/L or hypokalemia accompanied by clinical symptoms (eg, muscle cramps) or significant ECG changes (eg, T wave depression, U wave elevation)
 - c. Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² (according to the updated Schwartz formula for children and Chronic Kidney Disease – Epidemiology Collaboration [CKD-EPI] formula for adults)
 - d. Total bilirubin > ULN, except with known Gilbert's disease.
7. Subject has been hospitalized or had outpatient surgery (other than minor skin and dRTA disease-related procedures or ear tube placement) in the past 6 months or is planning surgery in the next 6 months;
8. In the opinion of the Investigator, the subject has a major medical or psychiatric condition (eg, significant cardiac disease, schizophrenia) or an unstable condition (eg, uncontrolled hypertension, asthma, diabetes, hypercholesterolemia, or cardiac disease) that would potentially interfere with the subject safely completing the study;
9. In the opinion of the Investigator, the subject has a history of difficulty taking oral medication and/or conditions that may hamper absorption of the study drug (eg, any difficulty of swallowing, malabsorption, delayed gastric emptying, esophageal compression, intestinal obstruction, or other chronic gastrointestinal disease);
10. Self-reported or parent/guardian reported alcohol abuse or drug abuse within the past 12 months;
11. Subject is a solid organ or bone marrow transplant recipient;
12. Subject has a history of malignancy within 5 years prior to Visit 1, except for localized skin or cervical carcinoma; or
13. Subject is known to have an allergy or intolerance to any ADV7103 or placebo constituents.

7.3. Subject Withdrawal Criteria

Subjects will be withdrawn from the study if any of the following apply:

- failure to achieve targeted serum bicarbonate levels as specified in this protocol;
- failure to achieve targeted serum potassium levels as specified in this protocol;
- occurrence of an adverse event related to the study product, placing the subject at an unacceptable risk with continued study participation (as determined by the Investigator);
- pregnancy;
- significant nonadherence to treatment or study procedures as determined by the Investigator; or
- withdrawal of informed consent.

All subjects withdrawn from the study should complete assessments associated with Visit 4 in [Section 17.1](#). There is no plan to replace randomized subjects who are withdrawn from the study. If a subject is withdrawn from the study due to an adverse event, the subject will be followed as specified in [Section 11.6](#).

8. TREATMENT OF SUBJECTS

8.1. Description of Study Product

8.1.1. ADV7103

The test product in this study is ADV7103 prolonged-release granules taken orally approximately every 12 hours (just prior to both the morning and evening meals/snacks/feedings) at a dose titrated to achieve desired serum bicarbonate levels.

An ADV7103 fixed dose is 1/3 potassium citrate (green granules, ADV7103-CK) and 2/3 potassium bicarbonate (white granules, ADV7103-BK) by weight. Open-label ADV7103 will originate from sachets including either 8 or 24 mEq of alkali. Study product dispensed in blinded fashion during Period 3 will originate from sachets of active ADV7103 granules and will be placed in drug vials.

8.1.2. Placebo

The reference study product is matched placebo granules taken orally approximately every 12 hours (just prior to both the morning and evening meals/snacks/feedings) at a dose equal to the weight of granules in the ADV7103 dose determined in Period 2; 1/3 of the placebo dose by weight will be green granules, and 2/3 of the placebo dose by weight will be white granules. Placebo granules will be identical in appearance to ADV7103 granules. Placebo will be dispensed in a blinded fashion from bulk supply and placed in drug vials.

8.2. Concomitant Medications

Therapy with potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, trimethoprim, drospirenone and other progestins, nephrotoxic antibiotics, penicillins, or tacrolimus is not permitted during participation in this study. Other medications known to delay gastric emptying or otherwise interfere with absorption of study product are prohibited during study participation.

All other concomitant medications are permitted during study participation.

8.3. Treatment Adherence

Adherence to protocol-specified administration of study products will be monitored in the following ways:

- daily entries into electronic patient reported outcomes (ePRO) diaries;

- the number of empty open-label ADV7103 sachet boxes and unused sachets returned to the investigational site will be counted and compared against anticipated use based on dosing instructions provided to the subject and against the ePRO data;
- serum bicarbonate and potassium levels will be monitored per protocol; results that do not reasonably align with prescribed study product dosing during Period 2 or Period 4 will be further investigated; and
- Period 3 study product administration will be directly observed.

8.4. Randomization and Blinding

Randomization will be completed and prior to blinded study product administration. It is expected that subjects will consent (or assent, when applicable) to participation in Periods 1 through 4 during the Screening Visit.

After admission into Period 3, and completion of baseline evaluations, subjects will either continue their stabilized ADV7103 dose or switch to a weight-matched identical-appearing placebo dose according to their randomized treatment assignment (without potassium supplementation).

The Investigator and staff (except for the pharmacist) will be blinded to Period 3 study product assignments but will have access to laboratory results and other information pertinent to clinical care of the subjects. The pharmacist will be unblinded to treatment assignment for the purposes of preparing, controlling, dispensing study product and documenting accountability of study product.

Unblinded DMC members will have access to Period 3 treatment assignments in order to interpret Period 3 data and make recommendations concerning sequential randomization of age groups or any potential safety issues ([Section 11.8.1](#)).

8.4.1. Procedure for Unblinding

Unblinding of study product assignment for a subject should occur only when subject safety is clearly at risk and knowledge of study product assignment is important for medical care of the subject. If an Investigator is considering breaking the blind and the clinical status of the subject allows, she/he should first contact the Medical Monitor or his designee to discuss the justification for unblinding. If the clinical status of the subject precludes a discussion with the Medical Monitor, the Investigator may obtain study product assignment information from the pharmacist. She/he should notify the Medical Monitor that the blind was broken as soon as possible following this activity and measures necessary to care for the subject have been taken. Following breaking of the blind, the subject should be withdrawn from the study following completion of Visit 4 (early withdrawal) activities. If the Investigator and Medical Monitor agree concerning appropriateness, the subject may continue to receive ADV7103 in the open-label ARENA 2 extension study.

9. STUDY PRODUCT AND ITS MANAGEMENT

9.1. Study Products

The study products used in this study include ADV7103 (Periods 2, 3, and 4) and placebo matching ADV7103 in appearance and weight (Period 3).

9.1.1. ADV7103

ADV7103 is a combination of potassium citrate granules (ADV7103-CK) and potassium bicarbonate granules (ADV7103-BK) and has alkalinizing properties.

The ADV7103-CK granules are prepared as 2 mm green coated prolonged-release granules for oral administration containing approximately 67% of potassium citrate monohydrate. The coating allows a release over 2-3 hours.

The ADV7103-BK granules are prepared as 2 mm white coated prolonged-release granules for oral administration containing approximately 66% of anhydrous potassium hydrogen carbonate. The combination of matrix and coating polymer allows approximately zero-order release over 10 to 12 hours.

Each dose of ADV7103 contains a fixed ratio of 1/3 of ADV7103-CK (potassium citrate) and 2/3 of ADV7103-BK (potassium bicarbonate) based on the mass of active substances. The strength is 6.44 ($\pm 10\%$) mEq/g of ADV7103 (alkalinizing power).

ADV7103 is manufactured by Elaiapharm company in the European Union (EU). ADV7103 is packaged in sachets by Ivers-Lee company (EU) and sachets are packed in boxes of 60 units and released (pharmaceutical certification) as clinical batches by Amatsi group (EU). ADV7103 will be supplied to the investigational sites by Almac (US). All the manufacturing operations are done in accordance with current Good Manufacturing Practices (cGMP).

9.1.2. Placebo

Placebo is a combination of 2 mm green coated lactose granules and 2 mm white coated lactose granules.

Each dose of placebo contains a fixed ratio of 1/3 of green granules and 2/3 of white granules.

Placebo is manufactured, packaging and released by Amatsi in accordance with the cGMP. Almac is in charge of supplying ADV7103 placebo to the applicable Period 3 investigational sites.

9.2. Study Product Packaging and Labeling

ADV7103 will be provided to the investigational sites in sachets (stick packs) packed in boxes of 60 units. There are 2 strengths of sachet: 8 mEq and 24 mEq.

- ADV7103 8 mEq sachets are green and contain 267 mg of monohydrate potassium citrate and 527 mg of potassium bicarbonate.
- ADV7103 24 mEq sachets are purple and contain 800 mg of monohydrate potassium citrate and 1582 mg of potassium bicarbonate.

This study is open-label during Periods 1, 2, and 4 (and a portion of Period 3 if re-stabilization is needed). ADV7103 will be supplied in boxes of 60 sachets for Periods 2 and 4.

This study is double-blinded during Period 3. In order to preserve blinding, a pharmacist will be responsible for preparing the treatment packaging and labelling in a manner to make the study products indistinguishable. Each subject's treatment will be packed in small polypropylene vials.

Placebo will be provided in high-density polyethylene vials with polypropylene caps including an integrated desiccant. Green granules and white granules will be provided separately, both in vials of 20g. The doses will be prepared in small polypropylene vials.

Labeling of primary packaging (sachet) and secondary packaging (box of 60 sachets) will be done in accordance with cGMPs, local laws, and study requirements.

Labeling of the primary packaging (vials) containing ADV7103-CK placebo and containing ADV7103-BK placebo and secondary packaging (box with 1 vial of ADV7103-CK placebo and 2 vials of ADV7103-BK placebo) will be done in accordance with cGMPs, local law, and study requirements.

The vials (small packaging) of ADV7103 or of placebo and secondary packaging (zip bag) will be labeled in accordance with cGMPs, local law, and study requirements. Labeling of the primary and secondary packaging will ensure the double-blind is maintained as appropriate during Period 3.

9.3. Study Product Storage

Boxes of ADV7103 sachets should be stored, not above 30°C or 86°F for not longer than the expiration date.

Placebo vials should be stored at a temperature between 15 and 25°C or 59 and 77°F and according to the expiration date.

ADV7103 or placebo vials should be stored at a temperature between 15 and 25°C or 59 and 77°F for not longer than the expiration date.

Extension of the expiration date may be granted. Investigational site pharmacies will be informed about any modification of the expiration date of study products.

9.4. Study Product Preparation

During Periods 2 and 4 no preparation is required. Study product (ADV7103) will be dispensed in boxes of 60 sachets as provided by the investigational site pharmacy, with the appropriate dosage(s) and number of boxes to cover the longest possible duration of the period (12 weeks for Period 2).

During Period 3, the pharmacist will have the responsibility to prepare the doses of ADV7103 or placebo for each subject.

The single doses of ADV7103 or placebo (in vials) will be prepared specifically for the study by and unblinded site pharmacist.

For ADV7103, the investigational site pharmacist will be responsible for preparing vials using 2 strengths of sachets (8 mEq and 24 mEq).

For placebo, the investigational site pharmacist will be responsible for preparing vials, using a quantity of granules (in mg) from vials of ADV7103-CK placebo and from vials of ADV7103-BK placebo equivalent to the quantity of ADV7103 granules needed for the dose. The ratio should be 2/3 ADV7103-BK placebo to 1/3 ADV7103-CK placebo. One or two vials may be needed per dose.

Any preparation must be done and controlled by an unblinded pharmacist; blinding must be maintained during the course of the trial.

During Period 3, if any re-stabilization is needed and for the potential 4 weeks of treatment up to the Visit 4, ADV7103 will be provided (without preparation) in boxes of 60 sachets with the appropriate dosages and in an appropriate number for the longest possible duration of the period if needed.

9.5. Administration

Open-label ADV7103 and blinded study products (ADV7103 or placebo) will be taken orally twice daily, as close as possible to 12 hours apart (in the morning and in the evening). It is recommended to take the study products just before a meal/snack/feeding.

The granules must be swallowed without having been chewed, crushed, or sucked. Administration will be done with the subject in a standing position, if possible; otherwise, administration to a seated subject is acceptable. For children, the caregiver will ensure that the granules and water are fully swallowed. The study product can be given alone with water or mixed with semi-liquid foods.

If the study product is given alone, the granules will be directly administered in the mouth of the subject (by the subject himself or by the caregiver), then swallowed with a full glass water. The dose can be divided in several parts if necessary.

If the study product is mixed with not-hot, semi-liquid foods (such as puree, stewed fruit, or yogurt) to be given to youngest children, the granules will be mixed with the food then placed directly in the child's mouth with a teaspoon. The dose can be divided in several parts (mouthfuls or teaspoons) if necessary. The dose must be taken within 15 minutes after mixing with food.

Alcohol must be avoided for at least 15 minutes prior to dosing and at least 30 minutes following dosing.

9.6. Study Product Accountability

The Investigator is responsible for ensuring ADV7103 accountability and any other study material needing accountability, including reconciliation of study product and maintenance of study product records.

Upon receipt of study product and any associated materials, the Investigator (or the pharmacist) will check for accurate delivery and acknowledge receipt with appropriate documentation as instructed by Advicenne Pharma or its designee.

Dispensing of study product and any associated materials will be carefully recorded in the interactive response technology system and/or on the appropriate drug accountability forms

provided by Advicenne Pharma or its representative as described in the pharmacy manual and an accurate accounting will be available for verification by Advicenne Pharma or its representative at monitoring visits.

Study product and associated materials accountability records will include the following:

- confirmation of delivery of the study product and any associated materials to the investigational site;
- inventory of study product and any associated materials at investigational site;
- return to Advicenne Pharma or its designee, or alternative disposition of unused study product and any associated materials, and
- dates, quantities, batch numbers, formulation of the study product prepared at the investigational site, expiration dates, and study numbers assigned to the subjects.

The Investigator or her/his designee should maintain records that adequately document the following:

- subjects were provided the doses specified by the study protocol; and
- all study product and any associated materials were fully reconciled.

Unused study product and associated materials must not be discarded or used for any purpose other than this study. The study product and associated materials that have been dispensed to a subject must not be re-dispensed to a different subject.

The Monitor will periodically collect the study product and associated materials accountability forms and check all study product and associated materials returns (both unused and used containers) prior to making arrangements for their return to Advicenne Pharma or its designee or authorizing their destruction by investigational site staff.

9.7. Study Product Handling and Disposal

Instructions for study product handling and disposal are provided in the Pharmacy Manual.

10. STUDY PROCEDURES AND ASSESSMENTS

Prior to performing any study procedure and/or assessment (ie, that which is not part of the subject's usual medical care), the Investigator or her/his designee must ensure that the subject or her/his parent/legal guardian has provided informed consent (and/or assent, when applicable) according to the procedure described in [Section 13.5](#), and that the consent has not been withdrawn.

10.1. Study Schedule

The complete study schedule including all procedures and assessments is located in [Section 17.1](#).

10.2. Descriptions of Study Procedures and Assessments

10.2.1. Review of Eligibility Criteria

A review of all eligibility criteria for entry into the study will be performed in association with Visit 1 (ie, during Period 1) to ensure that subjects fulfill all inclusion criteria and do not meet any exclusion criteria (see [Section 7.1](#) and [Section 7.2](#)).

A review of criteria for randomization will be performed in association with Visit 2 to ensure that only subjects fulfilling all of these criteria are randomized ([Section 6.2.2.2](#)).

10.2.2. Demographic Information

Demographic information (age, gender, race, ethnicity) will be collected in association with Visit 1.

10.2.3. Medical History

A complete medical history and review of systems will be performed in association with Visit 1. The medical history should capture all relevant surgeries and procedures as determined by the Investigator.

10.2.4. Vital Signs

Vital signs (supine blood pressure, heart rate, respiratory rate, and oral temperature) will be determined in association with Visits 1, 2, 3, 4, and any unscheduled visits. Vital signs will be determined once per visit for this study.

10.2.5. Weight and Height

Total body weight and height of subjects will be measured in association with Visits 1 and 4.

10.2.6. Targeted Physical Examination

A single targeted physical examination will be conducted in association with Visits 1, 2, 4, and any unscheduled visits. During Period 3, a targeted physical examination will be conducted prior to the first dose of randomized, blinded study product and again on the last day of activities in Period 3 (including the day of early withdrawal, if applicable).

10.2.7. Tanner Staging

Tanner staging will be performed to assess physical development, if appropriate, in association with Visit 1.

10.2.8. Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed during Visit 1. If serum potassium is < 3.0 mEq/L in association with an unscheduled visit, a 12-lead ECG will be performed.

10.2.9. Cardiac Monitoring

Subjects will undergo cardiac monitoring (eg, Holter monitoring, cardiac telemetry, or other appropriate method). Monitoring will begin prior to the first dose of study product in Period 3 and continue as needed throughout Period 3, including during Visit 4.

10.2.10. Renal Ultrasound

A renal ultrasound will be performed in association with Visit 1 (ie, during Period 1). This must be completed and results assessed before open-label ADV7103 is dispensed to the subject.

10.2.11. Laboratory Assessments

10.2.11.1. Hematology

A complete blood count with differential and platelets will be obtained in association with Visit 1 and prior to the first dose of blinded study product in Period 3. These samples will be analyzed and reported by the central laboratory (ACM Global Laboratories).

10.2.11.2. Serum Chemistry

A serum chemistry panel will be obtained in association with Visit 1. During Period 3, a serum chemistry panel will be obtained prior to the first dose of blinded study product and on the last day of Period 3. In the event of early study withdrawal by a subject following at least 4 weeks of study participation, a serum chemistry panel will be obtained in association with the Early Withdrawal Visit.

The serum chemistry panel will include the following analytes (at a minimum): sodium, potassium, chloride, bicarbonate/total carbon dioxide, blood urea nitrogen, serum creatinine, glucose, calculated eGFR, aspartate transaminase, alanine transaminase, total bilirubin, alkaline phosphatase, calcium, phosphorus, magnesium, and uric acid. These samples will be analyzed and reported by the central laboratory (ACM Global Laboratories).

10.2.11.3. Spot Urine Collection

A spot urine sample will be collected once in association with Visit 1 and twice during Period 3.

During Period 3, the first of 2 urine sample will be collected during the second void of the day (Day 1 of Period 3). This second void of the day follows the first study product dose of the day (morning dose); the first void of the day (not collected) precedes the first study product dose of the day. The second urine sample will be collected on Day 2 of Period 3, within 30 minutes prior to the second study product dose of the day (evening dose).

The urine sample collected during Visit 1 and one of the 2 urine samples during Period 3 will be used for microscopic analysis and dipstick measurement of pH.

Both urine samples collected during Period 3 will be used to provide SS calcium oxalate (CaOx), SS calcium phosphate (CaP), and SS uric acid results. In addition, urinary calcium/creatinine and citrate/creatinine ratios will be provided from these spot urine samples collected during Period 3.

10.2.11.4. 24-hour Urine Preparation/Logistics

Subjects will be given instructions for 24-hour urine collection and, where appropriate, supplies for 24-hour collection. During Visit 2, the investigational site team should confirm that the second 24-hour urine collection was completed and sample sent to Litholink.

10.2.11.5. 24-hour Urine Collection

A 24-hour urine collection will be performed by subjects at home during Period 1 and Period 2 as a remote interaction (with assistance from parents or caregivers, as applicable, during each step of the process). The 24-hour urine collections (a total of 2) will not take place at each remote interaction. Rather, the first of two 24-hour urine collections will take place in association with Visit 1, and the second 24-hour urine collection will be completed during or prior to Visit 2 (ie, via a remote interaction) during the Stabilization Phase of Period 2. In cases where 24-hour urine collections are not feasible, spot urine samples will be requested. All other remote interactions will NOT involve a 24-hour urine collection.

Total urine volume will be recorded, and a well-mixed urine sample will be sent at ambient temperature to Litholink (according to directions from Litholink) or returned to the investigational site. Planned results from these collections include the following: urine volume, SS CaOx, SS CaP, SS uric acid, urine calcium excretion, urine oxalate excretion, urine uric acid excretion, urine citrate excretion, 24-hour urine pH, and potentially others. Spot urine samples may be collected in lieu of 24-hour urine collections in situations when 24-hour urine collection is not feasible.

10.2.11.6. Serum Bicarbonate and Serum Potassium

Blood samples will be collected for the measurement of serum bicarbonate and serum potassium levels during Period 2 as specified in [Section 6.2.2](#), with attention paid to proper blood volume limitations for pediatric subjects. During Period 3, samples will be collected pre-dose (AM) for the first 24 hours following administration of the first dose of blinded study product and every 24 hours thereafter unless the Investigator determines that additional sampling is necessary for safe management of the subject ([Section 6.2.3](#)). Blood samples will also be collected for the measurement of serum bicarbonate and serum potassium levels in association with Visit 4.

Samples for measurement of serum bicarbonate will be analyzed within 2 hours after obtaining the sample.

In the event a blood sample appears hemolyzed to any degree, another sample should be collected as soon as possible for measurement of a serum potassium level. If the degree of hemolysis is severe, another sample should be collected as soon as possible for measurement of a serum bicarbonate level, too.

Utilizing whole blood samples (0.1 cc), an electrolyte panel (Cl⁻, K⁺, Na⁺, tCO₂) will be prepared by a qualified delegate/nurse for measure of serum bicarbonate and serum potassium, analyzed and reported at point-of-care via the portable iSTAT System (Abbott Inc.).

10.2.11.7. Serum Pregnancy Test

Whole blood will be collected during Visits 1, 2, and 3 (prior to the administration of the first dose of blinded study product during Visit 3) to obtain serum for pregnancy testing in females of childbearing potential. Females of childbearing potential are those who have reached the onset of menarche (or 8 years of age, whichever comes first) and are not postmenopausal (≥ 1 year without menses prior to Visit 1)], surgically sterile, or status post hysterectomy (≥ 1 month prior to Visit 1). This includes females using oral, injectable, mechanical, or barrier contraception; females who are single and/or abstinent; and females whose male partners have been vasectomized or whose male partners have received or are utilizing contraceptive devices.

10.2.11.8. Genetic Screening

A blood sample will be collected during Visit 1 for genetic testing. Results from this testing will be recorded but not used to determine eligibility for participation in this study. In order to minimize the volume of blood collected during Visit 1, the genetic testing sample may be collected at a later study visit. Subjects can decline genetic screening and still be eligible for the study.

10.2.12. Review of ADV7103 Dosing Diary

Each subject (or parent or caregiver, on behalf of the subject) will enter ADV7103 dosing information into an ePRO diary. These should be reviewed during Period 2 and Visit 4.

10.2.13. Concomitant Medication Assessment

All medications taken within 30 days prior to Visit 1 will be documented during that visit. A review of all medications taken by the subject will be performed during every subsequent study visit (including each day of Period 3). All prescription and over-the-counter medications, herbal or nutritional products, and consumption of carbonated drinks will be captured and documented at each visit.

10.2.14. Review of Adverse Events

During all study visits, and in association with remote interactions, the subject will be questioned in a general manner about experiencing any AEs; no specific signs or symptoms will be suggested to the subject. Assessment of any previously reported AEs will be performed to ascertain current status (ongoing or resolved) and severity (if ongoing).

10.2.15. Questionnaires

The order/timing of administration of questionnaires in association with Visits 1 and 2 will be specified in the Study Manual. In the event of early study withdrawal by a subject following at least 4 weeks of study participation, questionnaires will be completed in association with the Early Withdrawal Visit. Subjects may opt out of questionnaire completion without being withdrawn from the study.

