10 December 2020
EMA/1419/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sibnayal

Common name: potassium citrate / potassium hydrogen carbonate

Procedure No. EMEA/H/C/005407/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

Abbreviation	Explanation
ADR	Adverse Drug Reaction
AE	Adverse Event
AE1	Anion Exchanger 1
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé
AUC	Area Under the Curve
BID	Twice daily dosing
BK	Potassium Bicarbonate
BMD	Bone Mineral Osteodensity
BMI	Body Mass Index
Ca	Calcium
CA	Carbonic Anhydrase
CK	Potassium Citrate
CKD	Chronic Kidney Disease
Ci	Citrate
Cl^-	Chloride
CHMP	Committee for Medicinal Products for Human Use
CMC	Chemistry, Manufacturing and Control
CKD	Chronic Kidney Disease
CO_2	Carbon dioxide
COMP	Committee for Orphan Medicinal Products
Cr	Creatinine
CSP	Clinical Study Protocol
DDI	Drug Drug Interaction
dRTA	Distal Renal Tubular Acidosis
DSMB	Data Safety Monitoring Board
EC	European Commission
ECG	Electrocardiogram
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FDC	Fixed-Dose Combination
GI	Gastro-Intestinal
GFR	Glomerular Filtration Rate
GTS	Genetic Target Stature
HCO_3^-	Bicarbonate
ITT	Intend-to Treat
KCC4	Cl^-/K^+ co-transporter
M	Month
MAA	Marketing Authorisation Application
mEq	Milliequivalent
PDCO	Paediatric Committee
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PP	Per Protocol
PPI	Proton Pump Inhibitors
QoL	Quality of Life
RMP	Risk Management Plan
SAE	Serious Adverse Event
SA	Scientific Advice
SAWP	Scientific Advice Working Party
SD	Standard Deviation

SoC	Standard of Care
SOC	System Organ Class
SP	Study Period
SPC	Summary of Product Characteristics
U	Urine
TEAE	Treatment Emergent Adverse Event
VAS	Visual Analogue Scale
WHO	World Health Organisation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Advicenne S.A. submitted on 9 November 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Sibnayal, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 27 June 2019.

Sibnayal, was designated as an orphan medicinal product EU/3/17/1888 on 20 June 2017 in the following condition: Treatment of distal renal tubular acidosis.

Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on 25 March 2021 on request of the sponsor. The relevant orphan designation withdrawal assessment report can be found under the 'Assessment history' tab on the Agency's website ema.europa.eu/en/medicines/human/EPAR/sibnayal.

The applicant originally applied for the following indication: Sibnayal is indicated for the treatment of distal renal tubular acidosis (dRTA) in patients aged 6 months and older.

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC – relating to applications for fixed combination medicinal products

The application submitted is a fixed combination medicinal product.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0355/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0355/2018 was completed.

The PDCO issued an opinion on compliance for the PIP P/0355/2018.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant indicated the active substances potassium citrate / potassium hydrogen carbonate contained in the above medicinal product to be considered as known active substances.

Protocol assistance

The applicant received the following Scientific advice / Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
21 February 2013	EMA/CHMP/SAWP/69792/2013	*Dr Monique Wakelkamp, Dr Caroline Auriche*
9 November 2017	EMA/CHMP/SAWP/712772/2017	*Dr Sheila Killalea, Dr Elmer Schabel*
26 April 2018	EMA/CHMP/SAWP/233860/2018	*Dr Kerstin Wickström, Dr Sheila Killalea*
20 September 2018	EMA/CHMP/SAWP/615804/2018	*Dr Angeles Alonso, Dr Jeanette McCallion*
28 February 2019	EMA/CHMP/SAWP/129833/2019	*Dr Elmer Schabel, Dr Jeanette McCallion*

The Scientific advice / Protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

Multidisciplinary quality, non-clinical, and clinical:

- The dispensation of ADV7103.
- Acceptability testing regarding palatability and easiness of swallowing of the proposal pharmaceutical form and administration approach in the Phase II/III clinical study.

Quality:

- Active substance quality documentation, control of impurities.
- Batch size and manufacturing issues.
- How to express the two strengths in the label.

Non-clinical:

- Agreement that no additional data of non-clinical tests are required for MAA.

Clinical:

- Primary endpoint and design of the Phase II/III study and clinical development plan.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Tomas Radimersky

The application was received by the EMA on	9 November 2019
The procedure started on	28 November 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	17 February 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	17 February 2020

The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	24 February 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 March 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	29 July 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	21 September 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	01 October 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	15 October 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	06 November 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	26 November 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Sibnayal on	10 December 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Sibnayal (potassium citrate and potassium hydrogen carbonate) was initially proposed by the applicant to be indicated for the treatment of distal renal tubular acidosis (dRTA) in adults, adolescents and children aged 6 months and older.

dRTA is a condition characterised by a renal defect in hydrogen ion secretion (distal renal tubule localisation) inducing a hyperchloremic metabolic acidosis (blood pH ≤ 7.35) due to no urine acidification occurring. Usually, in non-RTA patients, blood pH is about 7.4 corresponding to a blood concentration of bicarbonate of 22 to 29 mmol/l. Metabolic acidosis corresponds to a blood pH below 7.35 with a bicarbonate blood concentration lower than 22 mmol/L.

2.1.2. Epidemiology

dRTA (also known as Type 1 RTA) is a rare and severe condition. The disease can be of inherited origin (arising from a genetic mutation) most commonly observed in children, or of acquired origin due to an underlying autoimmune systemic disease, such as Sjögren syndrome, systemic lupus erythematosous or autoimmune hepatic diseases as usually observed in adults.

Overall, dRTA occurs when the α-intercalated cells of the distal tubule fail in their homeostatic function, due to a defect in their primary function of proton excretion into the urine, which leads a reduced secretion of HCO_3^- into the blood. The disorder is either inherited when there is a primary failure of the H^+-ATPase or AE1 transporter of the α-intercalated cells due to a genetic mutation or acquired when such capacity is intrinsically intact but secondarily impacted. At time of the orphan designation dRTA was estimated to affect approximately 2.1 per 10,000 persons in the EU.

2.1.3. Biologic features

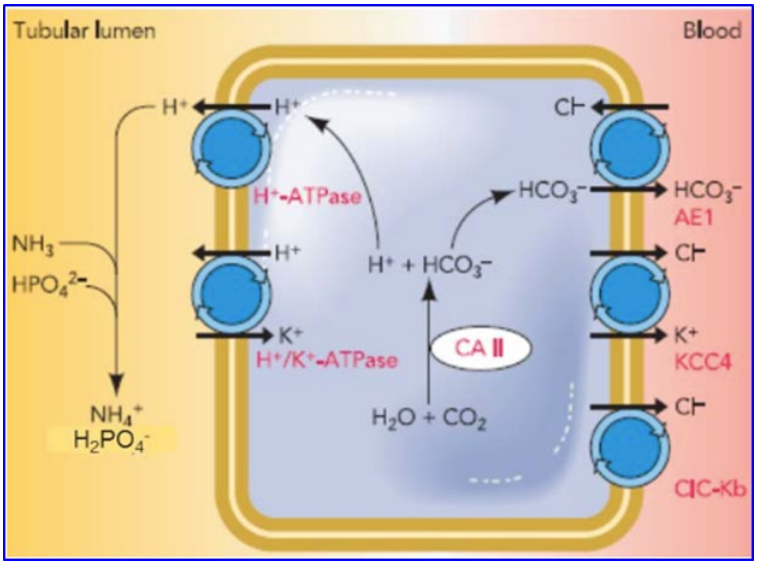
dRTA is a hyperchloraemic metabolic acidosis disorder due to an insufficient renal excretion of protons (H^+) by the distal segment of the renal tubule and insufficient secretion of bicarbonate (HCO_3^-) into the blood, which is the most important blood acid buffer. The α-intercalated cells, which are essential to maintain acid-base homeostasis, fail to effectively function, which leads to urine alkalisation and blood acidification.

The cellular mechanisms involved in the acid-base homeostasis by α-intercalated cells of the distal tubule are presented in figure below. The main pump for luminal proton secretion into the urine is an apical vacuolar H^+-ATPase. A second ATPase, the H^+/K^+-ATPase, is involved to a lesser extent with proton urinary secretion, but its physiologic role is probably more related to potassium reabsorption than to acid-base homeostasis.

Other ion movements compensate for the H^+ transport in these proton-secreting cells by the extrusion of bicarbonate from the cell into the blood via an electroneutral mechanism involving the Cl^-/HCO_3^- exchange pump (i.e. Anion Exchange AE1). The activity of both transporters, H^+-ATPase and AE1, are functionally linked since their substrates (H^+ and HCO_3^-, respectively) are produced by the same catalytic activity of the cytosolic carbonic anhydrase II (CA II).

Similarly, as the effect on the Cl-/HCO3- exchange pump impacts the intracellular concentration of chloride (Cl-), other transporters in the α-intercalated cells of the distal tubule are also affected, particularly those associated with the transport of CI- into the blood. Of particular relevance are the Cl-/K+ co-transporter (KCC4) and the Cl- transporter (ClC-Kb).

Figure 1 Schematic Model of H+ Secretion from α-Intercalated Cells in Cortical Collecting Tubule



2.1.4. Clinical presentation, diagnosis

Patients with dRTA can suffer from major biological symptoms, such as hyperchloremic metabolic acidosis, hypokalaemia, hypocitraturia and hypercalciuria, with a relatively high urine pH (>6.5), which if left untreated or poorly treated will induce several clinical consequences.

Clinical consequences of metabolic acidosis

Diagnosis of dRTA is often in infancy on stunted growth, on sensorineurinal hearing loss, bone deformities, or lithiasis, but in all cases, all have biological abnormalities. Other additional clinical symptoms include vomiting, diarrhoea and/or constipation, dehydration episodes, tachypnoea, loss of appetite and polydipsia.

Metabolic acidosis triggers bicarbonate and phosphate efflux from the bone in an attempt to buffer the acid blood pH. This results in bone softening manifestations such as osteomalacia in adults and rickets in children, and fractures. Hypercalciuria, together with hyperphosphaturia, hypocitraturia and a high urine pH, promote abnormal renal calcium deposition, such as nephrocalcinosis and/or nephrolithiasis (more particularly, multiple and bilateral type IVa2 renal stones), both of which may result in chronic kidney disease (CKD) (85% stage 2-4 in adults and 35% CKD stage $\geqslant$2 in children) then end-stage renal disease in the long term of chronic metabolic acidosis and finally kidney transplant.

As blood pH homeostasis is essential for the secretion of growth hormone, particularly at night when its secretion is maximal, metabolic acidosis also induces stunted growth in children, which will most often trigger a visit to the physician and a dRTA diagnosis.

Clinical consequences of hypokalaemia

Hypokalaemia results mostly in muscle weakness, but also in mild signs of fatigue, constipation, myalgia, bone pain, and even severe muscular paralysis. Hypokalaemia is present in a high proportion of dRTA patients (47-63%) and can even be presented as a metabolic emergency (hypokalaemic paralysis, metabolic coma, shock or death).

Overall, if left untreated or mistreated, dRTA is highly debilitating as it can lead to renal function impairment, weaken muscle strength, affect bone structure and result in adults of short stature.

2.1.5. Management

In dRTA, alkali replacement therapy is given to correct metabolic acidosis. Potassium supplements should also be given to maintain plasma potassium levels in the normal range as needed.

Treatment with alkalising agents restores normal acid-base balance, prevents the consumption of the skeleton and muscle mass by buffering processes, and improves growth in children. In order to avoid formation and/or expansion of nephrocalcinosis, it is well recognised that alkali therapy should be initiated as early as possible, including if possible, citrate to reduce hypocitraturia. Night intakes of the current immediate release alkalising agents are also particularly necessary for children, since growth hormone is secreted mainly at night, but at physiological pH. The treatment should be maintained even beyond the growing period to prevent metabolic acidosis and its lifelong bone and renal consequences such as to reduce the risk of bone deformities, lithiasis, nephrocalcinosis and/or CKD progression.