10.2.15.1. Chronic Treatment Acceptance Questionnaire

Treatment acceptance will be evaluated with a questionnaire - the Chronic Treatment Acceptance Questionnaire (ACCEPT). The ACCEPT questionnaire is a generic medication acceptance measure assessing how subjects weigh advantages and disadvantages of long-term medications. ACCEPT may be a predictor of subjects' future adherence to and/or persistence with their treatment ([Marant, 2012](#)). With 25 items, ACCEPT measures six treatment-attribute specific dimensions, covering all specific attributes of drug (Medication inconvenience, Long-term treatment, Regimen constraints, Side effects, Effectiveness, Numerous medications), and one general acceptance dimension. The structure of ACCEPT enables the interpretation of scores on several different levels including a first level of general treatment acceptance with the score of General domain ([Arnould, 2017](#)). The ACCEPT questionnaire will be completed by all subjects themselves aged from 13 years old and above (not applicable for subjects aged from 6 months to 12 years old).

10.2.15.2. Treatment Satisfaction Questionnaire for Medication

Treatment satisfaction will be measured by a questionnaire - Treatment Satisfaction Questionnaire for Medication (TSQM), version II. The TSQM is a generic instrument that measures subjects' satisfaction with medication ([Atkinson, 2004](#)). Four scores can be calculated: Side effects, Effectiveness, Convenience and Global satisfaction, with higher scores indicating higher satisfaction. The TSQM will be completed by all subjects themselves aged from 13 years old and above (not applicable for subjects aged from 6 months to 12 years old).

10.2.15.3. Pediatric Quality of Life Inventory Generic Core Scale

Quality of life will be estimated with a quantitative approach. Health-related quality of life will be measured by the Pediatric Quality of Life Inventory Generic Core Scale (PedsQL). The PedsQL is a generic measure of health-related quality of life applicable for healthy school and community populations, as well as patient populations with acute and chronic health conditions ([Varni, 2001](#); [Varni, 1999](#)). Its targeted population is comprehensive, ranging from 1 month of age to adults (1-12 months; 13-24 months; toddlers: 2-4 years; young children: 5-7 years; children: 8-12 years; teens: 13-18 years; young adults: 18-25 years; adults: > 25 years). The PedsQL is either self- (except for infant and toddler versions) or proxy- reported.

10.2.15.4. Treatment Preference

Treatment preference will be measured via a specific question which has three possible answers to measure the subject's treatment preference between ADV7103 and the subject's previous SOC treatment.

10.2.15.5. Face Hedonic Scale and Visual Analog Scale

Acceptability of ADV7103 or SOC in the different age subsets will be evaluated based on 5 specific parameters: palatability, ease of administration, ease of swallowing, number of study product daily intakes, and gastrointestinal tolerability.

These 5 parameters will be evaluated using a face hedonic scale and/or a visual analog scale (VAS) independently, at each time-point ([Section 17.2](#)). The evaluation will be global

impression based and not relative to a specific intake. The evaluation will be accomplished in one of the following ways:

- completed independently by the subject and reflects her/his impressions of the product;
- completed by the subject with help from a parent reflecting the subject's impressions of the product; or
- completed by a parent reflecting the parent's impressions about the product.

10.2.15.5.1. Palatability

- Adolescents and adults: palatability will be evaluated by the subject using a VAS scale.
- Children between 4 and 11 years old: palatability will be evaluated by the child subject using a hedonic scale and a VAS, with the help of parents/guardians if necessary.
- Infants and children between 6 months and 3 years old: palatability will be evaluated by one of the parents/guardians using a VAS scale. The evaluation should be done by the same parent/guardian during each visit.

10.2.15.5.2. Ease of Administration

- Adolescents and adults: ease of administration will be evaluated by the subject using a VAS.
- Children between 4 and 11 years old: ease of administration will be evaluated by one of the parents/guardians using a VAS. The evaluation should be done by the same parent/guardian during each visit.
- Infants and children between 6 months and 3 years old: ease of administration will be evaluated by one of the parents/guardians using a VAS. The evaluation should be done by the same parent/guardian during each visit.

10.2.15.5.3. Ease of Swallowing

- Adolescents and adults: ease of swallowing will be evaluated by the subject using a VAS scale.
- Children between 4 and 11 years old: ease of swallowing will be evaluated by the child subject using a hedonic scale and a VAS, with the help of parents/guardians if necessary.
- Infants and children between 6 months and 3 years old: ease of swallowing will be evaluated by one of the parents/guardians using a VAS scale. The evaluation should be done by the same parent/guardian during each visit.

10.2.15.5.4. Number of Study Product Daily Intakes

- Adolescents and adults: the convenience of the number of study product daily intakes will be evaluated by the subject using a VAS scale.
- Children between 4 and 11 years old: the convenience of the number of study product daily intakes will be evaluated by the child subject using a hedonic scale and a VAS, with the help of parents/guardians if necessary.
- Infants and children between 6 months and 3 years old: the convenience of the number of study product daily intakes will be evaluated by one of the parents/guardians using a VAS scale. The evaluation should be done by the same parent/guardian during each visit.

10.2.15.5.5. Gastrointestinal Tolerability

- Adolescents and adults: the gastrointestinal tolerability will be evaluated by the subject using a VAS scale.
- Children between 4 and 11 years old: the gastrointestinal tolerability will be evaluated by the child subject using a hedonic scale and a VAS, with the help of parents/guardians if necessary.
- Infants and children between 6 months and 3 years old: the gastrointestinal tolerability will be evaluated by one of the parents/guardians using a VAS scale. The evaluation should be done by the same parent/guardian during each visit.

10.2.16. Semi-structured Interview

A semi-structured interview will be conducted near the time of Visit 1, near the time of the final visit in Period 2 (ie, last Stabilization Phase Visit), and associated with an Early Withdrawal Visit (involving Visit 4 activities) where no second interview has taken place (if applicable) if

more than 4 weeks from the first interview. The interviews will include the following elements (refer to [Section 17.3](#)):

- subject's experiences with dRTA including symptoms and impacts on performance or activities of daily living;
- subject's experiences with metabolic acidosis (if applicable) when the disease was not well-controlled;
- how, if at all, the disease has evolved over time;
- subject's experiences and likes/dislikes with her/his current treatment;
- subject's motivations to participate in the clinical study and her/his expectations regarding the study products;
- consistent with the planned stratification, interviewing the pediatric population (< 18 years old) participants as follows:
 - subjects aged <7 years old: Only one of the parents will be interviewed for approximately 60 minutes.
 - subjects aged 7 to 14 years old: The child will be interviewed during the first part of the interview (~10 minutes); the remainder of the interview (~50 minutes) will be dedicated to the parent.
 - subjects aged 15 to 17 years old: The adolescent and her/his parent will be interviewed separately at two separate times for approximately 60 minutes each.

Interviews will be conducted by trained experienced interviewers and will last approximately 60 minutes each. Interviews will be conducted via phone or, when possible, with video support (via Skype or other video applications). With participants' verbal permission, the interviews will be audio recorded. Audio files will be stored in a de-identified way on a secure server and will be destroyed at the end of the project.

The objective of the stabilization qualitative interviews will be to compare subject experiences on their SOC with their experiences with ADV7103 and get subjects' perspectives regarding the evolution of their dRTA after they are stabilized on treatment with ADV7103 but before Period 3. The discussion will include:

- change over time of specific topics identified in the previous interview;
- any other physical, mental, or emotional changes that may have occurred;
- use experience with ADV7103;
- any differences perceived between using ADV7103 and the therapy they were using prior to the clinical study;
- whether ADV7103 offers benefits to subjects that they consider to be meaningful.

All subjects who participated in the Period 1/baseline qualitative interview will be invited to participate in an interview during the Stabilization Phase of Period 2 (and during an Early Withdrawal Visit, if applicable, for subjects who participated in the study for at least 4 weeks).

The interviews will be conducted by trained experienced interviewers from the Mapi Group/ICON, including interviewers who specialize in pediatric interviewing, and will last approximately 60 minutes each. Interviews will be conducted via phone with video support when possible (via Skype or another video application) with the exception of interviews with hearing impaired subjects who may be interviewed in person, if required. For in-person interviews with subjects experiencing hearing impairment, the clinical site will be responsible for obtaining the assistance of a caregiver or interpreter. All interviews will be audio recorded with participants' permission. Audio files will be stored in a de-identified way on a secure server and will be destroyed at the end of the project.

Subjects who opt out of the interviews will be eligible to continue in the study.

10.2.17. Dispensing Open-label ADV7103

An appropriate supply of open-label ADV7103 sachets will be dispensed to subjects at appropriate face-to-face visits, via home care visits, or other arrangements. Open-label ADV7103 will be dispensed during Visit 1 ONLY if all study eligibility criteria have been confirmed during the visit. During Visit 2, an appropriate supply of open-label ADV7103 will be provided to subjects to enable continuous dosing until Period 3, for any re-stabilization during Period 3, and until the study exit visit (Visit 4).

For subjects wishing to participate in the open-label extension study, Visit 4 of this study (Study B23CS; ARENA 2 Study) will be conducted on the same day as Visit 1 of the open-label extension study (Study B24CS; ARENA 2 Open-label Extension Study). An appropriate supply of open-label ADV7103 will be dispensed on this day for participation in the open-label extension study.

10.2.18. Administration of Blinded Study Product

Beginning with the first morning in Period 3, blinded study product (ADV7103 or placebo) will be administered orally approximately every 12 hours (just prior to both the morning and evening meals/snacks/feedings) to study subjects. Subjects who develop metabolic acidosis during Period 3 will be discontinued from randomized study product in a blinded fashion and receive active ADV7103 at the pre-randomization dose. They will remain in Period 3 for approximately 6 days, or until re-stabilized, whichever is longer. Subjects who do not develop metabolic acidosis during Period 3 will remain for a total of approximately 6 days unless the bDMC approves a shorter duration. Potassium supplementation, if applicable, should be stopped or dose-reduced at restoration of ADV7103.

10.2.19. Collection of Unused Open-label ADV7103

Unused open-label ADV7103 will be collected at admission to Period 3 for the purpose of sequestering open-label ADV7103 during the period of blinded study product administration. This open-label ADV7103 supply will be returned to the subject at discharge from Period 3 as appropriate. During Visit 4, all empty boxes and unused open-label ADV7103 for this study will be collected and not returned to the subject.

10.2.20. ADV7103 Accountability

During Visits 2 and 4, both the number of empty boxes of ADV7103 sachets and the number of unused sachets brought in by the subject will be counted and recorded for accountability purposes and compared against anticipated use based on dosing instructions provided to the subject and to the ePRO data.

10.3. Study Visits and Remote Interactions (Including Healthcare Provider Visits)

Study “visits” are required face-to-face encounters between the subject and investigational site staff. Many study assessments and activities can be performed without the necessity of face-to-face encounters with investigational site staff (eg, blood collection, urine collection, provision of ADV7103 dosing guidance via phone, resupply of open label ADV7103, etc) and will be referred to as “remote interactions” in this protocol.

Some study activities included in the above description of remote interactions (and others, if needed) will involve home visits by healthcare providers.

Lists of procedures and assessments to be performed at designated study visits are included in the following sections.

10.3.1. Period 1 (Enrollment/Screening)

Subjects are enrolled at the time informed consent is obtained.

10.3.1.1. Visit 1

The following procedures and assessments will be conducted in association with Visit 1:

- informed consent (and assent, when applicable) ([Section 13.5](#)). Informed consent must be obtained prior to performing any study-specific procedures or assessments.
- demographic information ([Section 10.2.2](#));
- medical history ([Section 10.2.3](#));
- vital signs ([Section 10.2.4](#));
- height of subject ([Section 10.2.5](#));
- total body weight of subject ([Section 10.2.5](#));
- targeted physical examination ([Section 10.2.6](#));
- Tanner staging, if appropriate ([Section 10.2.7](#));
- setup and instruction on the Medidata Patient Cloud for ADV7103 dosage recording;
- 12-lead ECG ([Section 10.2.7](#));
- renal ultrasound ([Section 10.2.10](#));
- hematology panel ([Section 10.2.11.1](#));
- serum chemistry panel ([Section 10.2.11.2](#));

- spot urine collection ([Section 10.2.11.3](#));
- preparation and instructions for 24-hour urine collection (urine needs to be collected prior to starting ADV7103) ([Section 10.2.11.4](#));
- serum pregnancy test (if applicable; [Section 10.2.11.7](#));
- genetic screening ([Section 10.2.11.8](#)); in order to minimize the volume of blood collected during Visit 1, the genetic testing sample may be collected at a later study visit;
- concomitant medications ([Section 10.2.13](#));
- adverse events ([Section 10.2.14](#));
- completion of questionnaires ([Section 10.2.13](#));
- arrangement for semi-structured interview ([Section 10.2.16](#));
- review of subject eligibility for the study; occurs prior to dispensing open-label ADV7103, if applicable ([Section 10.2.1](#)); and
- dispense open-label ADV7103 ONLY if all study eligibility criteria have been confirmed during this visit ([Section 10.2.17](#)).

10.3.2. Period 2 (Open-label, Lead-in)

Most subject encounters in Period 2 will be performed via a home healthcare service or via telephone (ie, as remote interactions) according to purpose as described in [Section 6.2.2](#). Visit 2 (last subject encounter in Period 2) must be conducted as an on-site visit.

10.3.2.1. Visit 2

The following procedures and assessments will be conducted in association with Visit 2:

- vital signs ([Section 10.2.4](#));
- targeted physical examination ([Section 10.2.6](#));
- ensure 24-hour urine collection was performed and results sent to Litholink ([Section 10.2.11.4](#));
- serum bicarbonate and serum potassium (all appropriate Period 2 remote interactions) ([Section 6.2.2](#) and [Section 10.2.11.6](#));
- serum pregnancy test (if applicable; [Section 10.2.11.7](#));
- review of ADV7103 dosing diary ([Section 10.2.12](#));
- concomitant medications ([Section 10.2.13](#));
- adverse events ([Section 10.2.14](#));
- completion of questionnaires ([Section 10.2.13](#));
- semi-structured interview associated with Visit 2 ([Section 10.2.16](#));

- ADV7103 accountability ([Section 10.2.20](#));
- dispensing open-label ADV7103 (as needed; [Section 10.2.17](#)); and
- review of subject eligibility for randomization ([Section 10.2.1](#)).

10.3.3. Period 3 (Randomized, Double-blinded Study Product Withdrawal)

Period 3 study visits will take place at the subject's home, via telehealth (audio/visual supported virtual visit) or if preferred and feasible at the investigator's site, on an outpatient/ office-level basis.

10.3.3.1. First Full Day in Period 3

The following procedures and assessments will be conducted in association with the first full day of Period 3:

- vital signs prior to the first dose of blinded study product ([Section 10.2.4](#)), and again later in the day;
- targeted physical examination prior to the first dose of blinded study product ([Section 10.2.6](#));
- begin cardiac monitoring prior to the first dose of blinded study product ([Section 10.2.9](#))
- hematology panel prior to the first dose of blinded study product ([Section 10.2.11.1](#));
- serum chemistry panel prior to the first dose of blinded study product ([Section 10.2.11.2](#));
- spot urine collection ([Section 10.2.11.3](#));
 - Urine samples will be collected during the second void of the day. This second void of the day follows the first study product dose of the day (ie, morning dose); the first void of the day (not collected) precedes the first study product dose of the day. The second daily urine sample will be collected within 30 minutes prior to the second study product dose of the day.
 - The urine sample collected during the first full day of Period 3 will be used for microscopic analysis and dipstick testing for determination of pH, as well as to provide SS CaOx, SS CaP, and SS uric acid results.
- serum bicarbonate and serum potassium ([Section 6.2.3](#) and [Section 10.2.11.6](#));
 - blood samples will be collected every 6 hours for the first 24 hours following the first dose of study product unless the Investigator determines that additional sampling is necessary for safe management of the subject.
- serum pregnancy test, prior to administration of blinded study product (if applicable; [Section 10.2.11.7](#));
- concomitant medications prior to the first dose of blinded study product ([Section 10.2.13](#));

- adverse events ([Section 10.2.14](#));
- collect unused ADV7103 prior to first dose of study product ([Section 10.2.19](#)); and
- administration of blinded study product just prior to the morning and evening meals/snacks/feedings ([Section 10.2.18](#)).

10.3.3.2. Remaining Days in Period 3

As described in [Section 6.2.3](#), the planned duration of stay in Period 3 is 6 days. If required for correction of metabolic acidosis, the duration may be extended beyond 6 days.

The following procedures and assessments will be conducted in association with each subsequent day that a subject remains in Period 3:

- vital signs daily ([Section 10.2.4](#));
- serum bicarbonate and serum potassium ([Section 6.2.3](#) and [Section 10.2.11.6](#));
 - blood samples will be collected every 24 hours after the first dose of blinded study product, unless the Investigator determines that additional sampling is necessary for safe management of the subject.
- spot urine collection ([Section 10.2.11.3](#));
 - The urine sample will be collected during the second void of each day. This second void of each day follows the first study product dose of each day (ie, morning dose); the first void of each day (not collected) precedes the first study product dose of each day.
 - The urine sample collected will be used for microscopic analysis and dipstick testing for determination of pH, as well as to provide SS CaOx, SS CaP, and SS uric acid results.
- concomitant medications ([Section 10.2.13](#));
- adverse events ([Section 10.2.14](#));
- administration of blinded study product ([Section 10.2.18](#)); and
- discharge from Period 3 (on last day).

10.3.4. Period 4 (Study Completion)

Period 4 represents the time between completion of Period 3 activities and completion of the study exit visit (ie, Visit 4) activities. The study exit visit (Visit 4) can be conducted immediately following the completion of all Period 3 activities or within 4 weeks of discharge from Period 3. Subjects will take their stable ADV7103 dose during this time between the end of Period 3 and the study exit visit..

In the unexpected situation where unacceptably low Period 3 baseline serum bicarbonate and/or serum potassium levels preclude dosing of blinded study product ([Section 6.2.3](#)), Period 4 will consist of the time from discharge from Period 3 through Visit 4. The subject will take

open-label ADV7103 or a SOC regimen, at the Investigator's discretion, during this time and will complete Visit 4 within 4 weeks of discharge.

In the event of early study withdrawal by a subject, an Early Withdrawal Visit should be performed (early withdrawal activities match those of Visit 4, as applicable).

10.3.4.1. Visit 4 or Early Withdrawal (Study Exit)

The following procedures and assessments will be conducted in association with Visit 4:

- vital signs ([Section 10.2.4](#));
- height of subject ([Section 10.2.5](#));
- total body weight of subject ([Section 10.2.5](#));
- targeted physical examination ([Section 10.2.6](#));
- serum chemistry panel, only if Visit 4 represents an Early Withdrawal Visit ([Section 10.2.11.2](#));
- serum bicarbonate and serum potassium; not needed if Visit 4 represents an Early Withdrawal Visit ([Section 10.2.11.6](#));
- review of ADV7103 dosing diary ([Section 10.2.12](#));
- concomitant medications ([Section 10.2.13](#));
- adverse events ([Section 10.2.14](#));
- completion of questionnaires ([Section 10.2.13](#)), only if the visit represents an Early Study Withdrawal Visit after at least 4 weeks of study participation;
- arrangement for semi-structured interview ([Section 10.2.16](#)), only if the visit represents an Early Study Withdrawal Visit after at least 4 weeks of study participation;
- collection of empty boxes of ADV7103 and unused ADV7103 for this study; and
- ADV7103 accountability ([Section 10.2.20](#)).

10.3.5. Unscheduled Visits

The Investigator or her/his designee may schedule a visit to the subject's home via telehealth or if feasible ask the subject to visit the investigational site for a variety of reasons depending on the clinical status of the subject. Laboratory and other tests are not mandatory for Unscheduled

Visits but may be performed at the Investigator's discretion. The following procedures and assessments can be conducted in association with Unscheduled Visits:

- vital signs ([Section 10.2.4](#));
- targeted physical examination ([Section 10.2.6](#));
- serum chemistry panel ([Section 10.2.11.2](#)), if the visit represents a study withdrawal visit;
- 12-lead ECG ([Section 10.2.8](#)), if clinically indicated for serum potassium < 3.0 mEq/L;
- concomitant medications ([Section 10.2.13](#)); and
- adverse events ([Section 10.2.14](#)).

11. ASSESSMENT OF SAFETY

11.1. Safety Parameters

The safety of ADV7103 will be assessed, in part, using parameters included in Section 10.2.1 through Section 10.2.11.7. Adverse events (AEs), defined in Section 11.2.1, will be captured during every study encounter following signature of the informed consent form.

11.2. Adverse Events and Serious Adverse Events

11.2.1. Definitions

11.2.1.1. Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a subject administered an IP or has undergone study procedures and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the IP, whether or not related to the IP.

An abnormality identified during a medical test (eg, laboratory parameter, vital sign, ECG data, physical examination finding) should be defined as an AE only if the abnormality meets at least one of the following criteria:

- induces clinical signs or symptoms;
- requires active intervention;
- requires interruption or discontinuation of the IP;
- the abnormality or test result is clinically significant in the opinion of the Investigator.

11.2.1.2. Serious Adverse Event (SAE)

An AE is considered “serious” if, in the view of either the Investigator or Sponsor, it:

- results in death;
- is life threatening (An AE is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death);
- results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- results in a congenital anomaly or birth defect;
- requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious); or
- represents a medically important event as determined by the Investigator.

Medical and scientific judgment should be exercised in deciding whether AEs are serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The following are not considered SAEs:

- hospitalization for elective or preplanned treatment for a pre-existing condition unrelated to the condition under study and which has not worsened since informed consent; and
- hospital admission due to social or situational events (eg, travel conditions that interfere with ability to leave hospital setting).

11.2.1.3. Suspected Unexpected Serious Adverse Reaction (SUSAR)

A suspected unexpected serious adverse reaction (SUSAR) is any adverse drug reaction (ADR) that is serious, unexpected, and suspected, meaning there is a reasonable possibility that the IP caused the adverse event. An AE or suspected adverse reaction (ie, an AE related to the IP) is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed.

11.3. Relationship of Adverse Event to Study Product

An Investigator who is qualified in medicine must make a determination of relationship to the study product for each AE. [Table 3](#) includes the criteria for determining relationship between the AE and the study product.

Table 3: Criteria for Determining Causal Relationship to the Study Product

Causal Relationship to the Study Product	Criteria for Determining Causal Relationship
Definitely Related	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to administration of the study product and cannot be explained by concurrent disease or other devices, drugs, or chemicals.
Possibly Related	There is some evidence to suggest a causal relationship (eg, the event occurred within a reasonable time after administration of the study product). However, the influence of other factors may have contributed to the event (eg, the subject's clinical condition, other concomitant events). Although an adverse effect may rate only as "possible" soon after discovery, it can be flagged as requiring more information and later be upgraded to probable or certain as appropriate.
Unlikely Related	A clinical event, including an abnormal laboratory test result, whose temporal relationship makes a causal relationship improbable (eg, the event did not occur within a reasonable time after administration of the study product) and in which other drugs or chemicals or underlying disease provide plausible explanations (eg, the subject's clinical condition, other concomitant treatments).
Not Related	A clinical event, including an abnormal laboratory test result, which occurs when the subject was not exposed to the study product or, another cause is obvious and in which there is sufficient information that the etiology of the event is not related to the study product.

If the relationship between the AE and the study product is determined to be "definitely related" or "possibly related," the AE will be considered to be related to the study product for the purposes of expedited regulatory reporting.

11.4. Severity of an Adverse Event

The severity of AEs, including abnormal clinical laboratory results, will be assessed according to the criteria in [Table 4](#).

TBDpTable 4: Criteria for Determining the Severity Grade of an Adverse Event

Severity Grade	Severity Assessment Standard
Grade 1 (Mild)	The AE requires minimal or no treatment. The AE doesn't interfere with the subject's daily activities.
Grade 2 (Moderate)	The AE results in a low level of inconvenience or concerns with the therapeutic measures. The AE may cause some interference with functioning or reduction with the usual level of activity of the subject.
Grade 3 (Severe)	The AE may require systemic drug therapy or other treatment. The AE causes a significant impairment of functioning, interrupts a subject's usual daily activity and is usually incapacitating.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of the onset and duration of each episode.

It is important to distinguish between SAEs and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria listed in Section 11.2.1.2. An AE of severe intensity may not be considered serious.

11.5. Reporting Adverse Events

11.5.1. All Adverse Events

At each study visit (on-site or via telephone), the subject will be questioned in a general manner, and no specific signs or symptoms will be suggested. If any AEs have occurred, they will be recorded on the AE pages of the electronic case report form (eCRF) and in the subject's medical record. If known, the diagnosis should be recorded in preference to the listing of individual signs and symptoms.

11.5.2. Serious Adverse Events

Any SAE which occurs at any time following informed consent through the last study visit, whether or not causally related to the study product, must be reported by the Investigator to CTI Safety immediately (**no later than 24 hours after learning of its occurrence**):

Vigipharme Global Safety & Pharmacovigilance

SAE eFax #: +33 (0)4 67 10 72 53

E-mail: pharmacovigilance@advicenne.com

If there are any questions, or if clarification is needed regarding the SAE, please contact the Medical Monitor for this study ([Table 1](#)).

Follow-up information for the event should be sent promptly (within 7 days of the initial notification).

Full details of the SAE should be recorded on the medical records and in the eCRF. The following minimum information is required:

- study number (B23CS);
- subject number, gender and age;
- date of report;
- description of the SAE (event, seriousness of the event); and
- causal relationship to the study product.

Advicenne Pharma or its designee will submit expedited safety reports to the regulatory agencies as necessary, and will inform the investigators of such regulatory reports. Investigators must submit safety reports as required by their IRB/IEC within timelines set by applicable regulations. Documentation of the submission to and receipt by the IRB/IEC of expedited safety reports should be retained by the site.

Investigators will also be notified of all unexpected, serious, study product-related events (7/15 day safety reports) that occur during the clinical study. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

11.6. Duration of Adverse Event Follow Up

If any AEs are present when a subject completes her/his last study visit (including early termination, if applicable), the subject will be re-evaluated within an appropriate period of time. At the Investigator's discretion, minor AEs can be re-evaluated via telephone and documented. If the AE has still not resolved, additional follow up will be performed as appropriate. Every effort should be made by the Investigator or her/his delegate to contact the subject until the AE has resolved or stabilized or the Medical Monitor and Investigator agree that further follow up is not necessary. This should be documented in the subject's medical records.

11.7. Reporting of Pregnancy

If a subject becomes pregnant during study participation, basic information about the pregnancy will be recorded in the Pregnancy eCRF and submitted to CTI Safety. Pregnancy in itself is not regarded as an AE unless there is a suspicion that a study product may have interfered with the effectiveness of a contraceptive medication. If there are complications during the pregnancy, the complications are recorded as AEs. The subject will be asked to report the outcome of the pregnancy even if her study participation is discontinued, and the site should submit the information to CTI Safety within 30 days after the outcome of the pregnancy. All reports of congenital abnormalities/birth defects are SAEs to be entered on the mother's (ie, subject's) SAE form. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be reported as AEs. Partner pregnancies do not need to be reported.

11.8. Data Monitoring Committees

11.8.1. Unblinded Data Monitoring Committee

An uDMC will be established to review study data and approve randomization of subjects following blinded dosing of study product in the initial age group. Starting with the oldest group (≥ 12 years old), each subsequently younger group will be randomized after 4 subjects from the preceding older age group have completed Period 3 and the uDMC approves randomization in the next younger group. During uDMC review of data from an age group, enrollment into that age group may continue unless the uDMC recommends cessation of this activity. The uDMC may request additional subjects complete the study in the age group under uDMC review prior to approving randomization of the next younger group. In addition, after reviewing data from randomized subjects who do not complete the Withdrawal Period, the uDMC may recommend changes to the protocol (including, but not limited to, increasing the total number of subjects enrolled in the study) to ensure a reasonable balance of early withdrawals between treatment groups. Lastly, if laboratory data, clinical symptoms, and cardiac monitoring data warrant, the uDMC may recommend modification of cardiac monitoring.

The uDMC will consist of individuals who are not directly involved in the conduct of the study. All uDMC activities will be organized to ensure that blinding is preserved for Investigators, the Sponsor, and Sponsor representatives during study conduct. A charter will be prepared to further describe membership and the roles and responsibilities of the uDMC.

11.8.2. Blinded Data Monitoring Committee

A bDMC will review data from an initial subset of at least 8 subjects completing Period 3 to determine if the duration of Period 3 may be adjusted in order to adequately capture primary endpoints while maximizing subject retention. The subjects to be evaluated for this purpose will include at least 4 subjects ≥ 12 years old and at least 2 subjects 2-11 years old. A charter will be prepared to further describe membership and the roles and responsibilities of the bDMC.

12. STATISTICS

12.1. Number of Subjects

Approximately 40 subjects will enter the Open-label Lead-in Period (Period 2), so that at least 32 are randomized and complete the Withdrawal Period (Period 3). Sixteen evaluable subjects per arm provides at least 90% power to show superiority of ADV7103 over placebo in the proportion of subjects who develop hyperchloremic metabolic acidosis up to Day 6. This calculation assumes that approximately 85% of placebo subjects and 15% of ADV7103 subjects will develop hyperchloremic metabolic acidosis. Significance will be assessed at the 2-sided 5% level.

Randomization will be stratified according to the following age categories:

- 6 months - 23 months old
- 2 - 11 years old
- ≥ 12 years old.

12.2. Analysis Sets

The Intent-to-Treat (ITT) analysis set is defined as all randomized subjects in Period 3.

The Modified Intent-to-Treat (mITT) analysis set is defined as all subjects in the ITT Analysis Set who received study product in Period 3 and who have both a baseline and at least one post baseline efficacy assessment in Period 3.

The Per-Protocol (PP) analysis set is defined as all subjects in the mITT analysis set who have no major protocol deviations affecting the assessment of efficacy. Membership of the PP analysis set will be confirmed prior to unblinding the data.

The ITT, mITT, and PP analysis sets will be analyzed per planned study product assignment.

The Safety analysis set is defined as all subjects who receive at least one dose of study product in any period or phase. The Safety analysis set will be analyzed per actual study product received.

12.3. Primary Analysis

The primary endpoint is the proportion of subjects with at least one episode of metabolic acidosis up to Day 6. All non-missing serum bicarbonate measurements from first study product dose in Period 3 to Day 6 (≤ 24 hours post-last dose) or early discontinuation will be considered.

The primary analysis will be based on the ITT set. The primary study product comparisons will be made using the two-sided Cochran-Mantel-Haenszel (CMH) test stratified by age category.

12.4. Secondary Analyses

The proportion of subjects with significant hypokalemia up to Day 6 of Period 3 will be similarly analyzed with a CMH test.

The proportion of subjects who fail to maintain serum bicarbonate levels ≥ 18 mEq/L for subjects ≥ 4 years old or ≥ 17 mEq/L for subjects < 4 years old up to Day 6 will be compared

with the CMH test. Time to first episode of metabolic acidosis and time to first episode of hypokalemia will be compared with a log-rank test. Mean change in serum bicarbonate level, mean change in serum potassium level, mean change in urine calcium/creatinine ratio, and mean change in urinary citrate/creatinine ratio will be compared at a last observation carried forward (LOCF) endpoint with an analysis of covariance model, having study product assignment and age category as factors and baseline as a covariate.

Descriptive summaries will be provided by study product and overall for the Open-label Lead-in Period (Period 2).

Safety data will be summarized in the safety analysis set by study product and over time, for each period separately and overall.

12.5. Multiplicity Adjustment Strategy

A sequential gatekeeping approach will be used to control the Type I error rate for testing primary and secondary efficacy endpoints.

12.6. Additional Analyses

The primary and secondary analyses will be repeated on the mITT and PP Sets. Furthermore, selected sensitivity analyses will be performed on the ITT set including multiple imputation and worst case methods.

12.7. Subgroup Analyses

A subgroup analysis of key efficacy and safety data will be performed by age category. Given the expected small sample size, no study product comparison will be made.

12.8. Interim Analysis

No formal interim analysis of efficacy is planned.

13. STUDY MANAGEMENT

13.1. Ethical Conduct of the Study

The study will be conducted according to the protocol and the following regulatory and ethical standards:

- Declaration of Helsinki adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, as last amended by the World Medical Assembly in 2013;
- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), E6 Good Clinical Practice: Consolidated Guidance (ICH E6);
- ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting;
- ICH E8 Guidance on General Considerations for Clinical Trials;
- Applicable regional, national, and local regulatory requirements.

13.2. Specific Ethical Considerations Involving Pediatric Subjects

Since the study involves pediatric subjects, attempts will be made to minimize potential discomforts inherent to study procedures and associated constraints.

13.2.1. Blood sampling

The volume of blood withdrawn and the number of venipunctures per subject will be minimized. For example, whenever possible, collection of blood samples for efficacy and safety assessments will be planned at the same time to limit the number of venipunctures; micro-volumes and micro-assays will be used whenever possible. To reduce pain, topical anesthesia can be applied to the sampling area as appropriate. In order to minimize the volume of blood collected during Visit 1, the genetic testing sample may be collected at a later study visit. In addition, a heparin lock (or similar device) may be used during Period 3 for collection of blood samples.

13.2.2. Study visits

Whenever possible, the frequency of study visits will be minimized. Visits will be planned in a manner that minimizes disruption of the subject's usual activities. Many protocol-specified encounters can be conducted via telephone.

The parents/legal guardian will be fully informed concerning all procedures performed during the clinical study (ie, invasive or not; standard care or study-specific). An age-appropriate explanation will be given to the subject prior to any investigation or procedure.

13.3. Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be provided only after approval of the subject is given to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

Advicenne Pharma shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

Advicenne Pharma affirms the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials (where allowed by local or national regulations) will identify subject data retrieved by Advicenne Pharma or its designee. However, Advicenne Pharma requires the Investigator to permit Advicenne Pharma, Advicenne Pharma's representative(s), the IRB/IEC, and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

Advicenne Pharma will ensure that the use and disclosure of protected health information obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information.

13.4. Institutional Review Board/Independent Ethics Committee

Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) must be constituted according to the applicable requirements, including ICH GCP.

It is the responsibility of each Principal Investigator (or designee) to submit the protocol, IB, subject informed consents, subject recruitment materials (if applicable), and other documentation (eg, ePRO diary) as required by the IRB/IEC to her/his IRB/IEC for review and approval. A copy of the written approval must be provided to the CRO (contract research organization). The documentation should clearly mention the approval/favorable opinion of the protocol, the subject informed consent form, and subject recruitment materials (if applicable), including respective version dates. The written approval and a list of current membership, or Department of Health and Human Services Assurance Number or letter from the IEC/IRB stating that the membership list is on file, must be obtained from the IRBs/IECs and provided to the CRO prior to the release of clinical study supplies to the investigational site and commencement of the study. If any member of the IRB/IEC has direct participation in this trial, written notification regarding his or her abstinence from voting must also be obtained.

Each investigator must adhere to all requirements stipulated by her/his respective IRB/IEC. This includes notification to the IRB/IEC regarding protocol amendments, updates to the subject informed consent, recruitment materials intended for viewing by subjects, expedited safety reports, SAEs and unexpected AEs, reports and updates regarding the ongoing review of the trial at intervals specified by the respective IRB/IEC, and submission of final study reports and summaries to the IRB/IEC.

13.5. Informed Consent/Assent

The informed consent document will embody the elements of informed consent as described in the World Medical Association Declaration of Helsinki, applicable national regulations, ICH E6 guideline (GCP), and in accordance with any local regulations. The Investigator (or designee such as the CRO) is responsible for the preparation, content, and IRB/IEC approval of the informed consent document and any other written information to be provided to the subjects. The consent form must be approved by the site's IRB/IEC and be acceptable to Advicenne Pharma.

13.5.1. Adults Capable of Providing Informed Consent

Adults capable of providing informed consent must provide it prior to participation in any aspect of this study. Each subject will receive a signed and dated copy of the informed consent. In addition, this information should be recorded in the subject's medical record (ie, source document). The consent form must be written in a language fully comprehensible to the prospective subject. The investigator or designee shall give the subject adequate opportunity to read it before it is signed and dated. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB/IEC. Subjects must be given ample opportunity to inquire about details of the study.

13.5.2. Minors/Vulnerable Subjects

If a subject cannot provide informed consent and requires that a parent or legally authorized representative fulfill this function (eg, minor), the subject should be informed about the study to the extent compatible with the subject's understanding. If capable, the subject should assent and sign and personally date the written consent form. A separate IRB/IEC approved assent form may be used, describing (in simplified terms, with pictures for small children) the details of the study product, study procedures, and risks of study participation. Assent forms do not substitute for the consent form signed by the subject's legally authorized representative.

Resources should be made available for hearing-impaired subjects in order to make sure that they are informed about the study to the extent compatible with their understanding. These resources may include availability of someone who can ask and address questions effectively via sign language, additional visual diagrams/aids, and others as appropriate.

A pediatric subject is legally unable to provide informed consent. Therefore, pediatric study subjects are dependent on their parent(s)/legally authorized representative to assume responsibility for their participation in the clinical study. Fully informed consent will be obtained from the subject's legally authorized representative in accordance with regional laws or regulations, at the same time as assent will be sought from the child.

The explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical study at any time will be fully considered and respected by the Investigator.

If the child's assent is not obtained, it will be documented with justification in the consent form which is signed by the parent(s)/legally authorized representative, and Investigator.

If an adolescent reaches an age to legally provide informed consent during the study, informed consent will be sought directly from the subject as soon as possible. Precautions will be taken to ensure that information provided is sufficiently understood.

13.6. Substantial Amendments to the Protocol

A substantial amendment must be agreed to in writing by Advicenne Pharma and submitted to and approved by the respective regulatory authority and IRB/IEC before the amendment can be implemented. Written approval of a protocol amendment is not required prior to implementation of changes to the protocol which eliminate an immediate hazard to the study subject; however,

approval must be obtained as soon as possible thereafter. Any amendments must also be signed by the PI.

13.7. Study Monitoring

It is the responsibility of the PI to ensure that the study is conducted in accordance with the protocol, GCP, applicable regulatory requirements, and the currently approved Declaration of Helsinki, and that valid data are entered into the eCRF.

To achieve this objective, the monitor's duties are to ensure the maintenance of complete, legible, well-organized, and easily retrievable data. The monitor will review the protocol and any amendments with the PI and study team. In addition, the monitor will explain the PI's reporting responsibilities and all applicable regulations concerning the clinical evaluation of the study product.

The investigator will permit representatives of Advicenne Pharma and the CRO to monitor the study as frequently as Advicenne Pharma or the CRO deem necessary to determine that data recording and protocol adherence are satisfactory. The eCRF data and related source documents will be reviewed in detail by the monitor at each visit, in accordance with relevant Standard Operating Procedures (SOPs) and ICH GCP regulations. This includes results of tests performed as a requirement for participation in this study and any other medical records required to confirm information contained in the eCRF such as past medical history and secondary diagnoses. The PI and her/his staff will be expected to cooperate with the monitor and provide any missing information whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by the monitor's signature and date on the study-specific monitoring log.

13.8. Case Report Form

An eCRF will be used for this study. The data will be entered in the eCRF in a timely manner on an ongoing basis.

The PI is responsible for ensuring that data are properly recorded in each subject's eCRF and related documents. The PI should personally sign the eCRFs in accordance with the procedure described in the eCRF completion guidelines to ensure that the observations and findings are correct and complete.

For data handled by the CRO, eCRF data and some or all of the study-related data will be managed and stored electronically in the CRO's database system. Validated data will subsequently be transferred to Advicenne Pharma.

13.9. Data Verification Procedures

It is the PI's obligation to ensure documentation of all relevant data in the subject's medical record. The subject's medical record will be considered the source document. The eCRF should not be used as the source for study information.

The PI will maintain a subject identification code list to enable unambiguous identification of the subjects (subject names and corresponding subject numbers). The subject identification code list is an essential document and as such should be maintained according to the ICH GCP guidelines.

13.10. Retention of Records

All documentation pertaining to the study will be kept by Advicenne Pharma or its designee in accordance with ICH guidelines and applicable national and local regulations.

The PI agrees to keep records and those documents that include (but are not limited to) the identification of all participating subjects, medical records, study-specific source documents, all original signed and dated informed consent forms, query responses, and detailed records of study product disposition to enable evaluations or audits from regulatory authorities and Advicenne Pharma or its designees. These documents are to be retained until at least two 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 IP. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or if needed by Advicenne Pharma. Advicenne Pharma will notify the site/PI if the marketing application is approved or if the investigational new drug (IND) application/Investigational Medicinal Product Dossier is discontinued. The PI agrees to obtain Advicenne Pharma's agreement prior to disposal, moving, or transferring of any study-related records. Advicenne Pharma will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records. All data will be entered into the eCRFs supplied for each subject.

13.11. Protocol Deviations

A protocol deviation is any nonadherence to the protocol or associated GCP requirements. The nonadherence may be either on the part of the participant, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. Although in principle protocol deviations are not permitted, under emergency circumstances, deviations may proceed without prior approval of Advicenne Pharma and the IRB/IEC to protect the rights, safety, and well-being of human subjects.

All protocol deviations will be documented and reported by the CRO during the course of the study in the monitoring reports. All deviations will be reported to Advicenne Pharma who will agree on the necessary actions to be taken.

If required per their guidelines, reports concerning protocol deviations must be provided to the local IRB/IEC.

13.12. Reporting

Following database lock and analysis of study data, a clinical study report (CSR) will be developed. The CSR will include a summary of available data, statistical methods, results, and interpretation of the results. The CSR will be submitted to regulatory authorities in a timely manner as appropriate.

14. QUALITY CONTROL AND QUALITY ASSURANCE

Following written SOPs, the monitors will verify that the clinical study is conducted and data are generated, documented (recorded), and reported according to the protocol, GCP, and applicable regulatory requirements. Reports of monitoring activities will be submitted to Advicenne Pharma in a timely manner.

The investigational site will provide direct access to all study-related areas, source data/documents, and reports for the purpose of monitoring and auditing by Advicenne Pharma or its designee and inspection by local and regulatory authorities.

Quality control procedures will be implemented for data entry, and data quality control checks will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

It is the responsibility of Advicenne Pharma or its designee to perform auditing (if applicable) as part of implementing quality assurance. The purpose of an audit, which is independent of and separate from routine monitoring or quality control functions, is to evaluate study conduct and adherence to the protocol, SOPs, GCP, and the applicable regulatory requirements.

Authorized representatives from Advicenne Pharma, regulatory authorities, and IEC/IRB will be granted access to the site and relevant study documentation to perform audits or inspections. The PI should contact Advicenne Pharma or the CRO immediately if contacted by a regulatory agency about an inspection involving this protocol.

15. RESPONSIBILITIES OF THE PRINCIPAL INVESTIGATOR

The role of the PI is to implement and manage the day-to-day conduct of the clinical investigation as well as to ensure data integrity and the rights, safety, and well-being of the subjects involved in the clinical investigation.

15.1. Informed Consent

The PI shall ensure that the process for obtaining informed consent:

- Includes all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation;
- Avoids any coercion or undue improper influence on, or inducement of, the subject to participate;
- Does not waive or appear to waive the subject's legal rights;
- Uses native non-technical language that is understandable to the subject;
- Provides ample time for the subject and/or her/his legally authorized representative to read and understand the informed consent form and to consider participation in the clinical investigation;
- Provides the subject and/or her/his legally authorized representative with a copy of the signed and dated informed consent form and any other written information.

The PI shall ensure and document appropriate training if an authorized designee is appointed to conduct the informed consent process.

15.2. Adherence to the Protocol

The PI will do all of the following:

- Indicate her/his acceptance of the protocol in writing;
- Conduct the clinical investigation in accordance with the protocol;
- Create and maintain source documents throughout the clinical investigation and make them available as requested during monitoring visits or audits;
- Ensure that the IP is used solely by authorized users, and in accordance with the protocol and instructions for use;
- Propose to Advicenne Pharma any appropriate modification(s) of the protocol;
- Refrain from implementing any modifications to the protocol without agreement from Advicenne Pharma, IRB/IEC, and, if required, regulatory authorities;
- Document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation;
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation;

- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable;
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to Advicenne Pharma in the eCRFs and in all required reports;
- Maintain the IP accountability records or assign a designee to do this (with PI oversight);
- Allow and support Advicenne Pharma or its designee to perform monitoring and auditing activities;
- Be accessible to the monitor and respond to questions during monitoring visits;
- Allow and support regulatory authorities and the IRB/IEC when performing auditing activities;
- Ensure that all clinical-investigation-related records are retained as specified in this protocol.

15.3. Medical Care of Subjects

The PI will do all of the following:

- Provide adequate medical care to a subject during and after a subject's participation in a clinical investigation in the case of AEs;
- Inform the subject and/or her/his legally authorized representative of the nature and possible cause of any AEs experienced;
- Inform the subject and/or her/his legally authorized representative of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required;
- Provide the subject and/or her/his legally authorized representative with well-defined procedures for possible emergency situations related to the clinical investigation, and make the necessary arrangements for emergency treatment;
- Ensure that clinical records are clearly marked to indicate that the subject is enrolled in a particular clinical investigation;
- Inform, with the subject's (or legally authorized representative's) approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation;
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from the clinical investigation while fully respecting the subject's rights.

15.4. Safety Reporting

The PI will do all of the following:

- Record every AE together with an assessment, in accordance with [Section 11](#) of this protocol;
- Report to Advicenne Pharma or its designee, without unjustified delay, all SAEs and medically significant events as specified in [Section 11.5](#) of this protocol;
- Supply Advicenne Pharma or its designee, upon request, with any additional information related to the safety reporting of a particular event.