In dRTA adults, the patient may be started with a daily dose of 1 to 3 mEq/kg of alkali given in divided doses. The dose is titrated to raise bicarbonataemia and blood pH to normal. Children with dRTA usually require higher doses (up to 5-8 mEq/kg/day in infants) of alkali.

Several alkalising salts have been authorised in the EU for indications that encompass treatment of the symptoms and consequences of dRTA, but none of them is indicated specifically in the dRTA

population. Indications of existing therapies include metabolic acidosis, hypokalaemia or nephrolithiasis, but without any clinical evidence in the dRTA population and without indications or data supporting use in the paediatric population. The only exception is the labelling on Alcaphor which includes all types of acidosis. These include, among others, potassium citrate and potassium bicarbonate, each as a single active substance or in different product combinations. All products are immediate-release formulations; except for Acalka, which is a modified release formulation. Furthermore, these medications have noticeable limitations, particularly in children, e.g. inappropriate pharmaceutical form, bitter taste, poor gastro-intestinal (GI) tolerability (such as nausea, vomiting, flatulence, abdominal pain and/or discomfort, or diarrhoea), and multiple daily intakes (including at night), which would hinder compliance and consequently clinical outcomes.

About the product

The applicant Advicenne S.A. submitted a marketing authorisation application for Sibnayal. Sibnayal is a fixed-dose combination of prolonged-release granules of potassium citrate (CK) and potassium hydrogen carbonate or potassium bicarbonate (BK).

Within this procedure, the applicant initially applied for the following therapeutic indication: *"Sibnayal is indicated for the treatment of distal renal tubular acidosis (dRTA) in patients aged 6 months and older."*

The medicinal product acts as an alkalising agent and buffers the metabolic acidosis that occurs in patients with dRTA. It also provides a source of potassium to correct hypokalaemia. In addition, citrate acts also as a calcium chelating agent.

The applicant claims that this is one single product containing an alkalising product plus potassium supplement, which is sodium-free, which is presented in a pharmaceutical form appropriate for all age groups, including children and elderly, and which improves treatment compliance due to bad taste masking, bid dosing and better Gastrointestinal (GI) tolerability. Further, citrate has calcium chelating properties.

Type of Application and aspects on development

Legal basis

The legal basis for this application refers to

Article 10(b) of Directive 2001/83/EC, as amended – relating to applications for new fixed combination products.

Scientific Advice / Protocol Assistance

The applicant received scientific advice / protocol assistance pertaining to the quality, non-clinical and clinical development (see section 1.1.).

The Applicant stated that they sought regulatory advice from Health Authorities on Sibnayal (company code: ADV7103) development programme:

- In November 2012, the design of the Phase II/III study was discussed in depth in addition to questions on Chemical, Pharmaceutical and Biological development, Toxico-Pharmacological, and Clinical programme at a CHMP/SAWP Scientific Advice (EMEA/H/SA/2474/2/2012/SME/III).
- In September 2017 (EMEA/H/SA/2474/3/2017/PA/SME/I), some quality aspects (e.g. on

impurities) were discussed.

- In February 2018 (EMEA/H/SA/2474/3/FU/1/2018/PA/SME/I), some aspects on the quality process were discussed. In September 2018, a follow-up Scientific Advice was completed to clarify how to express the product's strengths (EMA/CHMP/SAWP/615804/2018). Of note, in clinical practice as well as in the literature, doses of alkali agents for the treatment of dRTA in children and adults are usually expressed in mEq/day or mEq/kg/day. In order to facilitate SoC switch to ADV7103 and dose titration by a physician for each patient, ADVICENNE suggested simplifying the expression of the strength in the name of the product, i.e. ADV7103 8mEq and ADV7103 24mEq. Moreover, Section 2 of the proposed Summary of product characteristics (SmPC) also mentions the quantity of both active ingredients in mg. In line with the EMA SmPC guideline which specifies that other information (different units) can be added if they have an interest for clinical practice, it was agreed at the (co-)rapporteur meeting in October 2018 that both mEq and mg could be included since their clinical interest is justified.

During the CHMP/SAWP advice completed in February 2013, the following considerations were discussed and endorsed by the regulatory authorities, and subsequently followed when performing the pivotal study (B21CS) and its open extension long-term study (B22CS):

- The CHMP/SAWP discussed the appropriateness of the formulation for patients including children and suggested a fixed-dose combination.
- The dispensation of ADV7103 was discussed, and considering all the options, it was decided to develop unit-dose sachets combining a fixed quantity of CK and BK, with appropriate strengths for treatment initiation, titration and maintenance. This was viewed by the CHMP as the most attractive option to resolve potential concerns such as risks for dosing errors with the spoons, and dispenser performance issues. The CHMP also considered that there is no need for patients to adjust their dose on a daily basis, and that a fixed dose, as determined by the treating physician after careful titration and adjusted during clinic visits, would suffice.
- Considering that both compounds have a well-known safety profile, the CHMP agreed that the nonclinical part of the dossier, based on the well-established use of the components might be supported by adequate literature references. The CHMP also mentioned that it was not considered necessary that any additional non-clinical studies are undertaken, including juvenile studies or combination toxicity testing.
- Evaluation of the acceptability of ADV7103 in various age groups, using age appropriate rating systems was encouraged by the CHMP. Such recommendation was indeed followed, since ADV7103 acceptability (i.e. palatability and ease of swallowing and of administration) were assessed as secondary endpoints in Study B21CS, using validated instruments.
- The design of the pivotal B21CS study and its extension study (Study B22CS) including their endpoints, were discussed in-depth at the discussion meeting, and the proposal of a switch study with a longer treatment period and using sequential SOC as the comparator, if SOC was optimised, was endorsed by the CHMP. In particular, bicarbonataemia was seen as a direct reflection of the metabolic acidosis in patients with dRTA. CHMP also pointed out that the goal of such efficacy analyses is not the formal demonstration of superiority or inferiority but rather to obtain adequate data for CHMP to evaluate the effectiveness (and safety) of ADV7103 treatment.
- The CHMP recommended that patients be titrated to their correct dose level based on individual blood bicarbonate levels, similar to clinical practice.

- It was also recommended that the paediatric patients should be included in the same clinical study as adults but, from a safety point of view, with older children and adolescents included first. A staggered approach was indeed considered necessary for the younger paediatric patients.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as 8 mEq and 24 mEq prolonged-release granules packed in unit-dose sachets. Each sachet contains a fixed dose combination of potassium citrate prolonged-release granules and potassium bicarbonate prolonged-release granules.

8 mEq prolonged-release granules

One sachet contains 282 mg of potassium citrate and 527 mg of potassium hydrogen carbonate as active substances.

This corresponds to 7.9 mEq of alkali (i.e. 2.6 mEq of citrate and 5.3 mEq of hydrogen carbonate) and to 7.9 mEq of potassium (i.e. 308 mg of potassium).

24 mEq prolonged-release granules

One sachet contains 847 mg of potassium citrate and 1,582 mg of potassium hydrogen carbonate as active substances.

This corresponds to 23.6 mEq of alkali (i.e. 7.8 mEq of citrate and 15.8 mEq of hydrogen carbonate) and to 23.6 mEq of potassium (i.e. 924 mg of potassium).

Other ingredients are:

Granules: hypromellose (E464), microcrystalline cellulose (E460(i)), glycerol dibehenate, magnesium stearate (E470b), silica colloidal anhydrous, and magnesium oxide, heavy (E530)

Coating: ethylcellulose (E462), chlorophyllin (E140 (ii))

Technological agent: talc

The product is available in three-layered foil (polyethylene terephthalate polyester/aluminium/low density polyethylene) sealed sachet for single use as described in section 6.5 of the SmPC.

2.2.2. Active Substance

Potassium hydrogen carbonate

General information

The chemical name of potassium hydrogen carbonate is potassium bicarbonate corresponding to the molecular formula $KHCO_3$. It has a relative molecular mass of 100.12 and the following structure:

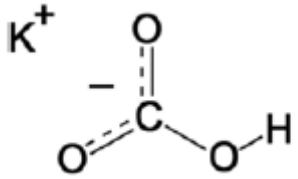


Figure 2: Active substance structure

The chemical structure of the active substance was elucidated by a combination of X-Ray diffraction and IR spectrometry analysis.

The active substance is a hygroscopic colourless crystal or white or almost white crystalline powder or white granular powder, freely soluble in water.

Potassium bicarbonate doesn't exhibit stereoisomerism and polymorphism has not been observed.

Manufacture, characterisation and process controls

Potassium bicarbonate is manufactured by one manufacturing site.

Potassium bicarbonate is a well-known inorganic chemical entity made from three starting materials.

The manufacturing process consists of a well-known and simple chemical reaction. The production is done in a well-defined continuous process occurring in a reactor in one step. The potassium bicarbonate is then centrifuged, dried, milled and packed for sale.

During the synthesis, three impurities can potentially be present.
The characterisation of the active substance and its impurities are in accordance with the current Ph. Eur. Monograph (1141).

Moreover, other impurities are controlled according to Ph. Eur. Monographs in force. This restricted control permits to assure that even other impurities that may not come from the manufacturing process but from the starting materialare tested and followed on a routine basis.

Potassium bicarbonate is considered as an inorganic chemical and is well-known to be chemically stable under ordinary condition of use and storage. Stability tests performed by the manufacturer on production batches do not show any degradation of the product.
Adequate in-process controls are applied during the synthesis.

The production is done in a well-defined continuous process occurring in a reactor in one step. There are no isolated intermediates.

The specifications and control methods for starting materials and reagents have been presented.

Potential and actual impurities were well discussed with regards to their origin and characterised.

Three different primary packaging configurations are described for the active substance. A heat sealed plastic bag (white opaque LDPE bag with 1 row of pinholes for venting), a kraft paper multiwall bag (inner layer of kraft paper followed by HDPE layer, kraft paper layer and full bleached white paper with a 5 inches PE lined valve) or a fibre drum with plastic liner. The three primary packaging materials are fully compliant to European Commission Regulation (UE) N° 10/2011 for food contact materials.

Specification

Specifications applied to control potassium bicarbonate batches are those of the monograph of the European Pharmacopoeia in force (1141)

The active substance specification includes tests for: appearance (Ph. Eur), identification (Ph. Eur.), solution S appearance (Ph. Eur.), carbonates (pH) (Ph. Eur.), chlorides (Ph. Eur.), sulphates (Ph. Eur.), ammonium , calcium (Ph. Eur.), iron (Ph. Eur.), sodium (Ph. Eur.) and assay (Ph. Eur.).

Solubility test was omitted knowing that the pharmaceutical form is a granule. The risk assessment performed in the finished product according to ICH Q3D guidelines identifies potassium bicarbonate as a potential source of lead. The analysis of 16 batches of potassium bicarbonate raw material using ICP-MS analysis confirmed that it is not necessary to implement the lead analysis in routine. In accordance with ICH Q6A, potassium bicarbonate is not capable of supporting microbial growth or viability. For decades, it has been used and indicated for uses as a microbial disinfectant in food and agriculture industries and can have also bactericidal effect on *Escherichia coli*. Then, the microbiological analysis is not a requested test listed in the monograph.

The analytical methods used have been adequately described. Satisfactory information regarding the reference standards used has been presented.

Batch analysis data of 3 commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 commercial scale batches of active substance from the manufacturer of the finished product stored in Kraft paper multiwall bags for up to 24 months under long term conditions (25 ºC / 60% RH), for up 24 months under intermediate conditions (30 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* appearance, appearance of solution S, pH (carbonates), loss on drying, particle size distribution, potassium bicarbonate content and microbiological quality. The analytical methods used were the same as for release and were stability indicating.