16. LIST OF REFERENCES

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17. APPENDICES

- 17.1 Study Schedule
- 17.2 Face Hedonic Scale and Visual Analog Scale
- 17.3 Semi-structured Interview Guides

17.1. Study Schedule

Activities	Study Encounters					
	Period 1	Periods 1, 2, 4	Period 2	Period 3	Period 4	Periods 1, 2, 4
	Visit 1 ^a	Remote Interactions ^b	Visit 2 ^a	Visit 3 ^a	Visit 4 ^a or Early W/D	Unscheduled Visit(s) ^{a,c}
	Enroll/Screen [≤ 28d]		ADV7103 Titration; Stabilization [7-12 wk]	Blinded Withdrawal [~6 d]	Study Completion [≤ 4 wk]	
Informed Consent ^d	X			X		
Demographics	X					
Medical History	X					
Vital Signs ^e	X		X	X	X	X
Height of Subject	X				X	
Total Body Weight of Subject	X				X	
Targeted PE	X		X	X ^{f,g}	X	X
Tanner Staging, if appropriate	X					
Medidata Patient Cloud Setup/Instruction	X					
12-lead ECG	X					X ^h
Cardiac Monitoring (Holter monitor, telemetry, other)				X ⁱ		
Renal Ultrasound ^j	X					
Hematology Panel	X			X ^f		
Serum Chemistry Panel ^k	X			X ^{f,g}	X ^l	

Activities	Study Encounters					
	Period 1	Periods 1, 2, 4	Period 2	Period 3	Period 4	Periods 1, 2, 4
	Visit 1 ^a	Remote Interactions ^b	Visit 2 ^a	Visit 3 ^a	Visit 4 ^a or Early W/D	Unscheduled Visit(s) ^{a,c}
	Enroll/Screen [≤ 28d]		ADV7103 Titration; Stabilization [7-12 wk]	Blinded Withdrawal [~6 d]	Study Completion [≤ 4 wk]	
Spot Urine Collection ^m	X			X ⁿ		
24-hour Urine Prep/Logistics ^o	X		X			
24-hour Urine Collections ^p		X ^p				
Serum Bicarbonate ^q and Potassium		X	X	X (q6h x 24h) ^r then q8h	X	
Serum Pregnancy Test ^s	X		X	X ^r		
Genetic Screening ^t	X					
Review ADV7103 Dosing Diary (ePRO)			X		X	
Concomitant Meds	X	X	X	X	X	X
AEs	X	X	X	X	X	X
Questionnaires ^u	X		X		X ^l	
Semi-structured Interview	X		X		X ^l	
Review Inclusion/Exclusion Criteria	X					
Review Eligibility for Randomization ^v			X			
Dispense ADV7103	X ^w	X	X ^x			

Activities	Study Encounters					
	Period 1	Periods 1, 2, 4	Period 2	Period 3	Period 4	Periods 1, 2, 4
	Visit 1 ^a	Remote Interactions ^b	Visit 2 ^a	Visit 3 ^a	Visit 4 ^a or Early W/D	Unscheduled Visit(s) ^{a,c}
	Enroll/Screen [≤ 28d]		ADV7103 Titration; Stabilization [7-12 wk]	Blinded Withdrawal [~6 d]	Study Completion [≤ 4 wk]	
Administer Blinded Study Product				X		
Discharge from Period 3 (last day of Period 3)				X		
Collect Unused ADV7103 ^y				X ^f	X	
Perform ADV7103 Accountability ^z			X		X	

Abbreviations: AE, Adverse event; d, day(s); ECG, electrocardiogram; ePRO, electronic patient reported outcomes; PE, physical examination; W/D, withdrawal; wk, week(s).

^a Study “visits” are protocol-specified face-to-face encounters between the subject and investigational site staff. Included among these “visits” are those that are unscheduled but necessary for a variety of clinical reasons.

^b Many study procedures can be performed without the necessity of face to face encounters with investigational site staff (eg, blood collection, urine collection, provision of ADV7103 dosing guidance via phone, resupply of open label ADV7103, etc). These encounters that do not require a face to face interaction with investigational site staff will be referred to as “remote interactions” in this protocol, irrespective of where they occur.

^c Laboratory tests and other procedures to be done at the Investigator’s discretion.

^d Informed consent (and assent, when appropriate) should be obtained prior to any study-related activities; subjects are considered enrolled at the time of informed consent.

^e Vital signs (supine blood pressure, heart rate, respiratory rate, and oral temperature) to be done at protocol-specified visits.

^f Prior to the first dose of blinded study product.

^g During Period 3, both a targeted physical examination and a serum chemistry panel will be completed/obtained prior to the first dose of randomized, blinded study product and again on the last day of activities (including the day of early withdrawal, if applicable).

^h If clinically indicated for serum potassium < 3.0 mEq/L.

ⁱ Begin prior to the first dose of blinded study product and continue through the end of Period 3.

^j Must be completed and results assessed before open label ADV7103 is dispensed to the subject.

^k Serum chemistry panel includes, at a minimum, the following analytes: sodium, potassium, chloride, bicarbonate/total carbon dioxide, blood urea nitrogen, serum creatinine, glucose, calculated eGFR, aspartate transaminase, alanine transaminase, total bilirubin, alkaline phosphatase, calcium, phosphorus, magnesium, and uric acid.

^l Only if the visit represents an Early Study Withdrawal Visit after at least 4 weeks of study participation.

^m For microscopic urinalysis and dipstick testing for determination of pH.

ⁿ Please refer to [Section 10.2.11.3](#) of this protocol for additional important details. During each full day of Period 3, two spot urine samples will be collected. The first of 2 daily urine samples will be collected during the second void of the day. This second void of the day follows the first study product dose of the day (morning dose); the first void of the day (not collected) precedes

the first study product dose of the day. The second daily urine sample will be collected within 30 minutes prior to the second study product dose of the day (evening dose).

^o During Visit 1, subjects will be given instructions for 24-hour urine collection and, where appropriate, supplies for 24-hour collection. During Visit 2, the investigational site team should confirm that the second 24-hour urine collection was completed and sample sent to Litholink.

^p The 24-hour urine collections (a total of 2) will not take place at each remote interaction. Rather, the first of two 24-hour urine collections will take place in association with Visit 1 (ie, following Visit 1 during a remote interaction), and the second 24-hour urine collection will be completed during or prior to Visit 2 (ie, via a remote interaction) during the Stabilization Phase of Period 2. In cases where 24-hour urine collections are not feasible, spot urine samples will be requested. All other remote interactions will NOT involve a 24-hour urine collection.

^q Results to be determined within 2 hours after blood sample collection. During Period 2, blood sample collection should be prior to the morning dose of ADV7103. In the event a blood sample appears hemolyzed to any degree, another sample should be collected as soon as possible for measurement of a serum potassium level. If the degree of hemolysis is severe, another sample should be collected as soon as possible for measurement of a serum bicarbonate level, too.

^r Following first dose of blinded study product. The sampling frequency may be adjusted if the Investigator determines that additional sampling is necessary for safe management of the subject.

^s For females of childbearing potential only; serum test. Females of childbearing potential are those who have reached the onset of menarche (or 8 years of age, whichever comes first) and are not postmenopausal (≥ 1 year without menses prior to Visit 1)], surgically sterile, or status post hysterectomy (≥ 1 month prior to Visit 1). This includes females using oral, injectable, mechanical, or barrier contraception; females who are single and/or abstinent; and females whose male partners have been vasectomized or whose male partners have received or are utilizing contraceptive devices.

^t In order to minimize the volume of blood collected in association with Visit 1, the genetic testing sample may be collected at a later study visit (results will not be used to determine study eligibility).

^u Includes ACCEPT, TSQM, PedsQL, Treatment Preference, and Facial Hedonic Scales and VAS ([Section 10.2.15](#)).

^v Randomization will be completed after informed consent (and assent, when appropriate) for Period 3 is obtained and prior to blinded study product administration. It is expected that subjects will consent (or assent, when applicable) to participation in Periods 1 through 4 during the Screening Visit. Obtaining a separate informed consent/assent for Period 3 will be at the discretion of the IRBs providing oversight to the investigational sites selected for Period 3.

^w Dispense open-label ADV7103 during Visit 1 ONLY if all study eligibility criteria have been confirmed during the visit.

^x During Visit 2, estimate amount of ADV7103 needed through Visit 4 and dispense accordingly.

^y Unused open-label ADV7103 will be collected at admission to Period 3 for the purpose of sequestering open-label ADV7103 during the period of blinded study product administration. This open-label ADV7103 supply will be returned to the subject at discharge from Period 3 as appropriate. During Visit 4, all unused open-label ADV7103 for this study will be collected and not returned to the subject.

^z Collect empty boxes of ADV7103 sachets. Count both the number of empty boxes of sachets and the number of unused sachets brought in by the subject.

17.2. Face Hedonic Scale and Visual Analog Scale

 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done
	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Sub-set 1 (adults) and Sub-set 2 (adolescents from 12 to 17 years)				


Baseline

Site Number	Subject Number	Subject Initials
<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>

Sub-set 1 (adults) and Sub-set 2 (adolescents from 12 to 17 years)

Date of Completion (DD-MM-YYYY) <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	14 August 2018 V1.1
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CONFIDENTIAL

 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done
	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Sub-set 1 (adults) and Sub-set 2 (adolescents from 12 to 17 years)				

Evaluation of palatability

Indicate on the scale the answer to the question:

"How happy are you with the taste of the treatment?"

0 100

dislike very much *like very much*

mm *

For Site Staff Use Only:
 Study Coordinator Initials: _____
 Date of Completion (DD-MMM-YYYY)
--

* Do not write in the shaded box.

Evaluation of ease of administration

Indicate on the scale the answer to the question:

"How happy are you with the ease of preparation and administration of the treatment?"

0 100

very easy *very difficult*


mm *

For Site Staff Use Only:
 Study Coordinator Initials: _____
 Date of Completion (DD-MMM-YYYY)
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* Do not write in the shaded box.

Date of Completion (DD-MMM-YYYY) <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	14 August 2018 V1.1
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CONFIDENTIAL

 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done
	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Sub-set 1 (adults) and Sub-set 2 (adolescents from 12 to 17 years)				

Evaluation of the ease of swallowing

Indicate on the scale the answer to the question:

"How happy are you with the swallowing of the treatment?"

_____ mm *

0 100

very difficult very easy

For Site Staff Use Only:
 Study Coordinator Initials: _____
 Date of Completion (DD-MMM-YYYY)
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* Do not write in the shaded box.

Evaluation of the number of daily intakes

Indicate on the scale the answer to the question:

"How happy are you with the number of intakes of the treatment per day?"

_____ mm *

0 100


like very much dislike very much

For Site Staff Use Only:
 Study Coordinator Initials: _____
 Date of Completion (DD-MMM-YYYY)
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* Do not write in the shaded box

Date of Completion (DD-MMM-YYYY) <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	14 August 2018 V1.1
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CONFIDENTIAL

 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done
	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Sub-set 1 (adults) and Sub-set 2 (adolescents from 12 to 17 years)				

Evaluation of the gastro-intestinal tolerability

Indicate on the scale the answer to the question:

"How happy are you with the effect of the treatment on your stomach?"

0

*extremely severe
complaint*

mm *

100

no complaint

For Site Staff Use Only:
 Study Coordinator Initials: _____
 Date of Completion (DD-MMM-YYYY)
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* Do not write in the shaded box

Date of Completion (DD-MMM-YYYY) <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	14 August 2018 V1.1
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CONFIDENTIAL

 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done
	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Sub-set 1 (adults) and Sub-set 2 (adolescents from 12 to 17 years)				

Follow up

- ☐ B23CS Visit 2
- ☐ B23CS Early Withdrawal
- ☐ B24CS Period 2
- ☐ B24CS Month 6
- ☐ B24CS Study Exit Visit

Date of Completion (DD-MMM-YYYY) <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	14 August 2018 V1.1
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 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done
	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>
Sub-set 1 (adults) and Sub-set 2 (adolescents from 12 to 17 years)				

Evaluation of palatability

Indicate on the scale the answer to the question:

"How happy are you with the taste of the treatment?"



For Site Staff Use Only:

Study Coordinator Initials: _____

Date of Completion (DD-MMM-YYYY)

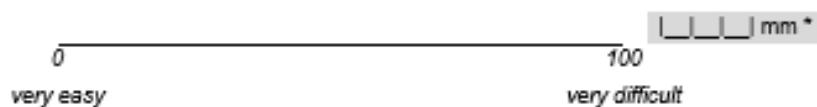
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* Do not write in the shaded box.

Evaluation of ease of administration

Indicate on the scale the answer to the question:

"How happy are you with the ease of preparation and administration of the treatment?"



For Site Staff Use Only:

Study Coordinator Initials: _____

Date of Completion (DD-MMM-YYYY)

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* Do not write in the shaded box.

Date of Completion (DD-MMM-YYYY)

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 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done
	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>
Sub-set 1 (adults) and Sub-set 2 (adolescents from 12 to 17 years)				

Evaluation of the ease of swallowing

Indicate on the scale the answer to the question:

"How happy are you with the swallowing of the treatment?"

0

very difficult

mm *

100

very easy

For Site Staff Use Only:
 Study Coordinator Initials: _____
 Date of Completion (DD-MMM-YYYY)
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* Do not write in the shaded box.

Evaluation of the number of daily intakes

Indicate on the scale the answer to the question:

"How happy are you with the number of intakes of the treatment per day?"

0

like very much

mm *

100


dislike very much

For Site Staff Use Only:
 Study Coordinator Initials: _____
 Date of Completion (DD-MMM-YYYY)
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* Do not write in the shaded box

Date of Completion (DD-MMM-YYYY) <input type="text"/> - <input type="text"/> - <input type="text"/>	14 August 2018 V1.1
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 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done
	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Sub-set 1 (adults) and Sub-set 2 (adolescents from 12 to 17 years)				

Evaluation of the gastro-intestinal tolerability

Indicate on the scale the answer to the question:

"How happy are you with the effect of the treatment on your stomach?"

0

*extremely severe
complaint*

mm *

100

no complaint

For Site Staff Use Only:
 Study Coordinator Initials: _____
 Date of Completion (DD-MMM-YYYY)
--

* Do not write in the shaded box

Patient Preference Assessment

Which alkalinizing treatment do you prefer?

Please choose one answer:

1. I prefer the previous treatment that I took before study entry. 1 ☐
2. I prefer the actual treatment ADV7103. 2 ☐
3. I have no preference. 3 ☐

Date of Completion (DD-MMM-YYYY) <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	14 August 2018 V1.1
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CONFIDENTIAL

 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done
	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Sub-set 3 (children from 4 to 11 years old inclusive)				

Baseline

Site Number	Subject Number	Subject Initials
<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>

Sub-set 3 (children from 4 to 11 years old inclusive)

Date of Completion (DD-MMM-YYYY) <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Form Completed By:	14 August 2018 V1.1
	<input type="checkbox"/> Mother	
	<input type="checkbox"/> Father	
	<input type="checkbox"/> Guardian	
For follow up only: <input type="checkbox"/> I confirm the same individual assisted with form completion as baseline		






CONFIDENTIAL

 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done
	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Sub-set 3 (children from 4 to 11 years old inclusive)				

Evaluation of palatability

Circle and indicate on the scale the answer to the question:
(to be completed by child with help from the parent/guardian if necessary)

"How happy are you with the taste of the treatment?"

1

2

3

4

5

"How happy are you with the taste of the treatment?"

0

100

dislike very much

like very much


mm *

For Site Staff Use Only:
Study Coordinator Initials: _____
Date of Completion (DD-MMM-YYYY)
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* Do not write in the shaded box.

Date of Completion (DD-MMM-YYYY) <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Form Completed By: <input type="checkbox"/> Mother <input type="checkbox"/> Father <input type="checkbox"/> Guardian For follow up only: <input type="checkbox"/> I confirm the same individual assisted with form completion as baseline.	14 August 2018 V1.1
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CONFIDENTIAL

 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done
	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>
Sub-set 3 (children from 4 to 11 years old inclusive)				

Evaluation of ease of administration Indicate on the scale the answer to the question: (to be completed by parent/guardian) <i>"How happy are you with the ease of preparation and administration of the treatment?"</i>	
<div style="display: flex; align-items: center; justify-content: space-between;"> <div> 0 very easy </div> <div style="flex-grow: 1; border-bottom: 1px solid black; position: relative;"> <div style="position: absolute; right: 0; top: -10px; background-color: #cccccc; padding: 2px;"> <input type="text"/> mm * </div> </div> <div> 100 very difficult </div> </div>	For Site Staff Use Only: Study Coordinator Initials: _____ Date of Completion (DD-MMM-YYYY) <input type="text"/> - <input type="text"/> - <input type="text"/>

* Do not write in the shaded box.

Date of Completion (DD-MMM-YYYY) <input type="text"/> - <input type="text"/> - <input type="text"/>	Form Completed By: <input type="checkbox"/> Mother <input type="checkbox"/> Father <input type="checkbox"/> Guardian For follow up only: <input type="checkbox"/> I confirm the same individual assisted with form completion as baseline	14 August 2018 V1.1
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CONFIDENTIAL

 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done
	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>
Sub-set 3 (children from 4 to 11 years old inclusive)				

Evaluation of the ease of swallowing

Circle and indicate on the scale the answer to the question:
(to be completed by child with help from the parent/guardian if necessary)

"How happy are you with the swallowing of the treatment?"



"How happy are you with the swallowing of the treatment?"




For Site Staff Use Only:
Study Coordinator Initials: _____
Date of Completion (DD-MMM-YYYY)
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* Do not write in the shaded box

Date of Completion (DD-MMM-YYYY) <input type="text"/> - <input type="text"/> - <input type="text"/>	Form Completed By: <input type="checkbox"/> Mother <input type="checkbox"/> Father <input type="checkbox"/> Guardian For follow up only: <input type="checkbox"/> I confirm the same individual assisted with form completion as baseline	14 August 2018 V1.1
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 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done <input type="checkbox"/>
	<input type="text"/>	<input type="text"/>	<input type="text"/>	
Sub-set 3 (children from 4 to 11 years old inclusive)				

Evaluation of the number of daily intakes

Circle and indicate on the scale the answer to the question:
(to be completed by child with help from the parent/guardian if necessary)

"How happy are you with the number of intakes of the treatment per day?"

1 2 3 4 5

"How happy are you with the number of intakes of the treatment per day?"

0

100

like very much

dislike very much

mm *

For Site Staff Use Only:

Study Coordinator Initials: _____


Date of Completion (DD-MMM-YYYY)

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* Do not write in the shaded box.

Date of Completion (DD-MMM-YYYY) <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Form Completed By: <input type="checkbox"/> Mother <input type="checkbox"/> Father <input type="checkbox"/> Guardian For follow up only: <input type="checkbox"/> I confirm the same individual assisted with form completion as baseline	14 August 2018 V1.1
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CONFIDENTIAL


 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done
	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
Sub-set 3 (children from 4 to 11 years old inclusive)				


Evaluation of the gastro-intestinal tolerability


Circle and indicate on the scale the answer to the question:
(to be completed by child with help from the parent/guardian if necessary)


"How happy are you with the effect of the treatment on your stomach?"


1


2


3


4


5

"How happy are you with the effect of the treatment on your stomach?"

0

extremely severe complaint

mm *

100


no complaint

For Site Staff Use Only:
 Study Coordinator Initials: _____
 Date of Completion (DD-MMM-YYYY)
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* Do not write in the shaded box.

Date of Completion (DD-MMM-YYYY) <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Form Completed By: <input type="checkbox"/> Mother <input type="checkbox"/> Father <input type="checkbox"/> Guardian For follow up only: <input type="checkbox"/> I confirm the same individual assisted with form completion as baseline	14 August 2018 V1.1
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 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done
	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Sub-set 3 (children from 4 to 11 years old inclusive)				

Follow up

- ☐ B23CS Visit 2
- ☐ B23CS Early Withdrawal
- ☐ B24CS Period 2
- ☐ B24CS Month 6
- ☐ B24CS Study Exit Visit

Date of Completion (DD-MMM-YYYY) <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Form Completed By: <input type="checkbox"/> Mother <input type="checkbox"/> Father <input type="checkbox"/> Guardian For follow up only: <input type="checkbox"/> I confirm the same individual assisted with form completion as baseline	14 August 2018 V1.1
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CONFIDENTIAL

 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done
	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>
Sub-set 3 (children from 4 to 11 years old inclusive)				

Evaluation of palatability

Circle and indicate on the scale the answer to the question:
(to be completed by child with help from the parent/guardian if necessary)

"How happy are you with the taste of the treatment?"



"How happy are you with the taste of the treatment?"



For Site Staff Use Only:

Study Coordinator Initials: _____


Date of Completion (DD-MMM-YYYY)

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* Do not write in the shaded box.

Date of Completion (DD-MMM-YYYY) <input type="text"/>	Form Completed By: <input type="checkbox"/> Mother <input type="checkbox"/> Father <input type="checkbox"/> Guardian For follow up only: <input type="checkbox"/> I confirm the same individual assisted with form completion as baseline	14 August 2018 V1.1
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 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done
	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>
Sub-set 3 (children from 4 to 11 years old inclusive)				

Evaluation of ease of administration

Indicate on the scale the answer to the question:
(to be completed by parent/guardian)

"How happy are you with the ease of preparation and administration of the treatment?"

0

100

mm *

very easy


very difficult

For Site Staff Use Only:
Study Coordinator Initials: _____
Date of Completion (DD-MMM-YYYY)
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* Do not write in the shaded box.

Date of Completion (DD-MMM-YYYY) <input type="text"/> - <input type="text"/> - <input type="text"/>	Form Completed By: <input type="checkbox"/> Mother <input type="checkbox"/> Father <input type="checkbox"/> Guardian For follow up only: <input type="checkbox"/> I confirm the same individual assisted with form completion as baseline	14 August 2018 V1.1
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 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done
	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Sub-set 3 (children from 4 to 11 years old inclusive)				

Evaluation of the ease of swallowing

Circle and indicate on the scale the answer to the question:
(to be completed by child with help from the parent/guardian if necessary)

"How happy are you with the swallowing of the treatment?"

1

2

3

4

5

"How happy are you with the swallowing of the treatment?"

mm *

0

100

very difficult


very easy

For Site Staff Use Only:
Study Coordinator Initials: _____
Date of Completion (DD-MMM-YYYY)
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* Do not write in the shaded box

Date of Completion (DD-MMM-YYYY) <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Form Completed By: <input type="checkbox"/> Mother <input type="checkbox"/> Father <input type="checkbox"/> Guardian For follow up only: <input type="checkbox"/> I confirm the same individual assisted with form completion as baseline	14 August 2018 V1.1
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 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done
	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>
Sub-set 3 (children from 4 to 11 years old inclusive)				

Evaluation of the number of daily intakes

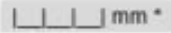
Circle and indicate on the scale the answer to the question:
(to be completed by child with help from the parent/guardian if necessary)

"How happy are you with the number of intakes of the treatment per day?"

1 **2** **3** **4** **5**

"How happy are you with the number of intakes of the treatment per day?"

 mm *

0
like very much
100
dislike very much

For Site Staff Use Only:
 Study Coordinator Initials: _____
 Date of Completion (DD-MMM-YYYY)
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* Do not write in the shaded box.

Date of Completion (DD-MMM-YYYY) <input type="text"/> - <input type="text"/> - <input type="text"/>	Form Completed By: <input type="checkbox"/> Mother <input type="checkbox"/> Father <input type="checkbox"/> Guardian	14 August 2018 V1.1
	For follow up only: <input type="checkbox"/> I confirm the same individual assisted with form completion as baseline	

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 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done
	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>

Sub-set 3 (children from 4 to 11 years old inclusive)

Evaluation of the gastro-intestinal tolerability

Circle and indicate on the scale the answer to the question:
(to be completed by child with help from the parent/guardian if necessary)

"How happy are you with the effect of the treatment on your stomach?"



"How happy are you with the effect of the treatment on your stomach?"




For Site Staff Use Only:
 Study Coordinator Initials: _____
 Date of Completion (DD-MMM-YYYY)
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* Do not write in the shaded box.

Date of Completion (DD-MMM-YYYY) <input type="text"/>	Form Completed By: <input type="checkbox"/> Mother <input type="checkbox"/> Father <input type="checkbox"/> Guardian For follow up only: <input type="checkbox"/> I confirm the same individual assisted with form completion as baseline	14 August 2018 V1.1
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 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done
	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Sub-set 3 (children from 4 to 11 years old inclusive)				

Patient Preference Assessment

Which alkalinizing treatment do you prefer?

Please choose one answer:

1. I prefer the previous treatment that I took before study entry.
2. I prefer the actual treatment ADV7103.
3. I have no preference.

1	<input type="checkbox"/>
2	<input type="checkbox"/>
3	<input type="checkbox"/>

Date of Completion (DD-MMM-YYYY) <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Form Completed By: <input type="checkbox"/> Mother <input type="checkbox"/> Father <input type="checkbox"/> Guardian For follow up only: <input type="checkbox"/> I confirm the same individual assisted with form completion as baseline	14 August 2018 V1.1
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CONFIDENTIAL

 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done
	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Sub-set 4 (infants from 6 months to 3 years old inclusive)				

Baseline

Site Number	Subject Number	Subject Initials
<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>

Sub-set 4 (infants from 6 months to 3 years old inclusive)

Date of Completion (DD-MMM-YYYY) <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Form Completed By: <input type="checkbox"/> Mother <input type="checkbox"/> Father <input type="checkbox"/> Guardian For follow up only: <input type="checkbox"/> I confirm the same individual assisted with form completion as baseline	14 August 2018 V1.1
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CONFIDENTIAL

 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done
	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>
Sub-set 4 (infants from 6 months to 3 years old inclusive)				

Evaluation of palatability

Indicate on the scale the answer to the question:
(to be completed by parent/guardian)

"How happy do you think your child is with the taste of the treatment?"

0

dislike very much

100

like very much


mm *

For Site Staff Use Only:
Study Coordinator Initials: _____
Date of Completion (DD-MMM-YYYY)
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* Do not write in the shaded box.

Date of Completion (DD-MMM-YYYY) <input type="text"/>	Form Completed By: <input type="checkbox"/> Mother <input type="checkbox"/> Father <input type="checkbox"/> Guardian For follow up only: <input type="checkbox"/> I confirm the same individual assisted with form completion as baseline	14 August 2018 V1.1
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 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done
	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>
Sub-set 4 (infants from 6 months to 3 years old inclusive)				

Evaluation of ease of administration

Indicate on the scale the answer to the question:
(to be completed by parent/guardian)

"How happy are you with the ease of preparation and administration of the treatment?"

0

very easy

100

very difficult

mm *

For Site Staff Use Only:
Study Coordinator Initials: _____
Date of Completion (DD-MMM-YYYY)
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* Do not write in the shaded box.

Date of Completion (DD-MMM-YYYY) <input type="text"/>	Form Completed By: <input type="checkbox"/> Mother <input type="checkbox"/> Father <input type="checkbox"/> Guardian For follow up only: <input type="checkbox"/> I confirm the same individual assisted with form completion as baseline.	14 August 2018 V1.1
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CONFIDENTIAL

 B23CS/B24CS	Site Number	Subject Number	Subject Initials	Not Done
	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>
Sub-set 4 (infants from 6 months to 3 years old inclusive)				

Evaluation of the ease of swallowing

Indicate on the scale the answer to the question:
(to be completed by parent/guardian)

"How happy are you with the swallowing of the treatment?"

0

very difficult

100

very easy

mm *

For Site Staff Use Only:
Study Coordinator Initials: _____
Date of Completion (DD-MMM-YYYY)
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* Do not write in the shaded box.

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Sub-set 4 (infants from 6 months to 3 years old inclusive)				

Evaluation of the number of daily intakes

Indicate on the scale the answer to the question:
(to be completed by parent/guardian)

"How happy are you with the number of intakes of the treatment per day?"

mm *

0 100
like very much *dislike very much*

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Sub-set 4 (infants from 6 months to 3 years old inclusive)				

Evaluation of the gastro-intestinal tolerability

Indicate on the scale the answer to the question:
(to be completed by parent/guardian)

"How happy are you with the effect of the treatment on your child's stomach?"

0

extremely severe complaint

100

no complaint


mm *

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Sub-set 4 (infants from 6 months to 3 years old inclusive)				

Follow up

- ☐ B23CS Visit 2
- ☐ B23CS Early Withdrawal
- ☐ B24CS Period 2
- ☐ B24CS Month 6
- ☐ B24CS Study Exit Visit

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Sub-set 4 (infants from 6 months to 3 years old inclusive)				

Evaluation of palatability

 Indicate on the scale the answer to the question:
 (to be completed by parent/guardian)

"How happy do you think your child is with the taste of the treatment?"

0

dislike very much

100

like very much

mm *

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Sub-set 4 (infants from 6 months to 3 years old inclusive)				

Evaluation of ease of administration

 Indicate on the scale the answer to the question:
 (to be completed by parent/guardian)

"How happy are you with the ease of preparation and administration of the treatment?"

mm *

0

100

very easy

very difficult

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Sub-set 4 (infants from 6 months to 3 years old inclusive)				

Evaluation of the ease of swallowing

 Indicate on the scale the answer to the question:
 (to be completed by parent/guardian)

"How happy are you with the swallowing of the treatment?"

0

very difficult

100

very easy

mm *

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Sub-set 4 (infants from 6 months to 3 years old inclusive)				

Evaluation of the number of daily intakes

Indicate on the scale the answer to the question:
(to be completed by parent/guardian)

"How happy are you with the number of intakes of the treatment per day?"

0

like very much

100

dislike very much


mm *

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Sub-set 4 (infants from 6 months to 3 years old inclusive)				

Evaluation of the gastro-intestinal tolerability

 Indicate on the scale the answer to the question:
 (to be completed by parent/guardian)

"How happy are you with the effect of the treatment on your child's stomach?"

mm *

0

100

extremely severe complaint


no complaint

For Site Staff Use Only:
 Study Coordinator Initials: _____
 Date of Completion (DD-MMM-YYYY)
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Sub-set 4 (infants from 6 months to 3 years old inclusive)				

Patient Preference Assessment

Which alkalinizing treatment do you think your child prefers?

Please choose one answer:

1. I think my child prefers the previous treatment that he/she took before study entry.
2. I think my child prefers the actual treatment ADV7103.
3. I think my child has no preference.

1	<input type="checkbox"/>
2	<input type="checkbox"/>
3	<input type="checkbox"/>

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17.3. Semi-structured Interview Guides

Protocol and Interview Guide

Patient and Parent

Baseline

Version 1.0

1. Context and objectives

Advicenne is currently developing ADV7103, an innovative formulation of potassium citrate in the form of micro-tablets for the treatment of distal renal tubular acidosis.

Distal renal tubular acidosis (dRTA) is a condition characterised by a renal defect in hydrogen ion secretion in the distal renal tubules, inducing a hyperchloremic metabolic acidosis (low blood pH = less than 7.35) with no urine acidification.

Usually in non-dRTA subjects, the blood pH is about 7.4 corresponding to a blood concentration of bicarbonate of 21 to 28 mmol/L. A metabolic acidosis corresponds to a blood pH below 7.35 with a bicarbonate blood concentration lower than 22 mmol/L (or 22 mEq/L) (Chan, Scheinman et al. 2001).

Major biological signs of dRTA are usually a hyperchloremic metabolic acidosis, hypokalaemia and hypercalciuria, with a high pH of urine (>6.5), inducing nephrocalcinosis or lithiasis without treatment. In most cases, the condition causes osteomalacia in adults and short stature to rickets in infantile forms. In some genetic forms, deafness could be linked to mutation.

Distal renal tubular acidosis could be an inherited condition induced by genetic mutations or a secondary condition related mainly to autoimmune diseases (e.g. primary Sjögren's syndrome, systemic lupus erythematosus, primary biliary cirrhosis, autoimmune hepatitis).

There is no curative treatment of dRTA. This blood pH dependence of symptoms is the basis of the medical treatment of dRTA, which relies on alkalisatation to maintain a blood pH of 7.4 with a bicarbonate blood concentration above 22 mmol/L (Chan, Scheinman et al. 2001).

Alkali therapy, as sodium bicarbonate and potassium bicarbonate or tripotassium citrate, is used in dRTA to stabilise correction of metabolic acidosis and improves clinical spectrum of patient inducing a minimisation of stone risk and a better growth if treatment is early instituted. No effect was noticed on deafness. The aim of alkali therapy is to achieve a normal blood bicarbonate concentration (22 to 24 mEq/L). A continuous treatment is necessary to observe clinical improvement, using a mean alkali therapy of 1-2 mEq/kg/day in adults and of 4-8 mEq/kg/day in children where bicarbonate losses are frequently higher than in adults (Chan, Scheinman et al. 2001; Rodriguez Soriano 2002).

Currently available potassium citrate formulations exhibit low adherence characteristics, particularly in the pediatric population. In fact, the doses must be administered up to every 6 hours in 24 hours, including an administration during the night. In addition the formulations involve gastro-intestinal side effects and have a bitter taste.

Comparatively, ADV7103 has three advantages. It: (1) is tasteless and easy administration, particularly in young children, (2) reduces gastrointestinal side effects with intestine, and (3) requires only two doses per 24 hours.

The ARENA clinical development program of ADV7103 for dRTA consists of

- ARENA 1 is a cross-over study comparing dRTA standard of care to ADV7103 and the associated long-term extension study. ADV7103 proved to be non-inferior to SoC in maintaining serum bicarbonate levels above the lower limit of normal, and in fact, demonstrated superiority on this parameter. ADV7103 also maintained serum potassium levels in a safe range and showed good tolerability compared to SoC.
- ARENA 2 is a randomized withdrawal study comparing the ability of ADV7103 to prevent the development of metabolic acidosis compared to placebo, over 6 days. B24CS is the associated long-term open label roll-over study.

As part of the B23CS (ARENA 2) study, Advicenne commissioned MAPI/ICON to conduct qualitative research based on semi-structured interviews at the beginning of the study ("baseline") and then at the conclusion of the stabilization period, approximately 8 weeks later. Over the course of the two interviews, the intent is to explore the patient's perspective on:

- dRTA and treatments that patients currently use to manage dRTA (standard of care/SOC) and the impact of dRTA and current treatment options on patients' daily lives;
- patients' attitudes, beliefs and behaviors related to dRTA and its treatment;
- how dRTA itself and how they have treated their dRTA have evolved over time;
- what changes, if any, they have experienced while taking ADV7103;
- whether the experience of taking ADV7103 is the same, better, or worse than taking the SOC;
- whether they would want to continue to use it, if ADV7103 is approved and becomes available, and why/why/not;
- whether having ADV available might cause them to make any changes in how they treat their dRTA.

This guide presents the instructions and the method to be used to conduct interviews at the beginning of the study ().

2. Methods

2.1. The Interviewer

The roles and responsibilities of the interviewer are detailed below.

Before and at the beginning of the interview :

- Schedule an appointment with the patient (and / or their parent) for an interview;
- Offer the patient (and / or his or her parent) to use a video platform to perform the interview (Skype, WebEx ...) ;
- Ensure that the interviewer and the patient (and / or their parent) are in quiet locations, respectively, where the conditions guarantee the free expression of the patient (and / or their relative) and confidentiality, without interruption;
- Ensure the proper operation of the recording device/system; if the recording equipment uses batteries, use new batteries at each interview;
- Receive training and know the procedure to follow in case of spontaneous notification of adverse effects;
- Check that the patient (and / or their parent) has been informed (s) and has / have agreed to participate in the interview;
- Recall the purpose of the interview to the patient (and / or parent), and what is expected of him / her / them;
- Remind the patient (and / or their parent) of the confidentiality and anonymity of the information they / he / she will report; his / their answers will be forwarded only to those involved in the study and will not be linked to his / her name (s);
- Remind the patient (and / or their parent) that the interview is being recorded and ask for verbal consent before starting the interview and while recording;
-
- Answer any questions that the patient (and / or their parent) may have before starting the interview

After the interview :

- Check the recording; in case the interview has not been recorded, take detailed notes based on recent memory (if convenient and not distracting, notes should also be taken during the interview);
- Rename the audio: 060482 _ [patient ID] _ [patient +/- parent] _ baseline_Date [DD-MMM-YYYY]. Download the audio file to the secure server. If notes have been taken, the annotated document must be scanned, renamed as before and uploaded to the secure server along with the audio file ;
- Classify the adverse reaction reporting report in the event that the patient (and / or their parent) has spontaneously reported an adverse reaction to a sponsor product during the course of the interview. The investigator must report an adverse event according to the procedure described in section 2.3 of this document.

2.2. Structure of the interview

The interview will be conducted by telephone (or internet) or may be face-to-face/in-person at a time chosen by the patient (and / or parent) and the interviewer. Each interview will last approximately one hour.

The interview is divided into three stages:

- **Introduction and Presentation of the study (5 minutes)** : Presentation of the interviewer, presentation of the purpose of the study and conduct maintenance.
- **Exploratory interview (50 minutes)**: It's important to use semi-directive interview techniques: let the patient (and / or their parent) speak spontaneously, then use probes to obtain information about specific topics and a complete understanding/knowledge of the patient's (and / or their parent's) experiences. All of the main themes described in the guide should be addressed, but it is not mandatory to follow the sequence exactly as written in this guide. If a topic is discussed earlier by the patient (and / or parent) during the interview, it can be explored and discussed at that time. The patient (and / or their parent) may take several minutes to answer the question. The interviewer will need to anticipate this possibility by giving sufficient time to the patient (and / or parent) to respond. The interview guide provides a non-exhaustive list of topics. Themes and probes are there as an indication and reminder of what needs to be explored during the interview.
- **End of the interview (5 minutes)**: Questions on the socio-demographic data form (separate document) should be answered by the patient (and / or their parent) at the conclusion of the interview.

2.3. Notification of an adverse event

During the interview, if the patient (and / or their parent) spontaneously reports an adverse event, the interviewer should notify the appropriate person(s) at the investigational site so that appropriate documentation, reporting, and follow up can be initiated as appropriate.

3. Baseline Interview Guide - Content

a) Introduction and purpose

- Thank the patient (and / or their parent) for agreeing to participate in the interview.
- Introduce the company, ICONi: a company that works with pharmaceutical companies to better understand diseases, their treatments and their impact on patients' lives.
- Introduce the objectives for the interview: To learn about the experiences of the patient with distal renal tubular acidosis and its treatment.

b) Confidentiality

- Remind the patient (and / or their relative) that:
 - The interview will be transcribed and analyzed confidentially and anonymously: anything that could identify the patient (and / or his parent) will be deleted (name, location ...);
 - The interview will be analyzed together with all other interviews conducted.

c) Conduct of the interview and registration

- Let the patient (and / or their parent) know that:
 - The duration of the interview: Approximately one hour;
 - you would like to record the interview to facilitate the conversation (and ask for their verbal agreement to record the conversation);
 - the recording is confidential and only accessible to the research team;
 - the recording will be destroyed at the end of the study;
 - he /she can stop the interview at any time and / or not to answer certain questions;
 - he/she should feel free to answer the questions honestly and not to be worried about or afraid to say what they think (s).

d) Questions

- Check that the participant (s) consents to be interviewed.
- Give the patient (and / or parent) the opportunity to ask questions before starting the interview.

e) Start recording

- Announce:
 - The date
 - The identification number of the patient
 - The participants): patient and / or parent
 - The type of interview (baseline)
- Obtain and record the consent of the patient to record the interview.

4. Exploratory interview

Theme 1: Daily Distal Renal Tubular Acidosis

- Diagnosis
 - When you were first diagnosed? *Date, moment*
 - *Symptom (s) that prompted the consultation* – Was there anything specific related to your dRTA that you were experiencing that made you decide to go to your doctor
 - *Health professional (s) consulted* – How long did it take and who diagnosed your dRTA?
 - *Feelings, emotions* – How did you feel and what did you think about it when you learned about the diagnosis?
- Evolution of dRTA – Have your experiences with dRTA changed over time? How so?
 - Have you experienced any physical symptoms that you think are caused by dRTA? (*Symptom (s): muscle weakness pain, bone or growth problems, feeling ill, weak*)
 - Have you experienced anything emotionally or mentally related to dRTA? *Feelings, emotions*
- Impact of dRTA on your quality of life
 - *Activities of everyday life*
 - *At school, at work*
 - *Relations with family, friends*
 - *Sports, leisure activities*
 - *Sleep*
 - *Emotions, mood*

Theme 2: Treatment of daily dRTA

- Description of treatment before entering the study Do you think of the things you use for your dRTA as medicines? Why/Why not?

- *Preparation (set-up)* – Have the products/medications you used to treat your dRTA required much preparation? Please tell me in as much detail as you can, how you prepare and take your product(s)
 - *Administration: intake (taste, texture), number of times actually taken per 24h* – Take me through a typical day (24 hour period) in your life describing where, when, how you would typically treat your dRTA? Does your routine vary from day-to-day?
- How often in a 24hr period do you take the medication? How do you know when it is time to take your product/medication? How, if at all, do you keep track of how often you dose?
 - Adherence / monitoring of the treatment
 - *Reasons / motivations to follow (or not) the prescription*
 - *If applicable: Adaptation of the prescription by the patient*
 - Using a scale from 1-10 with 1 = not satisfied at all and 10 = completely satisfied, How satisfied would you say you are with your current medication or product?
 - *Factors / reasons for satisfaction (or dissatisfaction)- list all*

Theme 3: The study for ADV7103

- Motivations to enter the study – What made you decide to participate or have your child participate in the study?
- Treatment expectations on ADV7103 treatment – Please list all the benefits and positive characteristics that the ideal medication or product for treating dRTA should have? Reviewing the list, how close does your current product or medication come to meeting each of these on the list? Where does it fall short?

5. End of the interview

5.1. Sociodemographic data form

- Complete with the patient (and / or parent) the Sociodemographic Data Form (separate document).

5.2. Conclusion

- Ask the patient (and / or their parent) if they / they wish to add anything.
- Thank the patient (and / or their parent) for their participation.
- Remind the patient (and / or their parent) that they will be contacted again in about 8 weeks (End of Stabilization Period) for a second telephone conversation.

Stop recording: make sure that the interview is properly recorded. In the event that the interview has not been recorded or is of poor quality, report the discussion.

Protocol and Interview Guide

Patient and Parent

Post Stabilization

Version 1.0

1. Context and objectives

Advicenne is currently developing ADV7103, an innovative formulation of potassium citrate in the form of micro-tablets for the treatment of distal renal tubular acidosis.

Distal renal tubular acidosis (dRTA) is a condition characterised by a renal defect in hydrogen ion secretion in the distal renal tubules, inducing a hyperchloremic metabolic acidosis (low blood pH = less than 7.35) with no urine acidification.

Usually in non-dRTA subjects, the blood pH is about 7.4 corresponding to a blood concentration of bicarbonate of 21 to 28 mmol/L. A metabolic acidosis corresponds to a blood pH below 7.35 with a bicarbonate blood concentration lower than 22 mmol/L (or 22 mEq/L) (Chan, Scheinman et al. 2001).

Major biological signs of dRTA are usually a hyperchloremic metabolic acidosis, hypokalaemia and hypercalciuria, with a high pH of urine (>6.5), inducing nephrocalcinosis or lithiasis without treatment. In most cases, the condition causes osteomalacia in adults and short stature to rickets in infantile forms. In some genetics forms, deafness could be linked to mutation.

Distal renal tubular acidosis could be an inherited condition induced by genetic mutations or a secondary condition related mainly to autoimmune diseases (e.g. primary Sjögren's syndrome, systemic lupus erythematosus, primary biliary cirrhosis, autoimmune hepatitis).

There is no curative treatment of dRTA. This blood pH dependence of symptoms is the basis of the medical treatment of dRTA, which relies on alkalisation to maintain a blood pH of 7.4 with a bicarbonate blood concentration above 22 mmol/L (Chan, Scheinman et al. 2001).

Alkali therapy, as sodium bicarbonate and potassium bicarbonate or tripotassium citrate, is used in dRTA to stabilise correction of metabolic acidosis and improves clinical spectrum of patient inducing a minimisation of stone risk and a better growth if treatment is early instituted. No effect was noticed on deafness. The aim of alkali therapy is to achieve a normal blood bicarbonate concentration (22 to 24 mEq/L). A continuous treatment is necessary to observe clinical improvement, using a mean alkali therapy of 1-2 mEq/kg/day in adults and of 4-8 mEq/kg/day in children where bicarbonate losses are frequently higher than in adults (Chan, Scheinman et al. 2001; Rodriguez Soriano 2002).

Currently available potassium citrate formulations exhibit low adherence characteristics, particularly in the pediatric population. In fact, the doses must be administered up to every 6 hours in 24 hours, including an administration during the night. In addition, the formulations involve any side effects are gastro-intestinal to and have a bitter taste.

Comparatively, ADV7103 has three advantages, it: (1) is tasteless and easy administration, particularly in young children, (2) reduces gastrointestinal side effects with intestine, and (3) requires only two doses per 24 hours.

The ARENA clinical development program of ADV7103 for dRTA consists of

- B21CS (ARENA 1) and B22CS: ARENA 1 is a cross-over study comparing dRTA standard of care to ADV7103 and the associated long-term extension study. ADV7103 proved to be non-inferior to SoC in maintaining serum bicarbonate levels above the lower limit of normal, and in fact,

demonstrated superiority on this parameter. ADV7103 also maintained serum potassium levels in a safe range and showed good tolerability compared to SoC.

- B23CS (ARENA 2) and B24CS: ARENA 2 is a randomized withdrawal study comparing the ability of ADV7103 to prevent the development of metabolic acidosis compared to placebo, over 6 days. B24CS is the associated long-term open label roll-over study.

As part of the B23CS (ARENA 2) study, Advicenne commissioned MAPI/ICON to conduct qualitative research based on semi-structured interviews at the beginning of the study (" baseline "), and then at the conclusion of the stabilization period, approximately 8 weeks later. Over the course of the two interview, the intent is to explore the patient's perspective on :

- dRTA and treatments that patients currently use to manage dRTA (standard of care/SOC) and the impact of dRTA and current treatment options on patients' daily lives;
- patients' attitudes, beliefs and behaviors related to dRTA and its treatment;
- how dRTA itself and how they have treated their dRTA have evolved over time.

This guide presents the instructions and the method to be used to conduct interviews at the end of Stabilization ("Period 2").

2. Methods

2.1. The Interviewer

The roles and responsibilities of the interviewer are detailed below.

Before and at the beginning of the interview :

- Schedule an appointment with the patient (and / or their parent) for an interview;
- Offer the patient (and / or his or her parent) to use a video platform to perform the interview (Skype, WebEx ...) ;
- Ensure that the interviewer and the patient (and / or their parent) are in quiet locations, respectively, where the conditions guarantee the free expression of the patient (and / or their relative) and confidentiality, without interruption;
- Ensure the proper operation of the recording device/system; if the recording equipment uses batteries, use new batteries at each interview;
- Receive training and know the procedure to follow in case of spontaneous notification of adverse effects;
- Check that the patient (and / or their parent) has been informed (s) and has / have agreed to participate in the interview;
- Recall the purpose of the interview to the patient (and / or parent), and what is expected of him / her / them;
- Remind the patient (and / or their parent) of the confidentiality and anonymity of the information they / he / she will report; his / their answers will be forwarded only to those involved in the study and will not be linked to his / her name (s);

- Remind the patient (and / or their parent) that the interview is being recorded and ask for verbal consent before starting the interview and while recording;
- Answer any questions that the patient (and / or their parent) may have before starting the interview.