At 25°C/60% RH no clear changes or trends were seen in any of the tested parameters. At 30°C/65% RH loss on drying increased, leading to out of specification (OOS) results. Furthermore, a decrease in potassium bicarbonate content, and increase of pH (carbonates) were observed. No changes or trends were observed for the other parameters. Except for loss on drying, all parameters were within their specification limits. At 40°C/75% RH an increase in loss on drying after 6 months was observed leading to OOS results already after 3 months. Furthermore, a decrease in potassium bicarbonate content was seen after 6 months. No changes or trends were observed for the other parameters. Except for loss on drying, all parameters were within their specification limits. The increase in loss on drying observed at 40°C/75% RH and 30°C/65% RH is closely linked to the increasing humidity conditions of storage and is not atypical for the active substance given its hygroscopic nature. It is indicated that the parameter loss on drying is not a requirement of the Ph. Eur. monograph. Meanwhile collection of additional stability data by the manufacturer of the finished product, loss on drying will be tested on every raw material batches before manufacturing use further ensuring the quality of used batches.

Kraft paper packaging is no longer used even though it was used for development batches. Now, potassium bicarbonate preferred packing is in heat seal packaging system and fibre drums. Thus, a second stability study was launched on three other industrial full-scale batches. Stability samples were stored in packaging system of plastic bags as LDPE bags of 100 µm thickness, closed with plastic ties, to support the two remaining presentations. This packaging quality presents the advantage to mimic the lowest thickness LDPE layer and the less tight closure system of both heat seal packaging system of plastic bag and fibre drum with plastic liner. Therefore, stability data for up to 3 months under long term conditions (25 ºC / 60% RH), under intermediate conditions (30 ºC / 60% RH) and under

accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The parameter tested as the same as above. At 25°C/60% RH and 30°C/65% RH no clear changes or trends were seen in any of the tested parameters. At 40 ºC / 75% RH, loss on drying values slightly increased close to the specification limit. This tendency was already observed in the study performed in Kraft paper multiwall bag but much more extended. This observation supports the claim that Kraft paper multiwall bag is less protective than heat seal packaging system of plastic bag and fibre drums with plastic liner.

Two supportive stability studies were performed by the active substance manufacturer; three full-scale batches were stored at 15-25°C / ambient RH for 24 months. The batches were packed in kraft paper multiwall bags of 50 pounds for the first stability study and in fibre drums with plastic liner for the second stability study. Only assay by control of total alkalinity was controlled, showing no changes during storage and compliance with the specification for each of the two packaging configurations.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of stored for 24 months in original packagings below 25°C and in a dry place.

Potassium citrate

General information

The chemical name of potassium citrate is tripotassium 2-hydroxypropane-1, 2, 3-tricarboxylate monohydrate corresponding to the molecular formula $C_6H_5K_3O_7$. H_2O. It has a relative molecular mass of 324.4 and the following structure:

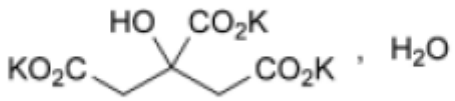


Figure 3: Active substance structure

Due to the existence of a certificate of suitability with the monograph of the European Pharmacopoeia in force (CEP) for potassium citrate, data relating to the elucidation of the structure of the active substance were provided in this CEP.

The active substance is a hygroscopic white or almost white, granular powder or colourless crystals very soluble in water.

Stereoisomerism and polymorphism have not been observed in the active substance.

As there is a monograph of potassium citrate in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for the active substance which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

As described in the CEP, potassium citrate is packed in High Density Polyethylene (HDPE) lined paper bags. Paper bags are sealed by welding the HDPE-liner and closing the bag by hot melt adhesive. The

material is in accordance with EU-directives relating to plastic materials and articles intended to come into contact with foodstuffs (EU directive 2002/72/EC).

Specification

The active substance specification includes tests for appearance (visual), identification (Ph. Eur.), solution S appearance (Ph. Eur.), acidity or alkalinity (Ph. Eur.), readily carbonisable substances (Ph. Eur.), chlorides (Ph. Eur.), oxalates (Ph. Eur.), sulphates (Ph. Eur.), sodium (Ph. Eur.), water (Ph. Eur.) , particle size distribution (Ph. Eur.), and assay (Ph. Eur.)

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for particle size distribution. The additional method has been adequately validated and described according to ICH Q2.

Non routine application of microbiological quality test is based on the ICHQ6A decision tree # 6 and additional results of water activity measurements on several batches. Water activity measurements has been performed as the presence of water is a prerequisite for the multiplication of microorganisms. It is confirmed that potassium citrate does not support proliferation or viability of microorganisms

Stability

The stability results justify the proposed retest period of 60 months, as stated in the CEP.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product consists of prolonged-release granules packed in unit-dose sachets that are available in two strengths, i.e. as 8 mEq and as 24 mEq sachets. Each sachet contains a fixed dose combination of potassium citrate prolonged-release granules and potassium bicarbonate prolonged-release granules. Potassium citrate prolonged-release granules are green and potassium bicarbonate prolonged-release granules are white.

The strengths are expressed and calculated as potassium milliequivalent (mEq). This expression is aimed at facilitating prescription and dose adaptation, which is done based on potassium mEq according to international clinical practices. Indeed, milliequivalent unit is often used to express the quantity of electrolytes involved knowing that 1 mEq = 1 mmol/valence.

Considering the finished product as a sachet, the percent formula is identical for the two strengths and the composition in weight, different for the two strengths.

The aim of the development is to obtain an innovative formulation that combines the advantage of two alkalizing agents, potassium citrate and potassium bicarbonate, in an appropriate pharmaceutical oral form for children and adults, with only a twice-a-day administration.

Relevant active substance attributes with a possible impact on the finished product manufacturability and performance have been discussed and were further taken into account during formulation and manufacturing process development.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards except silicified microcrystalline cellulose and magnesium chlorophyllin which are respectively controlled by manufacturer in accordance with internal monographs based on

microcrystalline cellulose current Ph. Eur. monograph and silicified microcrystalline cellulose current USP-NF monograph. Magnesium chlorophyllin is controlled according to an internal monograph based on European Pharmacopoeia current methods and on current E140 ii monograph described according to current food regulation (EU n°231/2012). There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

Compatibility of the excipients with the active substances was considered and has been proven by a differential scanning calorimetry (DSC) performed on pure potassium bicarbonate and on pure potassium citrate and on the prolonged-release granules and during the stability testing of the finished product.