After the interview :

- Check the recording; in case the interview has not been recorded, take detailed notes based on recent memory (if convenient and not distracting, notes should also be taken during the interview);
- Rename the audio file : 060482 _ [patient ID] _ [patient +/- parent] _ stabilization_Date [DD-MMM- YYYY]. Download the audio file to the secure server. If notes have been taken, the annotated document must be scanned, renamed as before and uploaded to the secure server along with the audio file ;
- Classify the adverse reaction reporting report in the event that the patient (and / or their parent) has spontaneously reported an adverse reaction to a sponsor product during the course of the interview. The investigator must report an adverse event according to the procedure described in section 2.3 of this document.

2.2. Structure of the interview

The interview will be conducted by telephone (or internet) or may be face-to-face/in-person at a time chosen by the patient (and / or parent) and the interviewer. Each interview will last approximately one hour.

The interview is divided into three stages:

Introduction and Presentation of the study (5 minutes): Presentation of the interviewer, presentation of the purpose of the study and conduct maintenance.

Exploratory interview (50 minutes): It's important to use semi-directive interview techniques: let the patient (and / or their parent) speak spontaneously, then use probes to obtain information about specific topics and a complete understanding/knowledge of the patient's (and / or their parent's) experiences. All of the main themes described in the guide should be addressed, but it is not mandatory to follow the sequence exactly as written in this guide. If a topic is discussed earlier by the patient (and / or parent) during the interview, it can be explored and discussed at that time. The patient (and / or their parent) may take several minutes to answer the question. The interviewer will need to anticipate this possibility by giving sufficient time to the patient (and / or parent) to respond. The interview guide provides a non-exhaustive list of topics. Themes and probes are there as an indication and reminder of what needs to be explored during the interview.

End of the interview (5 minutes): Questions on the socio-demographic data form (separate document) should be answered by the patient (and / or their parent) at the conclusion of the interview.

2.3. Collecting and Reporting Adverse Events

During the interview, if the patient (and / or their parent) spontaneously reports an adverse event, the interviewer should notify the appropriate person(s) at the investigational site so that appropriate documentation, reporting, and follow up can be initiated as appropriate.

3. Interview Guide - Content

a) Introduction and purpose

Thank the patient (and / or their parent) for agreeing to participate in the interview.

Introduce the company, ICON: a company that works with pharmaceutical companies to better understand diseases, their treatments and their impact on patients' lives.

Introduce the objectives for the interview: To learn about the experiences of the patient with distal renal tubular acidosis and its treatment.

b) Confidentiality

Remind the patient (and / or their relative) that:

The interview will be transcribed and analyzed confidentially and anonymously: anything that could identify the patient (and / or his parent) will be deleted (name, location ...);

The interview will be analyzed together with all other interviews conducted.

c) Conduct of the interview and registration

Let the patient (and / or their parent) know that:

- duration of the interview: Approximately one hour;
- you would like to record the interview to facilitate the conversation (and ask for their verbal agreement to record the conversation);
- the recording is confidential and only accessible to the research team;
- the recording will be destroyed at the end of the study;
- he /she can stop the interview at any time and / or not to answer certain questions;
- he /she should feel free to answer the questions honestly and not to be worried about or afraid to say what they think (s).

d) General Questions

Check that the participant (s) consents to be interviewed.

Give the patient (and / or parent) the opportunity to ask questions before starting the interview.

e) Start recording

Announce:

- The date
- The identification number of the patient
- The participant(s): patient and / or parent
- The type of interview : " baseline "
- Obtain and record the consent of the patient to record the interview.

4. Stabilization interview guide - Content

Theme 1: Experiences with Distal Renal Tubular Acidosis (dRTA)

What has changed, if anything, since you started taking the study medication?

If not discussed, probe on any changes in physical symptoms or impacts of dRTA that may have been mentioned at baseline.

Theme 2: Experiences with taking ADV7103

Is there anything in particular that you remember about the new study medication when you first started taking it during the clinical study?

Preparation (set-up) – What do you have to do, if anything, to prepare to take the study medication before you take it? Is this different than how it was with the medication you took before you started the clinical study? How so?

Please list all the things that are the same and all the things that are different about the new study medication as compared to the medication you took before the clinical study? If not mentioned, probe taste, texture, doses in 24 hrs, how you feel after you take it.

Adherence / monitoring of the prescription – how easy or difficult do you think it will be for you to follow the directions and take the medication as directed when you are no longer in the clinical study? Why?

Reasons / motivations to follow (or not) the prescription – During the baseline interview, if the patient mentioned reasons why he/she took the medication less often than he/she was supposed to take it, ask whether those same reasons would apply to the study medication.

Theme 3: Overall satisfaction, expectations for treatment, and meaningful improvements

Satisfaction

Using a scale from 1-10 with 1 = not satisfied at all and 10 = completely satisfied, how satisfied would you say you are overall with the study medication?

Factors / reasons for satisfaction (or dissatisfaction)- list all

Expectations

Overall, would you say the study medication has:

- Not met my expectations/is not as good as I thought it would be
- Has met my expectations/ about the same as I thought it would be
- Has exceeded my expectations/ is better than I thought it would be

Why did you say the study medication (did not meet, met, or exceeded) your expectations?

Meaningful Improvements

What, if any improvements, have you experienced on the study medication that are meaningful to you?

5. End of the interview

5.1. Conclusion

Ask the patient (and / or their parent) if they / they will wish to add anything.

Thank the patient (and / or their parent) for their participation.

Stop recording: make sure that the interview is properly recorded. If the interview has not been recorded or is of poor quality, report the discussion in as much detail as possible.

17.4. Summary of Changes to Protocol B23CS Version 3.0

Advicenne Pharma

Summary of Changes

From Protocol B23CS Version 2.0 – 14Aug2018

To Protocol B23CS Version 3.0 – 30Nov2020

**A PHASE 3 MULTICENTER, RANDOMIZED, DOUBLE-BLINDED, PLACEBO-
CONTROLLED WITHDRAWAL STUDY EVALUATING ADV7103 IN PEDIATRIC
AND ADULT SUBJECTS
WITH DISTAL RENAL TUBULAR ACIDOSIS**

(ARENA 2 STUDY)



Confidentiality Statement

This document is confidential information of Advicenne Pharma. It may not be disclosed to parties not associated with the clinical investigation or used for any purpose without the prior written authorization of Advicenne Pharma.

Amendment Change Overview

Rationale for Amendment to ADV7103-B23CS Study V 2.0: modification to study conduct due to COVID-19 Public Health Emergency.

Due to the COVID-19 Public Health Emergency, since March 2020, many clinical research units, hospitals conducting research, and outpatient investigator and research facilities placed holds on non-critical therapeutic areas so that COVID-19 investigational product research and drug development could be prioritized. Additionally, to reduce the risk of COVID-19 exposure to patients and health care providers (HCPs), many primary and specialized, non-critical HCPs are providing standard examinations, care and treatment via telemedicine visits. In response to the challenges of the COVID-19 Public Health Emergency, Advicenne is amending the protocol for Study B23CS in order to minimize the exposure to COVID-19 by research participants and to minimize the impact on the study data integrity.

Advicenne's Study B23CS is a Phase 3 study of ADV7103 (potassium citrate monohydrate and potassium hydrogen carbonate) in pediatric and adult subjects with distal renal tubular acidosis. Advicenne closed the study to enrollment of new subjects on April 9, 2020 due to the COVID-19 Public Health Emergency. This protocol amendment institutes operational changes that allow opening the study to subject enrollment once again.

The study consists of four periods:

- Period 1 Enrollment/ Screening (up to 28 days)
- Period 2 Open-label ADV7103 Lead-in (7-12 weeks)
- Period 3 Randomized, Double-blinded Withdrawal (6 days)
- Period 4 Study Completion (up to 4 weeks)

In the previous versions of the B23CS protocol (version 1.0 (20Jul2018) and 2.0 (14Aug2018), **Periods 1, 2, and 4** were conducted on an out-patient basis and allowed flexibility for subjects and investigators between on-site "study visits" and "remote interactions," including the home. **Period 3**, however, was to be conducted at in-patient clinical units to enable patient monitoring. Given the COVID-19 Public Health Emergency, in-patient monitoring will no longer be available. With this protocol amendment (3.0), Advicenne will execute immediate interventions to enable conduct of Period 3, in addition to Periods 1, 2, and 4, at the subject's home or the investigative site.

All study visits including: Visit 1-Screening, Visit 2-Titration and Stabilization, Visit 3-Randomized Blinded Withdrawal, Visit 4 -End of Study or Early Withdrawal, and all other Unscheduled Visits will be completed at the subject's home, via telehealth (audio/visual supported virtual) or if preferred and feasible, at the investigative site, on an outpatient / office-level basis. The priority will be to complete all protocol activities in the subject's home, via home health nurses visiting the subject, as well as the investigator and research staff conducting telehealth visits with the subject/caregivers. If the subject, subject's caregiver, the investigator and investigative staff are able and permit protocol activities (study visits or unscheduled visits) at the investigator's office, then the study visit may be performed at the investigator's office.

Effective immediately-Period 3-Visit 3 – Randomized Double-Blinded Withdrawal procedures will be conducted on an outpatient basis only.

This change in no way restricts the investigator from fulfilling his/her responsibilities to ensure the safety of clinical trial subjects. Based upon the discretion of the investigator, all safety interventions required to maintain the well-being of subjects, including diagnostics, treatment and/or referral related to adverse events and serious adverse events are permitted.

Interventions and resources implemented to ensure protocol activities can be performed within the subject's home or investigator's office include:

- Upgrades and system integration add-ons to B23CS virtual electronic source (minimizing paper source and shared tablets, etc.) that can be directly entered by patient, caregiver, and investigational staff including: ePro and eCOA and study activities via Science 37's virtual platform, and integration of datasets into Medidata Rave enabling SAS transfer and analyses
- Trained and delegated home-health or in-office nurses using mobile technologies and point-of-care collection:
 - where safety specimens (screening, baseline and end of study serum chemistry and hematology) will be transported to one central lab, ACM Global Laboratories (ACM);
 - where immediate analysis and reporting of total bicarbonate and potassium will be completed utilizing the point-of-care calibrated iSTAT System (Abbott Inc.); and
 - where mobile/point-of-care renal and cardiac monitoring (ECG, Holter monitors and/or telemetry) can be performed as needed.

To ensure subject safety within the subject's home or investigator's office during Period 3-Visit 3-Randomized Double-Blinded Withdrawal, as there is a risk that subjects in either the ADV7103 or placebo arm might experience hypokalemia or hyperkalemia, the Exclusion Criterion for Visit 1 – Screening potassium lab results-adding a lower limit for potassium levels - have been updated to insure screened subjects' potassium levels are within normal range prior to entering the study:

Exclusion Criterion: Subject has any of the following laboratory abnormalities associated with Visit 1:

Serum potassium > 5.0 mEq/L **or** <3.0 mEq/L or hypokalemia accompanied by clinical symptoms (eg, muscle cramps) or significant ECG changes (e.g., T wave depression, U wave elevation)

During Period 3 Randomized Double-Blinded Withdrawal, several activities including vital signs, spot urine sampling, serum bicarbonate and serum potassium currently (Protocol Version 2.0) are to be performed more frequently than once daily. In order to reduce the risk of exposure and transmission of COVID-19, we evaluated those activities that could safely be reduced to daily and determined that activities to be completed during all study visits and unscheduled visits will be restricted to being performed once daily and study visits will be limited to once daily.

To reduce inter-site potassium result variability and to standardize serum bicarbonate measures, the use of point-of-care / mobile iSTAT System will be the standardized analysis method.

References to other measurements of potassium, and allowances to adjust specified levels based on corresponding local lab reference ranges have been removed.

A second informed consent / assent was required originally prior to entry into Period 3- the in-clinic unit / inpatient stay. As the requirement for a Period 3 inpatient stay has been removed (due to the COVID-19 Pandemic), the second consent process specific to Period 3 has been removed. Laboratory procedures in children <12 years of age have been clarified to fit specified parameters appropriate for that age group.

Other changes include:

- Clarification that dose titration will be considered complete and a subject will enter the Stabilization Phase of Period 2 after two consecutive serum bicarbonate levels (**2-4 days apart**) \geq the lower limit of the age-specific target range.
- To ensure maximum safety for subjects who may experience a decline in serum potassium during Period 3 (Double-Blinded Randomized Withdrawal), repeat serum potassium measurements are recommended 2-4hrs after results found to be below 3.5mEq/L or to have decreased more than 15 percent since the last measurement.
- Potassium supplementation specified as potassium hydrochloride.
- 4mEq ADV7103 Sachets were removed from clinical supply dosage forms.
- Blood volume collected for subjects < 12 years of age was specified.
- Changes in sponsor and key study personnel.

In summary, the substance of the amendment to protocol B23CS (version 3.0) reflects changes needed to conduct the study during the COVID-19 Public Health Emergency. All changes will be reflected in an updated Informed Consent and Assent Form. The amended protocol allows study activities to be performed in the subject's home by home health care nurses, sets a baseline range for serum potassium to assure safety, introduces point-of-care analysis of serum bicarbonate, reduces sample collections to once daily, and allows telehealth exams/visits.

Summary of Changes to Protocol B23CS Version 3.0

Item	Section	Change From (v 2.0)	Change To (v 3.0)	Scope/Purpose/Rationale
1	Header	FINAL Version 2.0	FINAL Version 3.0	Version update
2	Page 1	Sponsor: Advicenne Pharma 30000 Nîmes – France	<i>Sponsor :</i> <i>Advicenne SA</i> <i>2 rue Briçonnet</i> <i>F-30 000 Nîmes – France</i>	Reflects company registration update
3	Page 1	Contract Research Organization: CTI Clinical Trial and Consulting 100 E. RiverCenter Blvd. Covington, KY 41011 Phone: +1 513 598 9290	<i>Contract Research Organization:</i> <i>Pharpoint Research</i> <i>5003 S Miami Blvd STE 100, Durham,</i> <i>NC 27703</i> <i>Phone: +1 919 433 2440</i>	Reflects change in CRO
4	Signature Page	Protocol Date/Version: 14 Aug 2018 (FINAL Version 2.0)	<i>Protocol Date/Version:</i> <i>30Nov2020</i> <i>(FINAL Version 3.0)</i>	Reflects amended protocol
5	Signature Page	Sponsor's Authorized Officer: Dr Luc-André Granier Advicenne Pharma 2 rue Briçonnet 30000 Nîmes – France Ph : +33 466 05 54 27 Fx : +33 466 21 23 35 lag@advicenne.com	<i>Sponsor's Authorized Officer:</i> <i>André Ulmann, MD, PhD</i> <i>CEO</i> <i>Advicenne SA</i> <i><u>22, rue de la Paix</u></i> <i><u>75002 Paris, FRANCE</u></i> <i><u>aulmann@advicenne.com</u></i> <i>Mobile: <u>+33680406257</u></i>	Reflects change in Advicenne leadership
6	Investigator's Agreement	(version 2.0)	(version 3.0)	Reflects amended protocol

Item	Section	Change From (v 2.0)	Change To (v 3.0)	Scope/Purpose/Rationale
7	Table 1: Contact Information for Key Study Personnel: SAE Reporting ,	CTI Global Safety and Pharmacovigilance Phone :+1 877 755 0742 E-mail :CTISafety@ctifacts.com eFax :+1 800 860 8785	Vigipharme Global Safety and Pharmacovigilance Phone:TBD E-mail: pharmacovigilance@advicenne.com eFax: +33 (0)4 67 10 72 53	Reflects update in Pharmacovigilance
8	Table 1: Contact Information for Key Study Personnel: Medical Monitor	Robert S. Gaston, MD, FAST Medical Director CTI Clinical Trial and Consulting	Anthony Robinson, CRNP VP, Head of Clinical Operations Advicenne Inc.	Reflects update in Medical Monitoring
9	Table 1: Contact Information for Key Study Personnel: Study Manager	Tracy Reed-Kessler, PhD Study Manager CTI Clinical Trial and Consulting Phone: +1 513 618 6709 E-mail: tkessler@ctifacts.com	Eric Berrios, BSN, RN Project Manager, Clinical Operations PharPoint Research Phone: 919-433-2519 E-mail: berrios@pharpoint.com	Reflects update in Study Management
10	Table 1: Contact Information for Key Study Personnel: Advicenne Medical Representative	Linda Law, MD, MBA Vice President, Clinical Development and Medical Affairs Advicenne Pharma Mobile: +1 513 739 0154 E-mail: llaw@advicenne.com	Andre Ulmann, MD, PhD Chief Medical and Executive Officer Advicenne SA aulmann@advicenne.com Mobile: +33680406257	Reflects update in Medical Representation

Item	Section	Change From (v 2.0)	Change To (v 3.0)	Scope/Purpose/Rationale
11	1.Synopsis Study Design and Methodology:Paragraph 4 Protocol: 6.2 Study Periods	Study Periods 1, 2, and 4 will involve activities conducted on an outpatient basis. Period 3 will be conducted at clinical units to enable inpatient cardiac monitoring (eg, Holter monitoring, cardiac telemetry, or other appropriate method). A subset of investigational sites will be selected by the Sponsor to perform Period 3 study procedures. Subjects enrolled at investigational sites that participate only in Periods 1, 2, and 4 (outpatient periods) will be referred to a participating clinical unit for Period 3 activities. Some or all of the institutions with clinical units conducting Period 3 activities may be able to accommodate all other study periods and be supervised by a single Principal Investigator.	Study Periods 1, 2, 3 , and 4 will involve activities conducted either at the subject's home or at the investigator's office (outpatient) by investigator telehealth visits and/or visiting qualified delegates (home-health visiting nurses). on an outpatient basis. Period 3 will be conducted at clinical units to enable inpatient cardiac monitoring (eg, Holter monitoring, cardiac telemetry, or other appropriate method). A subset of investigational sites will be selected by the Sponsor to perform Period 3 study procedures. Subjects enrolled at investigational sites that participate only in Periods 1, 2, and 4 (outpatient periods) will be referred to a participating clinical unit for Period 3 activities. Some or all of the institutions with clinical units conducting Period 3 activities may be able to accommodate all other study periods and be supervised by a single Principal Investigator.	Modification to Period 3 inpatient study conduct to home-based or investigative site conduct due to COVID-19 Public Health Emergency. .

Item	Section	Change From (v 2.0)	Change To (v 3.0)	Scope/Purpose/Rationale
12	1.Synopsis (Page 8) Study Design and Methodology:Paragraph 1	Study “visits” are required face-to-face encounters between the subject and investigational site staff. Many study procedures can be performed without the necessity of face-to-face encounters with investigational site staff (eg, blood collection, urine collection, provision of ADV7103 dosing guidance via phone, resupply of open-label ADV7103, etc). These encounters that do not require a face-to-face interaction with investigational site staff will be referred to as “remote interactions” in this protocol. When protocol-specified activities (eg, blood collection) are conducted at the investigational site even though they could be conducted elsewhere (eg, separate blood collection facility, home visit by a healthcare provider, etc), the encounters will also be	Study “visits” are required face-to-face encounters between the subject and investigational site staff. Many study procedures can be performed without the necessity of face-to-face encounters with investigational site staff (eg, blood collection, urine collection, provision of ADV7103 dosing guidance via phone, resupply of open-label ADV7103, etc). These encounters that do not require a face-to-face interaction with investigational site staff will be referred to as “remote interactions” in this protocol. When protocol-specified activities (eg, blood collection) are conducted at the investigational site even though they could be conducted elsewhere (eg, separate blood collection facility, home visit by a healthcare provider, etc), the encounters will also be referred to as “remote interactions” in this protocol. Home visits by healthcare providers will be offered to all subjects for the purpose of blood collection and other outpatient activities required by the protocol.	Due to COVID-19 precautions, “Study visits” and “Remote visits” have been replaced with study visits and unscheduled visits to be conducted in the subject’s home or in the investigator’s office (outpatient). Telehealth virtual visits are also permitted.

Item	Section	Change From (v 2.0)	Change To (v 3.0)	Scope/Purpose/Rationale
		referred to as “remote interactions” in this protocol. Home visits by healthcare providers will be offered to all subjects for the purpose of blood collection and other outpatient activities required by the protocol.		
13	1.Synopsis (Page 8) Study Design and Methodology:Period 1, Enrollment/Screening: Protocol: 6.2.1 Period 1 (Enrollment/Screening)	<u>Period 1, Enrollment/Screening:</u> Subjects are enrolled at the time informed consent is obtained. After obtaining informed consent from the subject or parent/guardian and assent from the subject if indicated, the Screening Visit (Visit 1) will take place on an outpatient basis at the investigational site. Subjects who do not initially meet all eligibility criteria may be re-screened at the Investigator’s discretion (in consultation with the Medical Monitor) and enroll in the study if all eligibility criteria are met. During this period, which may involve up to 28 days for each screening attempt (no more than 3 total attempts or 2 re-screens), each subject will remain on her/his SOC alkali regimen and have study baseline assessments performed.	<u>Period 1, Enrollment/Screening:</u> Subjects are enrolled at the time informed consent is obtained. After obtaining electronic informed consent from the subject or parent/guardian and assent from the subject if indicated, the Screening Visit (Visit 1) will take place on an outpatient basis at the investigational site or <i>within the safety of their home via a home health nurse and as needed, investigator telehealth sessions.</i> Subjects who do not initially meet all eligibility criteria may be re-screened at the Investigator’s discretion (in consultation with the Medical Monitor) and enroll in the study if all eligibility criteria are met. During this period, which may involve up to 28 days for each screening attempt (no more than 3 total attempts or 2 re-screens), each subject will remain on her/his SOC alkali regimen and have study baseline assessments performed.	To clarify study visit activities, all references to face-to-face and remote visits have been removed. Study visits: Visits 1-Screening, Visit 2-Titration and Stabilization, Visit 3-Randomized Double-Blinded Withdrawal, Visit 4-End of Study and/or Early Withdrawal, and Unscheduled Visits will be performed preferably in the subject’s home, or in the investigator’s office, and via telehealth visits. This change is due to the precautions and policies taken by healthcare facilities to

Item	Section	Change From (v 2.0)	Change To (v 3.0)	Scope/Purpose/Rationale
		It should be possible to complete nearly all of the required screening/study baseline assessments during the face-to-face Screening Visit (Visit 1). Any remaining activities/assessments (eg, completion of the study baseline 24-hour urine collection, renal ultrasound testing, etc) may be completed via remote interactions (ie, not necessarily face-to-face encounters with study team members at the investigational site).	It should be possible to complete nearly all of the required screening/study baseline assessments during the face-to-face Screening Visit (Visit 1). Any remaining activities/assessments (eg, completion of the study baseline 24-hour urine collection, renal ultrasound testing, etc) may be completed via remote interactions (ie, not necessarily face-to-face encounters with study team members at the investigational site).	reduce the risk of COVID-19 exposure and transmission to clinical research subjects and investigative staff. Informed consents and assents will be completed by electronic and paper documentation.
14	1.Synopsis Study Design and Methodology: Dose Titration Phase: AND 6.2.2 Period 2 (Open-label Lead-in) AND 6.2.2.1 Period 2 – Dose Titration Phase	<u>Period 2, Open-label Lead-in:</u> Throughout the Open-label Lead-in Period, subjects will be followed by phone interactions and undergo blood collection for local laboratory testing. <u>Dose Titration Phase:</u> After eligibility for the study has been confirmed by the	<u>Period 2, Open-label Lead-in:</u> Throughout the Open-label Lead-in Period, subjects will be followed by telehealth and phone interactions and undergo in-home, point-of-care blood collection, processing and analysis. for local laboratory testing. <u>Dose Titration Phase:</u> After eligibility for the study has been confirmed by the investigator, the subject will be registered into the study and	To clarify study visit activities, all references to face-to-face and remote visits have been removed. Study visits: Period 1, Visit 1- Screening, Period 2, Visit 2-Titration and Stabilization, Period 3, Visit 3-Randomized Double-Blinded Withdrawal, Period 4,

Item	Section	Change From (v 2.0)	Change To (v 3.0)	Scope/Purpose/Rationale
		Investigator, the subject will be registered into the study and open-label ADV7103 will be provided to the subject either during Visit 1 or during a remote interaction (eg, home visit by a healthcare provider, shipping method/mail delivery, pick up by the subject at the investigational site, etc).	open-label ADV7103 will be provided to the subject either during Visit 1 or during a remote interaction (eg, home visit by a healthcare provider, shipping method/mail delivery, pick up by the subject at the investigational site, etc).	Visit 4-End of Study and/or Early Withdrawal, and Unscheduled Visits will be performed preferably in the subject's home, or in the investigator's office, and via telehealth visits. This change is due to the precautions and policies taken by healthcare facilities to reduce the risk of COVID-19 exposure and transmission to clinical research subjects and investigative staff
15	1.Synopsis Study Design and Methodology: Dose Titration Phase: Protocol 6.2.2.1 Period 2-Dose Titration Phase	After ADV7103 dosing is initiated, pre-morning dose (t ₀) blood samples will be collected every 2 to 4 days via a remote interaction (eg, home visit by a healthcare provider, visit to a blood collection site) to obtain serum bicarbonate and potassium results. The	After ADV7103 dosing is initiated, pre-morning dose (t ₀) blood samples will be collected every 2 to 4 days via a remote interaction (eg, home visit by a healthcare provider, or subject visit to a blood collection-an outpatient site) to obtain serum bicarbonate and potassium results. Whole blood samples (0.1 cc) will be gathered and prepared by trained staff, and an electrolyte panel (Cl-, K+, Na+, tCO₂) will be analyzed and reported via portable point-of-care iSTAT System (Abbott Inc.).	To clarify study visit activities, all references to face-to-face and remote visits have been removed. Study visits: Period 1, Visit 1-Screening, Period 2, Visit 2-Titration and Stabilization, Period 3, Visit 3-Randomized Double-Blinded Withdrawal, Period 4, Visit 4-End of Study and/or Early Withdrawal, and Unscheduled Visits

Item	Section	Change From (v 2.0)	Change To (v 3.0)	Scope/Purpose/Rationale
				<p>will be performed preferably in the subject's home, or in the investigator's office, and via telehealth visits. This change is due to the precautions and policies taken by healthcare facilities to reduce the risk of COVID-19 exposure and transmission to clinical research subjects and investigative staff.</p> <p>The change also responds to FDA's Study May Proceed Letter issued September 2018, Comment 11.*</p>
16	1.Synopsis (Page 9) Study Design and Methodology: Dose Titration Phase: Protocol: 4.2.1 Rationale for the Study Design and Objectives (Paragraph 2, Page 34)	This protocol refers to "serum bicarbonate" without reference to assay technique. It is possible to assess this parameter via direct measurement (enzymatic method, commonly reported as "serum total carbon dioxide" or TCO ₂ , will be used at clinical units during Period 3), or indirectly calculate with Henderson-Hasselbach derived formulae from ionic determination. In the clinical settings relevant to this study,	This protocol refers to "serum bicarbonate" without reference to assay technique. It is possible to assess this parameter via direct measurement (enzymatic method, commonly reported as "serum total carbon dioxide" or TCO₂, will be used at clinical units during Period 3), or indirectly calculate with Henderson-Hasselbach derived formulae from ionic determination. In the clinical settings relevant to this study, differences between techniques are likely to be trivial. Therefore, in this protocol the term "serum bicarbonate" applies to both directly measured and	To reduce inter-site variability and standardize serum bicarbonate measures, the iSTAT System use of point-of-care / mobile i will be the standardized method. References to other measurements of potassium, and allowances to adjust specified levels based on

Item	Section	Change From (v 2.0)	Change To (v 3.0)	Scope/Purpose/Rationale
		<p>differences between techniques are likely to be trivial. Therefore, in this protocol the term “serum bicarbonate” applies to both directly measured and calculated bicarbonate levels from plasma, whole blood, or serum. The term “serum potassium” is used throughout this protocol; however, it is recognized that potassium may not always be measured in serum. Therefore, measurement of potassium in another blood-based biological matrix (eg, plasma, whole blood) is acceptable in this study if agreed by the Sponsor.</p> <p>It is further recognized that reference ranges for serum bicarbonate and serum potassium may differ slightly across investigational sites. This protocol specifies a serum bicarbonate target range, minimum acceptable levels for serum bicarbonate and serum potassium, and age-specific serum bicarbonate levels that constitute the primary endpoint. However, on an investigational site-specific basis, these specified levels may be adjusted slightly based on the corresponding reference range to enable</p>	<p>calculated bicarbonate levels from plasma, whole blood, or serum. The term “serum potassium” is used throughout this protocol; however, it is recognized that potassium may not always be measured in serum. Therefore, measurement of potassium in another blood-based biological matrix (eg, plasma, whole blood) is acceptable in this study if agreed by the Sponsor.</p> <p>It is further recognized that reference ranges for serum bicarbonate and serum potassium may differ slightly across investigational sites. This protocol specifies a serum bicarbonate target range, minimum acceptable levels for serum bicarbonate and serum potassium, and age-specific serum bicarbonate levels that constitute the primary endpoint. However, on an investigational site-specific basis, these specified levels may be adjusted slightly based on the corresponding reference range to enable integration and analysis of data from all investigational sites.</p>	<p>corresponding local lab reference ranges removed.</p> <p>This change is in response to FDA’s Study May Proceed Letter issued September 2018, Comment 11.*</p>

Item	Section	Change From (v 2.0)	Change To (v 3.0)	Scope/Purpose/Rationale
		integration and analysis of data from all investigational sites. .		
17a	1.Synopsis (Page 9) Study Design and Methodology: Dose Titration Phase: AND 6.2.2.1 Period 2 – Dose Titration Phase AND 6.6 Initial ADV7103 Dose and Dose Adjustment	After a dose results in 2 consecutive serum bicarbonate levels \geq the lower limit of the targeted range, dose titration will be considered complete, and the subject will enter the Stabilization Phase of Period 2. If the serum bicarbonate level is in the targeted range but the serum potassium level is below 3.5 mEq/L, ADV7103 may continue to be uptitrated if ADV7103 continues to be tolerated and serum bicarbonate levels remain in the targeted range. If a maximum tolerated dose of ADV7103 delivers a serum bicarbonate level in the targeted range and the serum potassium level is \geq 3.0 mEq/L and $<$ 3.5 mEq/L, an acceptable dose has been identified, if the patient is not symptomatically hypokalemic. If a maximum tolerated dose of ADV7103 delivers a serum bicarbonate level in the targeted range and the serum potassium level is $<$ 3.0 mEq/L, potassium supplementation may be considered in consultation with the Medical Monitor and Sponsor Medical Representative	After a dose results in at least 2 consecutive serum bicarbonate levels (2-4 days apart) \geq the lower limit of the targeted range, the investigator will determine that dose titration will be considered is complete, and the subject will enter the Stabilization Phase of Period 2. If the serum bicarbonate level is in the targeted range but the serum potassium level is below 3.5 mEq/L, ADV7103 may continue to be up titrated if ADV7103 continues to be tolerated, and serum bicarbonate levels remain in the targeted range, and serum potassium levels stay \leq 5.0 mEq/L. If a maximum tolerated dose of ADV7103 delivers a serum bicarbonate level in the targeted range and the serum potassium level is \geq 3.0 mEq/L and $<$ 3.5 mEq/L, an acceptable dose has been identified, if the patient is not symptomatically hypokalemic. If a maximum tolerated dose of ADV7103 delivers a serum bicarbonate level in the targeted range and the serum potassium level is $<$ 3.0 mEq/L, potassium supplementation (potassium hydrochloride) may be considered in consultation with the Medical Monitor and/or Sponsor Medical Representative.	Stabilization guidance further specified requiring consecutive serum bicarbonate levels to be obtained 2-4 days apart.. This is in response to FDA Study May Proceed Letter of 2018, Comment 10.* Lower and upper limits of serum potassium inserted to clarify safe stabilization. Potassium supplementation specified as potassium hydrochloride. This is in response to FDA Study

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				May Proceed Letter of 2018, Comment 13*
17b	Sec. 4.2.1 Rationale for the Study Design and Objectives	Subjects meeting all criteria for continuation into Period 3 will be admitted as an inpatient to a clinical unit to provide for the safety of the subject during this period. Period 3 involves administration of blinded ADV7103 or placebo to demonstrate the efficacy of ADV7103 in preventing metabolic acidosis. The inpatient setting enables close monitoring of the subject for changes in serum bicarbonate and potassium as well as quickly responding to clinical manifestations of abnormalities in these parameters. Randomization and blinding limits various sources of bias in the assessment of study subjects. Although the Investigator and all site staff (except for the pharmacist) will be blinded to study product, they will have full access to test results and other clinical information required to care for the subject. The planned 6 day duration of stay in the clinical unit is estimated to be an adequate length time to observe potential decreases in serum bicarbonate that are associated	Subjects meeting all criteria for continuation will be admitted into Period 3 will be admitted as an inpatient to a clinical unit to provide for the safety of the subject during this period. Period 3 involves administration of blinded ADV7103 or placebo to demonstrate the efficacy of ADV7103 in preventing metabolic acidosis. The inpatient setting enables close monitoring of the subject for changes in serum bicarbonate and potassium as well as quickly responding to clinical manifestations of abnormalities in these parameters. Randomization and blinding limits various sources of bias in the assessment of study subjects. Although the Investigator and all site staff (except for the pharmacist) will be blinded to study product, they will have full access to test results and other clinical information required to care for the subject. The planned 6 day duration of Period 3 stay in the clinical unit is estimated to be an adequate length time to observe potential decreases in serum bicarbonate that are associated with administration of placebo; however, a blinded Data Monitoring Committee (bDMC; independent of the unblinded Data Monitoring Committee, or uDMC) will review data from at least 8 subjects completing Period 3 and	

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		with administration of placebo; however, a blinded Data Monitoring Committee (bDMC; independent of the unblinded Data Monitoring Committee, or uDMC) will review data from at least 8 subjects completing Period 3 and determine whether Period 3 duration may be adjusted.	determine whether Period 3 duration may be adjusted.	
18	1.Synopsis (Page 10) Study Design and Methodology: Stabilization Phase: Protocol: 6.2.2.2 Period 2-Stabilization Phase	Stabilization Phase: During this phase, the subject will be followed by phone contact/remote interactions, if needed, with serum bicarbonate and potassium levels obtained every 2 weeks (or more often if determined by Investigator in consultation with Medical Monitor). At the end of the Stabilization Phase (ie, after 6-8 weeks post titration), the Stabilization Visit (ie, Visit 2) will take place at the investigational site at which the subject was enrolled in the study with the subject remaining on her/his stable dose of ADV7103. At this time, the enrolling site Investigator will assess the eligibility of the subject for the Randomized, Double-blinded Withdrawal Period (Period 3).	Stabilization Phase: During this phase, the subject will be monitored followed by phone contact/remote interactions, if needed, with serum bicarbonate and potassium levels obtained every 2 weeks (or more often if determined by Investigator in consultation with Medical Monitor). At the end of the Stabilization Phase (ie, after 6-8 weeks post titration), the Stabilization Visit (ie, Visit 2) will take place at the investigational site or in the subject's home and via telehealth, at which the subject was enrolled in the study with the subject remaining on her/his stable dose of ADV7103. At this time, the enrolling site investigator will assess the eligibility of the subject for the Randomized, Double-blinded Withdrawal Period (Period 3). Subjects eligible for randomization must meet all of the following criteria: <ul style="list-style-type: none"> • a stable ADV7103 dose, for a minimum of six weeks; • serum bicarbonate level within target range and serum 	A second informed consent / assent was required originally prior to entry into Period 3. As the requirement for a Period 3 inpatient stay has been removed (due to the COVID-19 Pandemic) and will now take place at the investigator's site or in the subject's home, the second consent process specific to Period 3 has been removed.

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		<p>Subjects eligible for randomization must meet all of the following criteria:</p> <ul style="list-style-type: none"> • a stable ADV7103 dose, for a minimum of six weeks; • serum bicarbonate level within target range and serum potassium level ≥ 3.0 mEq/L, both at Visit 2; • serum bicarbonate level is maintained in the corresponding age-specific normal range for at least 80% of available results obtained during the Stabilization Phase of Period 2; • serum potassium level ≥ 3.0 mEq/L for at least 80% of available results obtained during the Stabilization Phase of Period 2; • acceptable safety and tolerability as determined by the 	<p>potassium level ≥ 3.0 mEq/L, both at Visit 2;</p> <ul style="list-style-type: none"> • serum bicarbonate level is maintained in the corresponding age-specific normal range for at least 80% of available results obtained during the Stabilization Phase of Period 2; • serum potassium level ≥ 3.0 mEq/L for at least 80% of available results obtained during the Stabilization Phase of Period 2; • acceptable safety and tolerability as determined by the Investigator at the enrolling site. <p>Serum bicarbonate and potassium levels should be checked at least every 4 weeks between Visit 2 and admission to the clinical unit if the time between these encounters becomes protracted.</p> <p>Randomization will be completed after informed consent (and assent, when appropriate) for Period 3 is obtained and prior to blinded study product administration. It is expected that subjects will consent (or assent, when applicable) to participation in Periods 1 through 4 during the Screening Visit. Obtaining a separate informed consent/assent for Period 3 will be at the discretion of the institutional review boards (IRBs) providing oversight</p>	

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		<p>Investigator at the enrolling site.</p> <p>Serum bicarbonate and potassium levels should be checked at least every 4 weeks between Visit 2 and admission to the clinical unit if the time between these encounters becomes protracted.</p> <p>Randomization will be completed after informed consent (and assent, when appropriate) for Period 3 is obtained and prior to blinded study product administration. It is expected that subjects will consent (or assent, when applicable) to participation in Periods 1 through 4 during the Screening Visit. Obtaining a separate informed consent/assent for Period 3 will be at the discretion of the institutional review boards (IRBs) providing oversight to the investigational sites selected for Period 3.</p> <p>The Study Manual provides guidance for dose adjustments based on serum bicarbonate and potassium results that fall out of the targeted age-specific ranges during the Stabilization Phase.</p>	<p>to the investigational sites selected for Period 3.</p> <p>The Study Manual provides guidance for dose adjustments based on serum bicarbonate and potassium results that fall out of the targeted age-specific ranges during the Stabilization Phase.</p>	

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19	1.Synopsis (Page 10-12) Study Design and Methodology: Period 3, Randomized, Double- blinded Withdrawal Protocol: 6.2.3 Period 3 (Randomized, Double- blinded Withdrawal)	<p><u>Period 3, Randomized, Double-blinded Withdrawal:</u></p> <p>As soon as practicable following Visit 2, eligible subjects taking their pre-randomization dose of ADV7103 will be admitted to a clinical unit for an adequate period to monitor serum bicarbonate and potassium levels in the context of randomized, double-blinded treatment withdrawal. Admission may occur in the evening prior to the first dose of blinded study product the next morning or early in the morning prior to the first dose of blinded study product.</p> <p>After baseline clinical unit evaluations including laboratory tests are completed (ie, after admission and prior to dosing of blinded study product), subjects will either continue their stabilized ADV7103 dose or switch to a weight-matched identical-appearing placebo dose according to their randomized treatment assignment (without potassium supplementation). In the unexpected situation where these Period 3 baseline evaluations disclose a serum bicarbonate level < 18 mEq/L for subjects ≥ 4 years old and < 17 mEq/L for subjects</p>	<p><u>Period 3, Randomized, Double-blinded Withdrawal:</u></p> <p>As soon as practicable following Visit 2, eligible subjects taking their pre-randomization dose of ADV7103 will be admitted to a clinical unit enter Period 3 (Visit 3) randomization for an adequate period to monitor serum bicarbonate and potassium levels in the context of randomized, double-blinded treatment withdrawal. Admission Period 3 start and randomization may occur in the evening prior to the first dose of blinded study product the next morning or early in the morning prior to the first dose of blinded study product.</p> <p>After baseline clinical unit evaluations including laboratory tests are completed (ie, after admission and prior to dosing of blinded study product), subjects will either continue their stabilized ADV7103 dose or switch to a weight-matched identical-appearing placebo dose according to their randomized treatment assignment (without potassium supplementation). In the unexpected situation where these Period 3 baseline evaluations disclose a serum bicarbonate level < 18 mEq/L for subjects ≥ 4 years old and < 17 mEq/L for subjects < 4 years old and/or a serum potassium level <3.0 mEq/L for all subjects, the subject will not be dosed with blinded study product. Rather, at the Investigator's discretion, the subject may receive open-label ADV7103 or a SOC</p>	<p>Transfer of inpatient stay, site outpatient visits to home care by qualified designees reduces risk of COVID-19 exposure to subjects and mitigates risk of research facility closure or limited access disrupting clinical trial execution, while maintaining safety and laboratory monitoring of subjects.</p> <p>Potassium supplementation specified as potassium hydrochloride. This is in response to FDA Study May Proceed Letter of 2018, Comment 13.*</p>

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		<p>< 4 years old and/or a serum potassium level <3.0 mEq/L for all subjects, the subject will not be dosed with blinded study product. Rather, at the Investigator's discretion, the subject may receive open-label ADV7103 or a SOC regimen to address these abnormal laboratory results. When the clinical status of the subject allows, the subject will be discharged from the clinical unit with instructions to continue open-label ADV7103 or a SOC regimen and to return to the investigational site visited previously in Periods 1 and 2 within 4 weeks to complete Visit 4 study exit evaluations.</p> <p>The Investigator and staff at the clinical unit (except for the pharmacist) will be blinded to Period 3 study product assignments, but not to laboratory results. The subjects will remain blinded to treatment throughout Period 3. In all subjects, serum bicarbonate and potassium levels will be measured every 6 hours for the first 24 hours following administration of the first dose of blinded study product in the clinical unit, then every 8 hours</p>	<p>regimen to address these abnormal laboratory results. When the clinical status of the subject allows, the subject will be discharged from Period 3 the clinical unit with instructions to continue open-label ADV7103 or a SOC regimen and to return to the investigational site visited previously in Periods 1 and 2 within 4 weeks to complete Visit 4 study exit evaluations either at their site or virtually.</p> <p>The Investigator and staff at the clinical unit (except for the pharmacist) will be blinded to Period 3 study product assignments, but not to laboratory results. The subjects will remain blinded to treatment throughout Period 3. In all subjects, serum bicarbonate and potassium levels will be measured every 6 hours for the first 24 hours following administration of the first dose of blinded study product, in the subject's home clinical unit, then every 8 hours (or more frequently if deemed necessary for safe subject management) during through the remainder of Visit 3.</p> <p>To ensure maximum safety for the subjects who may experience a decline in serum potassium, repeat serum potassium measurements should be performed 2-4hrs (and not 24hrs) after the first measurement if serum potassium is found to be below 3.5 mEq/L or to have decreased by more than 15 percent since the last</p>	<p>In order to reduce the risk of exposure and transmission of COVID-19, activities to be completed during all study visits and unscheduled visits will be restricted to being performed once daily and study visits to be limited to once daily.</p> <p>We also determined it was safe to reduce the frequency of labs to manage the subject, and took both of these considerations into account to restrict study visits and procedures to be performed once daily.</p>

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		<p>(or more frequently if deemed necessary for safe subject management) during the remainder of</p> <p>They will remain in the clinical unit for approximately 6 days or until the metabolic acidosis (and any accompanying hypokalemia, if applicable) is corrected, whichever is longer. The frequency of laboratory evaluations for subjects who require correction of serum bicarbonate and/or potassium will be determined by the Investigator.</p> <p>Potassium supplementation initiated during Period 3, if applicable, should be stopped at restoration of ADV7103 dosing. Guidance for interactions between the unblinded pharmacist and blinded Investigator in the clinical unit will also be provided in the Study Manual.</p>	<p>measurement. Potassium (potassium hydrochloride) will be supplemented, as needed, for levels falling below 3.0 mEq/L.</p> <p>They will remain under <i>investigator monitoring</i> in the clinical unit for approximately 6 days or until the metabolic acidosis (and any accompanying hypokalemia, if applicable) is corrected, whichever is longer.</p> <p>Potassium supplementation initiated during Period 3, if applicable, should be stopped at restoration of ADV7103 dosing. Guidance for interactions between the unblinded pharmacist and blinded Investigator in the clinical unit will also be provided in the Study Manual.</p>	
20	1.Synopsis (Page 12) Study Design and Methodology: Stabilization Phase:	<p><u>Period 4, Study Completion:</u></p> <p>For subjects who will be followed by another investigational site (ie, the</p>	<p><u>Period 4, Study Completion:</u></p> <p>For subjects who will be followed by another investigational site (ie, the enrolling site) following discharge from</p>	Inpatient stay was eliminated due to COVID-19 precautions.