Direct compression has been chosen to obtain core granules as prolonged release granules. Both types of granules are then coated with a film-forming polymer that controls the prolonged-release of the active substance and permits taste masking. A colouring agent is added to the coating layer of potassium citrate in order to differentiate potassium citrate granules (green) from potassium bicarbonate granules (white). The major criteria for the development of both granules were a high drug load to limit the number or size of the granules to dispense, granules must be tasteless and granules should release the majority of potassium in order to achieve the long duration of action needed to cover a twice-a-day administration, without dose-dumping. Prolonged-release forms of the two active substances were separately developed.

Due to the endogenous nature of citrate, bicarbonate and potassium, their kinetics of absorption in blood cannot be assessed in human. In addition, the body permanently uses its powerful regulation systems to avoid any risks of acidosis or alkalosis, regulating and maintaining stable rates of those elements in blood. In that situation, it is not possible to establish a meaningful correlation between *in vitro* dissolution drug release and *in vivo* pharmacokinetic parameters. Consequently, *in vitro* dissolution methods were developed to test the release rate of both active ingredients with the objectives: discriminate batches with respect to efficiency of prolonged-release system, check the consistency of production throughout all development, i.e.: between clinical batches and routine production batches, and determine the stability of the products over the proposed shelf life and storage conditions.

Dissolution is performed separately on potassium citrate granules and on potassium bicarbonate granules. The results demonstrate that the sensitivity of the testing method is good, and that the method is able to discriminate between slight differences in amount of coating layer. The discriminatory capacity of the dissolution method was confirmed.

Bulks of potassium granules and bicarbonate potassium granules are manufactured and controlled separately as intermediate products. Each bulk is manufactured in a 3 steps process. At the end of those 3 steps, prolonged-release granules of potassium citrate and potassium bicarbonate are primary packed combined together in sachets.

Sachets as "Stick-packs" have been selected for the primary packaging due to their user friendliness. The form permits the user to take the dose directly in the mouth or pre-mixed with dairy products or stewed fruit. The type of packaging also offers a technical industrial solution to permit precise, reproducible, and adaptive filling of both granules in the same packaging without damaging the pharmaceutical forms. The suitability of the packaging was confirmed by the formal stability studies. A declaration of compliance of the foil with Regulation (EC) 1935/2004 has been provided, also confirming compliance with the inner LDPE material with Regulation (EC) 10/2011 as amended.

Food compatibility and alcohol interaction studies have been performed. When the granules were mixed with hot foods, release from both granules was significantly increased. Therefore, granules

should not be mixed with hot food or liquid. The product quality was not impacted after mixing with stewed foods and dairy products. These findings support the recommendations in the SmPC that the granules may be mixed (without crushing) with small amounts of soft food (e.g. fruit puree, yoghurt). Dissolution was slightly increased, but still within specification after mixing with 10% alcohol, but dose dumping and OOS results for dissolution were obtained after mixing with 40% alcohol. Granules were immediately dissolved in dissolution vessels when mixed with 40% alcohol. It is thus not recommended to mix the products with high levels of alcohol.

The finished product was concluded not to be suitable for tube feeding considering the high risk of tube blocking due to the granule size and impossibility of crushing without affecting the release profile. In case of nasogastric tube feeding already available in standard of care treatments could be used.

Manufacture of the product and process controls

Potassium bicarbonate granules and potassium citrate granules are considered as intermediate products and are manufactured, separately, according to three similar steps: manufacture of the powder blend manufacture of the uncoated granules and manufacture of the coated granules followed by primary and secondary packaging.

Manufacturing process of granules is considered as a non-standard process due to the prolonged release properties. However, due to the non-complex manufacturing steps outlined, the manufacturing process could be considered as standard due the acceptability of the manufacturer's understanding of the manufacturing process and their relevant experience of that process.

The manufacturing process has been adequately validated at the proposed scale on three commercial scale batches for both granules. The sachet filling process has been validated on two pilot scale and one smaller batch (less than 10% of the maximum production scale) for both finished product strengths. This is sufficient, as this part of the process is not considered critical with regards to upscaling. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this pharmaceutical form.

Product specification

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (citrate potassium, bicarbonate potassium, Ph. Eur.), uniformity of dosage units (Ph. Eur.), dissolution profile (ICP-OES), water content (Ph. Eur.), assay (ICP-OES), and microbiological quality (Ph. Eur.).

A risk assessment on elemental impurities was performed. The only identified potential sources of elemental impurities are the raw materials (active substances, excipients and manufacturing aids) used in the manufacture of the finished products. The combined results on the risk assessments for the separate potassium bicarbonate and potassium citrate granules revealed that three elemental impurities (As, Cd and Pb) might be expected to be higher than the limits authorised by the ICH Q3D guideline at the maximum daily dose. Six batches of potassium citrate prolonged-release granules and eight batches of potassium bicarbonate prolonged-release granules were tested by Inductive Coupled Plasma Mass Spectrometry (ICP-MS). Further analysis was also performed by ICP-MS on six batches of potassium bicarbonate raw material for Pb. Results confirmed that the levels of relevant elemental impurities (Cd, Pb, As, Hg, Co, V, Ni) were consistently below 30% of the PDE. No further control was therefore required.

During the assessment, the applicant was requested to provide a risk evaluation concerning the presence of nitrosamine impurities in the finished product in question and applying the principles outlined in the notice "Information on nitrosamines for marketing authorisation holders (EMA/189634/2019)". An evaluation was provided in order to assess the risk of presence of nitrosamine impurities in the finished products, using quality risk management principles. Based on supplier's information, no risk has been identified. Therefore, no further control is required.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and dissolution testing has been presented.

Batch analysis results are provided for 3 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from four production scaled batches and some pilot scaled batches of each strength of finished product stored for up to 12 - 48 months under long term conditions (25ºC / 60% RH), for up 12 months under intermediate conditions (30°/75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Stability data from 5 intermediate validation bulk batches of potassium bicarbonate granules and potassium citrate granules (ADV7103-CK & BK) packed in sachets stored under long term conditions for up 48 months, intermediate conditions for up 12 months and accelerated conditions for up 6 months were also provided.

The following parameters were investigated: appearance, water content of both granules, dissolution profile of both granules, active substances assays and microbiological quality.

A reduced design based on matrixing has been applied for the long-term and intermediate stability studies where not each batch was tested at each time points in the first 12 months of the studies. This reduced design is considered justified based on the same granules being present in both product strengths.

Based on available stability data, the proposed shelf-life of 4 years and do not store above 30°C as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

A risk evaluation concerning the presence of nitrosamine impurities was provided using quality risk management principles. Based on supplier's information, no risk has been identified. Therefore, no further control is required.

The applicant has applied Quality by Design (QbD) principles in the development of the finished product and its manufacturing process. However, no design spaces were claimed for the manufacturing process of the finished product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable

2.3. Non-clinical aspects

2.3.1. Introduction

The components of Sibnayal (potassium, bicarbonate, and citrate) are endogenous substances, which are already available in various other medicinal products and also within different food products. Therefore, no additional non-clinical studies have been undertaken. The non-clinical part of the dossier, based on the well-established use of the components, is supported by literature references.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In the context of the current procedure, the components of Sibnayal are therapeutically effective as alkalizing agents. In the case of metabolic acidosis, potassium citrate and potassium bicarbonate normalise blood bicarbonate concentrations and restore a normal physiological blood pH. This mechanism of action is described by the applicant without specific studies on the current product. Efficacy for the product under assessment will have to rely on clinical data. Which is acceptable to the CHMP.

Secondary pharmacodynamic studies

No data on secondary pharmacology was provided. Considering the nature of the product, this is considered acceptable by the CHMP.

Safety pharmacology programme

No safety pharmacology studies have been conducted with potassium citrate and potassium carbonate. Considering the endogenous nature of the substances together with extensive clinical experience as pharmaceutical ingredients, this is considered acceptable by the CHMP.

Pharmacodynamic drug interactions

Pharmacodynamic drug interactions are discussed in the clinical part (see section 2.4. and 2.6.).

2.3.3. Pharmacokinetics

Evaluation of absorption of unlabelled potassium citrate and potassium carbonate is not feasible due to different sources, readily convertible nature of citrate, and permanent regulation of the compounds within the body. However, an experiment cited from literature (Nakamura Y et al. Metabolism of citric acid, potassium citrate, sodium citrate and calcium citrate in the rat. J. Food Hyg. Soc. Japan. 1987;28(4):251-260.) with radiolabelled potassium citrate is described in which it was shown that absorption of citrate was still not complete at the latest evaluated time point of 4 hours, after oral intake of 1889 mg/kg which can be viewed as a clinically relevant dose. It is not clear if this can be extrapolated to the human situation.

No animal data on the absorption of potassium bicarbonate and potassium citrate was provided. The applicant claimed a delayed release profile for the potassium hydrogen carbonate component of the product and an early release of the potassium citrate component, based on *in vitro* dissolution studies. The *in-vitro* dissolution profiles indeed showed that more than 80% of the potassium citrate component is released within the first three hours, while the potassium bicarbonate is released gradually over a timeframe of about twelve hours. The combined *in-vitro* release profile of the Sibnayal fixed combination medicinal product (FCMP) formulation clearly showed an overall higher release effect in the first three hours, compared to the release profile of the potassium bicarbonate component alone. This combined release would then allow for a more consistent and complete alkalising effect over the twelve hours for twice-daily dosing, than each mono-component alone could achieve. The rate of absorption and effects on duration of efficacy are further discussed in the clinical section and benefit/risk assessment in this report.

Distribution of radiolabelled citrate is described in the same literature reference from Nakamura *et al*. The extent of distribution was measured at 0.5 and 24 hours after oral administration of 1889 mg/kg potassium citrate. These time points proved to be too far apart, as most of the citrate was still present in the GI tract at 0.5 hours after intake and therefore not yet absorbed and distributed, whereas at 24 hours after intake only ~1% of the dose was still present in blood, kidney, liver and lung compartments. No data on distribution of potassium hydrogen carbonate were provided. Conclusions about distribution cannot be drawn. However, considering the nature of the product, this is not of concern.

Circulating citrate can be converted into bicarbonate and constitutes a source of energy in the Krebs cycle. Bicarbonate is in equilibrium with carbonic acid and carbon dioxide (CO_2).

Circulating citrate is mainly eliminated as expiratory CO_2 or in urine. Citrate can be reabsorbed in the proximal tubule in order to regulate renal citrate absorption and excretion. Bicarbonate is excreted in the urine or as carbon dioxide and water.

2.3.4. Toxicology

The clinical safety profiles of potassium, bicarbonate, and citrate are well known. No additional toxicity studies have been performed as agreed by the CHMP and PDCO. An overview of the available literature data was provided.

Single and repeat dose toxicity

Acute toxicity was evaluated in several animal models, which showed high lethal dose 50 (LD_{50}) values for citric acid, potassium bicarbonate and different potassium salts. Repeated dose toxicity studies report a good safety profile for all components of the product. Main effects observed are those related to physiological adaptations to high doses of alkalizing salts. This has limited relevance for patients suffering from metabolic acidosis. Both potassium citrate and potassium bicarbonate are well known active substances and safety profiles are well established in humans.

Genotoxicity

Potassium citrate and potassium carbonate have no genotoxic potential.

Carcinogenicity

Carcinogenicity studies report a long-term but limited study on 20 male rats receiving 2g/kg/day citric acid. No increase in tumours was found. Other studies were performed in combination with different carcinogenic agents and are therefore of limited value.

Potassium bicarbonate and other potassium salts were tested in a 30-month study in rats and shown to be urinary bladder tumour promoters. The mechanism for this effect was further investigated and determined to be rat specific and therefore not relevant for humans.

Further, considering the long and intensive use of potassium citrate and potassium carbonate as food additives and for therapeutic indications without any concerns relating to carcinogenic risk in humans, both substances are considered not carcinogenic.

Reproduction Toxicity

The effects of citrate on reproduction toxicity has been sufficiently investigated No teratogenic or embryotoxic/foetotoxic effects were observed in mouse, rat, rabbit or hamster. Data on sodium carbonate from mouse, rat and rabbit indicate no effects on reproduction, although the doses in these studies were lower than clinical doses. There is a limited amount of published clinical experience (46 cases) with potassium citrate and potassium hydrogen carbonate, which do not point to any adverse effects on the foetus.