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	Protocol: 6.2.4 Period 4 (Study Completion)	<p>enrolling site) following discharge from the clinical unit, Period 4 will be defined as the time of discharge from the clinical unit through completion of the study exit visit (Visit 4) conducted at the enrolling site (ie, where site visits for Periods 1 and 2 took place). The study exit visit should take place within 4 weeks of discharge from the clinical unit. Subjects will take their stable ADV7103 dose during this time.</p> <p>For subjects who participated in all study periods at the same institution as the clinical unit, the study exit visit (Visit 4) can be conducted immediately following the completion of all Period 3 activities at the clinical unit. In this case Period 4 consists of Visit 4 activities only. However, these subjects may return to the investigational site within 4 weeks of discharge from the clinical unit for Visit 4 activities. In this case, Period 4 will be defined as the time of discharge from the clinical unit through completion of Visit 4, and subjects will take their stable ADV7103 dose during this time.</p>	<p>the clinical unit, Period 4 will be defined as the time of discharge from the clinical unit through completion of the study exit visit (Visit 4) conducted at the enrolling site (ie, where site visits for Periods 1 and 2 took place). The study exit visit should take place within 4 weeks of discharge from the clinical unit. Subjects will take their stable ADV7103 dose during this time.</p> <p>For subjects who participated in all study periods and completed Period 3, at the same institution as the clinical unit, the study exit visit (Visit 4) can be conducted immediately following the completion of all Period 3 activities at the clinical unit. In this case Period 4 consists of Visit 4 activities only. However, these subjects may complete Visit 4 return to the investigational site within 4 weeks of Period 3 completion discharge from the clinical unit for Visit 4 activities. In this case, Period 4 will be defined as the time of Period 3 completion discharge from the clinical unit through completion of Visit 4, and subjects will take their stable ADV7103 dose during this time.</p> <p>Subjects who were stabilized on ADV7103 during this study and adherent to the protocol will be offered the opportunity to receive open-label ADV7103 as part of a separate extension study. Subjects may elect to be administered</p>	

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		Subjects who were stabilized on ADV7103 during this study and adherent to the protocol will be offered the opportunity to receive open-label ADV7103 as part of a separate extension study. The initial extension study visit will take place at the same time as the exit visit (Visit 4) from this study (following informed consent/assent). Subjects declining participation in the extension study will return to their previous SOC regimen following completion of the exit visit from this study.	ADV7103 after completing Period 3, (within 4 weeks of Period 3 completion) the subject may complete Visit 4 and the initial extension study visit will take place at the same time as the exit visit (Visit 4) from this study (following informed consent/assent). Subjects declining participation in the extension study can elect to will return to their previous SOC regimen after completing Period 3, (within 4 weeks of Period 3 completion) the subject may complete Visit 4 as the following completion of the the exit visit from this study.	
21	1.Synopsis: Exclusion criteria Protocol: 7.2 Subject Exclusion Criteria	<i>Exclusion criteria:</i> 6. Subject has any of the following laboratory abnormalities associated with Visit 1: b. Serum potassium > 5.0 mEq/L or hypokalemia accompanied by clinical symptoms (eg, muscle cramps) or	<i>Exclusion criteria:</i> 6. Subject has any of the following laboratory abnormalities associated with Visit 1: b. Serum potassium > 5.0 mEq/L or <3.0 mEq/L or hypokalemia accompanied by clinical symptoms (eg, muscle cramps) or significant ECG changes (eg, T wave depression, U wave elevation)	Lower and upper potassium limits detailed, screened subjects with serum potassium levels within the normal reference range of 3.0-5.0 mg/dL will be eligible to enter the study. This is in response to FDA Study

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		significant ECG changes (eg, T wave depression, U wave elevation)		May Proceed Letter of 2018, Comment 14. *
22	8.1.1 ADV7103	Open-label ADV7103 will originate from sachets including either 4, 8, or 24 mEq of alkali.	Open-label ADV7103 will originate from sacehts including either 8 or 24 mEq of alkali.	ADV7103: 8 mEq and 24 mEq will be the clinical supply dosage strengths in the ADV7103 dRTA Clinical Development Program, ADV7103 4 mEq has been discontinued.
23	9.2 Study Product Packaging and Labeling	There are 3 strengths of sachet: 4 mEq, 8 mEq and 24 mEq. ADV7103 4 mEq sachets are orange and contain 133 mg of monohydrate potassium citrate and 262 mg of potassium bicarbonate.	There are 2 strengths of sachet: 8mEq and 24mEq. ADV7103 4 mEq sachets are orange and contain 133 mg of monohydrate potassium citrate and 262 mg of potassium bicarbonate	ADV7103: 8 mEq and 24 mEq will be the clinical supply dosage strengths in the ADV7103 dRTA Clinical Development Program, ADV7103 4 mEq has been discontinued.
24	9.4 Study Product Preparation	For ADV7103, the investigational site pharmacist will be responsible for preparing vials using 3 strengths of sachets (4 mEq, 8 mEq and 24 mEq).	For ADV7103, the investigational site pharmacist will be responsible for preparing vials using 2 strengths of sachets (8 mEq and 24 mEq).	ADV7103: 8 mEq and 24 mEq will be the clinical supply dosage strengths in the ADV7103 dRTA Clinical Development Program, ADV7103 4 mEq has been discontinued.

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25	10.2.4 Vital Signs	Vital signs (supine blood pressure, heart rate, respiratory rate, and oral temperature) will be determined in association with Visits 1, 2, 3, 4, and any unscheduled visits. During Period 3, vital signs will be determined twice daily for this study. Clinical units may have standard procedures for more frequent determination of one or more of these parameters.	Vital signs (supine blood pressure, heart rate, respiratory rate, and oral temperature) will be determined in association with Visits 1, 2, 3, 4, and any unscheduled visits. Vital signs will be determined once per visit for this study. Clinical units may have standard procedures for more frequent determination of one or more of these parameters.	COVID-19 precautions moved all visits to home or outpatient visits.
26	10.2.9 Cardiac Monitoring	Cardiac Monitoring Subjects will undergo cardiac monitoring (eg, Holter monitoring, cardiac telemetry, or other appropriate method) while in the clinical unit. Monitoring will begin prior to the first dose of study product and continue throughout the remainder of Period 3. A written summary of cardiac rhythm	Cardiac Monitoring Subjects will undergo cardiac monitoring (eg, Holter monitoring, cardiac telemetry, electrocardiogram, or other appropriate method) while in the clinical unit. Monitoring will begin prior to the first dose of study product in Period 3 and continue <i>as needed</i> throughout Period 3. <i>Including during Visit 4. A written summary of cardiac rhythm</i>	Portable and remote cardiac monitoring technologies will be available for use in subject home or in outpatient site offices. This is because COVID-19 precautions moved all visits to home or outpatient visits.

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		findings in each subject will be documented daily.	findings in each subject will be documented daily.	
27	Protocol 10.2.11.Laboratory Assessments/ Hematology	Laboratory Assessments 10.2.11.1 Hematology A complete blood count with differential and platelets will be obtained in association with Visit 1 and prior to the first dose of blinded study product in Period 3.	Laboratory Assessments 10.2.11.1 Hematology A complete blood count with differential and platelets will be obtained in association with Visit 1 and prior to the first dose of blinded study product in Period 3. These samples will be analyzed and reported by central laboratory ACM Global Laboratories.	Serum hematology and chemistry lab panels collected for safety analysis will be analyzed and reported by a central lab, ACM Global Laboratories Inc. This is in response to FDA's Study May Proceed Letter issued September 2018, Comment 11.*
28	Protocol 10.2.11.Laboratory Assessments/ Serum Chemistry	10.2.11.2 Serum Chemistry A serum chemistry panel will be obtained in association with Visit 1. During Period 3, a serum chemistry panel will be obtained prior to the first dose of blinded study product and on the last day in the clinical unit. In the event of early study withdrawal by a subject following at least 4 weeks	10.2.11.2 Serum Chemistry A serum chemistry panel will be obtained in association with Visit 1. During Period 3, a serum chemistry panel will be obtained prior to the first dose of blinded study product and on the last day of Period 3 in the clinical unit. In the event of early study withdrawal by a subject following at least 4 weeks of study participation, a serum chemistry panel will be obtained in association with the Early Withdrawal Visit.	Electrolyte panels (Cl-, K+, Na+, tCO2) collected for efficacy primary, secondary and exploratory analysis will be analyzed and reported by a qualified designee (home health nurse) utilizing the CLIA-Waived point-of-care Piccolo Express Chemistry Analyzer (Abbott Inc.). This is in response to FDA Study

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		<p>of study participation, a serum chemistry panel will be obtained in association with the Early Withdrawal Visit.</p> <p>The serum chemistry panel will include the following analytes (at a minimum): sodium, potassium, chloride, bicarbonate/total carbon dioxide, blood urea nitrogen, serum creatinine, glucose, calculated eGFR, aspartate transaminase, alanine transaminase, total bilirubin, alkaline phosphatase, calcium, phosphorus, magnesium, and uric acid.</p>	<p>The serum chemistry panel will include the following analytes (at a minimum): sodium, potassium, chloride, bicarbonate/total carbon dioxide, blood urea nitrogen, serum creatinine, glucose, calculated eGFR, aspartate transaminase, alanine transaminase, total bilirubin, alkaline phosphatase, calcium, phosphorus, magnesium, and uric acid. These samples will be analyzed and reported by central laboratory ACM Global Laboratories.</p>	<p>May Proceed Letter of 2018, Comment 11.*</p> <p>During Period 3 Randomized Double-Blinded Withdrawal, several activities including vital signs, spot urine sampling, serum bicarbonate and serum potassium currently (Protocol Version 2.0) are to be performed more frequently than once daily. In order to reduce the risk of exposure and transmission of COVID-19, activities to be completed during all study visits and unscheduled visits will be restricted to being performed once daily and study visits to be limited to once daily.</p>
29	Protocol	10.2.11.3 Spot Urine Collection	<p>10.2.11.3 Spot Urine Collection</p> <p>A spot urine sample will be collected once in association with</p>	<p>Visits are limited to once daily due to COVID-19 precautions.</p>

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	10.2.11 Laboratory Assessments/ Spot Urine Collection	<p>A spot urine sample will be collected once in association with Visit 1 and twice daily during Period 3 at the clinical unit.</p> <p>During Period 3, the first of 2 daily urine samples will be collected during the second void of the day. This second void of the day follows the first study product dose of the day (morning dose); the first void of the day (not collected) precedes the first study product dose of the day. The second daily urine sample will be collected within 30 minutes prior to the second study product dose of the day (evening dose).</p> <p>The urine sample collected during Visit 1 and one of the 2 daily urine samples during Period 3 will be used for microscopic analysis and dipstick measurement of pH.</p>	<p>Visit 1 and twice daily during Period 3 at the clinical unit.</p> <p>During Period 3, the daily urine sample will be collected during the second void of the day. This second void of the day follows the first study product dose of the day (morning dose); the first void of the day (not collected) precedes the first study product dose of the day. The daily urine sample will be collected within 30 minutes prior to the second study product dose of the day (evening dose).</p> <p>The urine sample collected during Visit 1 and the daily urine samples during Period 3 will be used for microscopic analysis and dipstick measurement of pH.</p> <p>The daily urine sample collected during Period 3 will be used to provide SS calcium oxalate (CaOx), SS calcium phosphate (CaP), and SS uric acid results. In addition, urinary calcium/creatinine and citrate/creatinine ratios will be provided from these spot urine samples collected daily during Period 3.</p>	

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		Both daily urine samples collected during Period 3 will be used to provide SS calcium oxalate (CaOx), SS calcium phosphate (CaP), and SS uric acid results. In addition, urinary calcium/creatinine and citrate/creatinine ratios will be provided from these spot urine samples collected twice daily during Period 3.		
30	Protocol 10.2.11.Laboratory Assessments/ Serum Bicarbonate and Serum Potassium	10.2.11.6 Serum Bicarbonate and Serum Potassium Blood samples will be collected for the measurement of serum bicarbonate and serum potassium levels during Period 2 as specified in Section 6.2.2., with attention paid to proper blood volume limitations for pediatric subjects. During Period 3, samples will be collected every 6 hours for the first 24 hours following administration of the first dose of blinded	10.2.11.6 Serum Bicarbonate and Serum Potassium Blood samples will be collected for the measurement of serum bicarbonate and serum potassium levels during Period 2 as specified in Section 6.2.2., with attention paid to proper blood volume limitations for pediatric subjects. During Period 3, samples will be collected pre-dose (AM) every 6 hours for the first 24 hours following administration of the first dose of blinded study product. in the clinical unit and every 8 24 hours thereafter unless the Investigator determines that additional sampling is necessary for safe management of	To reduce inter-site potassium result variability and to standardize serum bicarbonate measures, the use of point-of-care / mobile Piccolo Express Analyzers will be the standardized method. References to other measurements of potassium, and allowances to adjust specified levels based on corresponding local lab reference ranges have been removed.

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		<p>study product in the clinical unit and every 8 hours thereafter unless the Investigator determines that additional sampling is necessary for safe management of the subject (Section 6.2.3.). Blood samples will also be collected for the measurement of serum bicarbonate and serum potassium levels in association with Visit 4.</p> <p>Samples for measurement of serum bicarbonate will be analyzed within 2 hours after obtaining the sample. This protocol refers to “serum bicarbonate” without reference to assay technique, applying the term to both directly measured and calculated levels from plasma, whole blood, or serum. It is recognized that there may be variability in technique and defined normal levels from site to site. In periods 1, 2, and 4, serum</p>	<p>the subject (Section 6.2.3.). Blood samples will also be collected for the measurement of serum bicarbonate and serum potassium levels in association with Visit 4.</p> <p>Samples for measurement of serum bicarbonate will be analyzed within 2 hours after obtaining the sample. This protocol refers to “serum bicarbonate” without reference to assay technique, applying the term to both directly measured and calculated levels from plasma, whole blood, or serum. It is recognized that there may be variability in technique and defined normal levels from site to site. In periods 1, 2, and 4, serum bicarbonate will be measured and recorded according to local standards, including point of care measurement. In the Withdrawal Period, only enzymatic direct measurement of serum bicarbonate level will be performed, utilized in clinical care, and analyzed.</p> <p>The term “serum potassium” is used throughout this protocol; however, it is recognized that potassium may not always be measured in serum.</p>	<p>This is in response to FDA’s Study May Proceed Letter issued September 2018, Comment 11*</p>

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		<p>bicarbonate will be measured and recorded according to local standards, including point of care measurement. In the Withdrawal Period, only enzymatic direct measurement of serum bicarbonate level will be performed, utilized in clinical care, and analyzed. The term “serum potassium” is used throughout this protocol; however, it is recognized that potassium may not always be measured in serum. Therefore, measurement of potassium in another blood-based biological matrix (eg, plasma, whole blood) is acceptable in this study if agreed by the Sponsor. Samples for measurement of serum potassium will be analyzed within 2 hours after obtaining the sample. In the event a blood sample appears hemolyzed to any</p>	<p>Therefore, measurement of potassium in another blood-based biological matrix (eg, plasma, whole blood) is acceptable in this study if agreed by the Sponsor. Samples for measurement of serum potassium will be analyzed within 2 hours after obtaining the sample.</p> <p>In the event a blood sample appears hemolyzed to any degree, another sample should be collected as soon as possible for measurement of a serum potassium level. If the degree of hemolysis is severe, another sample should be collected as soon as possible for measurement of a serum bicarbonate level, too.</p> <p>Utilizing whole blood samples (0.1 cc), an electrolyte panel (Cl⁻, K⁺, Na⁺, tCO₂) will be prepared by a qualified delegate/nurse for measure of serum bicarbonate and serum potassium, analyzed and reported at point-of-care via the portable Piccolo Express Chemistry Analyzers (Abbott Inc.).</p>	

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		degree, another sample should be collected as soon as possible for measurement of a serum potassium level. If the degree of hemolysis is severe, another sample should be collected as soon as possible for measurement of a serum bicarbonate level, too.		
31	10.3.3 Period 3 (Randomized, Double-blinded Study Product Withdrawal)	Period 3 (Randomized, Double-blinded Study Product Withdrawal) All Period 3 study visits will take place at a clinical unit. Activities during this Period may be overseen by	Period 3 (Randomized, Double-blinded Study Product Withdrawal) All Period 3 study visits will take place at the subject's home, via telehealth (audio/visual supported virtual visit) or if preferred and feasible, at the investigator's site, on an outpatient / office-level basis. a clinical unit. Activities during this Period may be overseen by a different Principal Investigator at an investigational site that is distant from the site associated with activities in Periods 1 and 2. The entire duration of stay in the clinical unit is designated as Visit 3.	As the Inpatient stay required a second informed consent/assent for treatment in the inpatient facility, as the inpatient stay was removed from Period 3, the Period 3 Visit 3 informed consent/assent was removed and activities are now either at investigative site or in subject's home

Item	Section	Change From (v 2.0)	Change To (v 3.0)	Scope/Purpose/Rationale
		<p>a different Principal Investigator at an investigational site that is distant from the site associated with activities in Periods 1 and 2.</p> <p>The entire duration of stay in the clinical unit is designated as Visit 3.</p> <p>First Full Day in the Clinical Unit)</p> <p>The following procedures and assessments will be conducted in association with the first full day in the clinical unit:</p> <p>informed consent (and assent, when applicable), if not already obtained (Section 13.5.). Informed consent, using a form approved by the Period 3 investigational site IRB, must be obtained prior to performing any Period 3 study-specific procedures or assessments.</p> <p>Remaining Days in the Clinical Unit</p>	<p>First Full Day in the Clinical Unit)in Period 3</p> <p>The following procedures and assessments will be conducted in association with the first full day of Visit 3 in the clinical unit:</p> <p>informed consent (and assent, when applicable), if not already obtained (Section 13.5). Informed consent, using a form approved by the Period 3 investigational site IRB, must be obtained prior to performing any Period 3 study-specific procedures or assessments.</p> <p>Remaining Days in the Clinical Unit-Period 3</p> <p>As described in Section 6.2.3, the planned duration of stay in Period 3 the clinical unit is 6 days.</p> <p>The following procedures and assessments will be conducted in association with each subsequent day that a subject remains in Period 3:</p> <p>.....</p> <p>discharge from Period 3 the clinical unit (on last day).</p>	

Item	Section	Change From (v 2.0)	Change To (v 3.0)	Scope/Purpose/Rationale
		<p>As described in Section 6.2.3, the planned duration of stay in the clinical unit is 6 days.</p> <p>The following procedures and assessments will be conducted in association with each subsequent day that a subject remains in the clinical unit:</p> <p>.....</p> <p>discharge from the clinical unit (on last day).</p>		
32	10.3.4 Period 4 (Study Completion)	<p>Period 4 (Study Completion)</p> <p>Period 4 represents the time between completion of Period 3 activities and completion of the study exit visit (ie, Visit 4) activities.</p> <p>For subjects who will be followed by another investigational site (ie, the enrolling site) following discharge from the clinical unit, Period 4 will be defined as the time of discharge from the clinical unit through completion of</p>	<p>Period 4 (Study Completion)</p> <p>Period 4 represents the time between completion of Period 3 activities and completion of the study exit visit (ie, Visit 4) activities.</p> <p>For subjects who will be followed by another investigational site (ie, the enrolling site) following discharge from the clinical unit, Period 4 will be defined as the time of discharge from the clinical unit through completion of the study exit visit (Visit 4) conducted at the enrolling site (ie, where site visits for Periods 1 and 2 took place). The</p>	<p>Inpatient or in clinic stay language removed from Period 4 and where applicable replaced with investigative site or in subject's home</p>

Item	Section	Change From (v 2.0)	Change To (v 3.0)	Scope/Purpose/Rationale
		<p>the study exit visit (Visit 4) conducted at the enrolling site (ie, where site visits for Periods 1 and 2 took place). The study exit visit should take place within 4 weeks of discharge from the clinical unit. Subjects will take their stable ADV7103 dose during this time.</p> <p>For subjects who participated in all study periods at the same institution as the clinical unit, the study exit visit (Visit 4) can be conducted immediately following the completion of all Period 3 activities at the clinical unit. In this case, Period 4 consists of Visit 4 activities only. However, these subjects may return to the investigational site within 4 weeks of discharge from the clinical unit for Visit 4 activities. In this case, Period 4 will be defined as the time of discharge from the clinical unit through completion of Visit 4, and</p>	<p>study exit visit should take place within 4 weeks of discharge from the clinical unit. Subjects will take their stable ADV7103 dose during this time.</p> <p>For subjects who participated in all study periods at the same institution as the clinical unit, the study exit visit (Visit 4) can be conducted immediately following the completion of all Period 3 activities at the clinical unit. In this case, Period 4 consists of Visit 4 activities only. However, these subjects may return to the investigational site within 4 weeks of discharge from the clinical unit for Visit 4 activities. In this case, Period 4 will be defined as the time of discharge from the clinical unit through completion of Visit 4, and subjects will take their stable ADV7103 dose during this time.</p> <p>In the unexpected situation where unacceptably low Period 3 baseline serum bicarbonate and/or serum potassium levels preclude dosing of blinded study product (Section 6.2.3.), Period 4 will consist of the time from discharge</p>	

Item	Section	Change From (v 2.0)	Change To (v 3.0)	Scope/Purpose/Rationale
		<p>subjects will take their stable ADV7103 dose during this time.</p> <p>In the unexpected situation where unacceptably low Period 3 baseline serum bicarbonate and/or serum potassium levels preclude dosing of blinded study product (Section 6.2.3), Period 4 will consist of the time from discharge from the clinical unit through Visit 4.</p> <p>The subject will take open-label ADV7103 or a SOC regimen, at the Investigator's discretion, during this time and will complete Visit 4 at the investigational site visited previously in Periods 1 and 2 within 4 weeks of discharge.</p> <p>....</p>	<p>from <i>Period 3</i> the clinical unit through Visit 4.</p> <p>The subject will take open-label ADV7103 or a SOC regimen, at the Investigator's discretion, during this time and will complete Visit 4 at the investigational site visited previously in Periods 1 and 2 within 4 weeks of discharge.</p>	
33	10.3.5 Remote Interactions	<p>Remote Interactions</p> <p>All subject encounters that do not require a</p>	<p>Remote Interactions</p> <p>All subject encounters that do not require a face-to-face visit to the</p>	Modification to include site and/or home visit conduct due to COVID-19 Public Health Emergency.

Item	Section	Change From (v 2.0)	Change To (v 3.0)	Scope/Purpose/Rationale
		<p>face-to-face visit to the investigational site are considered remote interactions irrespective of where they occur (including the investigational site or blood collection facility associated with the investigational site). These remote interactions will primarily involve blood collection for serum bicarbonate and potassium levels, communications regarding titration of ADV7103 dose to achieve target levels, 24-hour urine collections (Periods 1 and 2), resupply of ADV7103, and other purposes consistent with this protocol. These encounters may occur during Periods 1, 2, and 4.</p> <p>The following procedures and assessments will be conducted in association with remote interactions in this study:</p>	<p>investigational site are considered remote interactions irrespective of where they occur (including the investigational site or blood collection facility associated with the investigational site). These remote interactions will primarily involve blood collection for serum bicarbonate and potassium levels, communications regarding titration of ADV7103 dose to achieve target levels, 24-hour urine collections (Periods 1 and 2), resupply of ADV7103, and other purposes consistent with this protocol. These encounters may occur during Periods 1, 2, and 4.</p> <p>The following procedures and assessments will be conducted in association with remote interactions in this study:</p> <p>24-hour urine collections in Periods 1 and 2 (Section 10.2.11.4);</p> <p>serum bicarbonate and serum potassium (Section 10.2.11.6);</p> <p>concomitant medications (Section 10.2.13);</p> <p>adverse events (Section 10.2.14);</p>	

Item	Section	Change From (v 2.0)	Change To (v 3.0)	Scope/Purpose/Rationale
		24-hour urine collections in Periods 1 and 2 (Section 10.2.11.4); serum bicarbonate and serum potassium (Section 10.2.11.6); concomitant medications (Section 10.2.13); adverse events (Section 10.2.14); dispense additional ADV7103, if needed (Section 10.2.17); and other procedures or activities as needed and consistent with this protocol.	dispense additional ADV7103, if needed (Section 10.2.17 and other procedures or activities as needed and consistent with this protocol.	
34	Multiple Sections and pages (p.34, 35, 36, 42, 44, 45, 52, 54, 55, 56, 57, 58, 59, 60, 65, 68, 69, 93, 94)	Reference to “clinical unit”	Reference to “Phase 3	References to inpatient stay in the clinical unit were replaced with activities conducted in the subject’s home for Period 3.

*This comment is intended as information for FDA. The comment refers to Advicenne’s responses in this protocol amendment to FDA’s Study May Proceed Letter issued September 2018. Comments regarding responses to the FDA’s Study May Proceed Letter will not be included in the protocol version submitted to Investigators.