The citrate and carbonate components of the product are unlikely to be of risk during pregnancy. The primary risk appears to be from hyperkalaemia, as this product could produce this in patients who have a condition predisposing them to high blood potassium levels. Because high levels are detrimental to maternal and embryo–foetal cardiac function appropriate warning statements have been added to sections 4.4. and 4.6 of the SmPC. No juvenile toxicity studies have been performed.

Toxicokinetic data

There are no toxicokinetic data available. Considering the nature of the active substances, this is not of concern.

Local Tolerance

No studies on local tolerance have been provided. This is agreed considering the oral route of administration and well-known safety profile of the active substances.

Other toxicity studies

There are no impurities of concern in the drug product or drug substances.

2.3.5. Ecotoxicity/environmental risk assessment

The active substances are natural substances, the use of which will not alter the concentration or distribution of the substances in the environment. Therefore, potassium citrate and potassium hydrogen carbonate are not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

The non-clinical development was discussed and agreed during CHMP protocol assistance. The components of Sibnayal (potassium, bicarbonate and citrate) are endogenous substances, which are already available in various other medicinal products and also within different food products. Therefore, no additional non-clinical studies have been undertaken. The non-clinical part of the dossier, based on the well-established use of the components, is supported by literature references. The non-clinical data reveal no special hazard for humans based on provided literature references on safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

The active substances are natural substances, the use of which will not alter the concentration or distribution of the substances in the environment. Therefore, potassium citrate and potassium hydrogen carbonate are not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The application is approvable from a non-clinical assessment point of view.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

The clinical development programme for Sibnayal consists of three studies: one phase I pharmacodynamics (PD)/Proof of Concept and Safety Study (B03CS), one Phase II/III study (B21CS) and its open-label extension study (B22CS). The studies are summarised in the table below:

Table 1*: Clinical development programme for ADV7103*

Study code	Design	Objectives	Number of subjects	Doses of ADV7103 Comparator Duration of treatment	Primary endpoint
Phase I PD/Proof of Concept & Safety Study					
B03CS France	Double-blind, placebo-controlled, cross-over study	Pharmacodynamics/Safety study to test the hypothesis that ADV7103 BID is a safe alkali treatment	Healthy Subjects Screened: 42 Planned: 16 Included: 16 Completed: 16	**Period I:** 17/34, 33/36 and 50/100 mg/kg (ie. approx. 0.5, 1.0 or 1.5 mEq/kg, ADV7103 respectively) CK/BK or placebo granules, BID for 5 days **Period II:** ADV7103 or placebo granules BID for 5 days. ADV7103 doses X, Y and Z were determined after the end of Period I, further to an interim review of safety and PD data. Selected doses were not to exceed 67/134 mg/kg CK/BK BID **Washout:** 7 days between the 2 periods	Urine pH values Dose effect and administration schedule to maintain a satisfactory increased urine pH throughout the nycthemeral period.
Phase II/III study					
B21CS Performed in France, Serbia, and Slovakia	Multicentre open label, sequential non-inferiority study	To evaluate the relative efficacy, safety, tolerability and acceptability of ADV7103 and standard of care (SoC) to correct the metabolic acidosis and identify the dose of ADV7103 to be used as maintenance dose in SPIII.	Screened and included: 37 patients with dRTA Completed: 32	ADV7103 BID or patients' usual SoC and regimen **Period I (SPI):** SoC at the well adapted dose, for 5 days **Period II (SPII):** Titration of ADV7103 BID up to the optimal dose, for a variable duration, up to 30 days BID **Period III (SPIII):** ADV7103 BID, at the optimal dose identified in SPII, for 5 days	Average bicarbonate blood pre-dose level during 3 days of treatment with ADV7103 (SPIII) and SoC (SPI).
Phase II/III extension study					
B22CS Performed in France, Serbia, and Slovakia	Multicentre open label extension study	To assess the long-term safety, tolerability, efficacy, compliance, acceptability and quality of life (QoL) of ADV7103 Over a 24-month period Analysis at Month 6, and at Month 24	Children and adults with dRTA who participated in Study B21CS	ADV7103 BID, at a dose identified in B21CS, which could be modified by the investigator where needed. For up to 24 months	Adverse events (AEs)

2.4.2. Pharmacokinetics

ADV7103 (i.e. Sibnayal) is a FCMP in a sachet, which includes:

- Potassium citrate formulated as prolonged-release granules (ADV7103-CK) allowing the release of the active substance for 3 hours, and
- Potassium hydrogen carbonate (also known as potassium bicarbonate) formulated as prolonged-release granules (ADV7103-BK) allowing the release of the active substance for 12 hours.

There are immediate release formulations of potassium citrate and potassium bicarbonate approved for the treatment of the symptoms of dRTA, but not as fixed combination medicinal product. The daily dose of ADV7103 is comparable with the immediate release formulations but recommended for twice daily instead of 3-6 times daily for the immediate release products. ADV7103 was proposed to be indicated for the dRTA patients with the age from 6 months. The patients start with a body weight-based loading dose then follow a up titration scheme to reach their optimum dose. The maximum dose, regardless of age group, is either 10 mEq/kg/day or a total daily dose of 336 mEq, whichever is lower.

No pharmacokinetic (PK) studies have been performed for ADV7103. All PK characteristics of potassium citrate and potassium bicarbonate are summarised based on literature.

Absorption

Based on literature, citrate, bicarbonate and potassium are all absorbed in the small intestine rapidly and almost complete. Citrate has a pH dependent absorption between pH 4.8 and 6.4 (along the upper side of the small intestine (duodenum, early part of jejunum)).

The food effect on ADV7103 has been investigated based on the PD parameter of urine pH level at steady state, and no significant difference in urine pH level has been observed one hour before and after meal. ADV7103 is recommended to be taken with a meal.

Alcohol and "hot" test were conducted *in vitro*, and it showed that the coating of the formulation can be affected, therefore both administrations with alcohol consumption and mixed with hot food (> 40°C) should be avoided. A statement on this aspect is included in section 4.2 of the SmPC and section 2 of the package leaflet.

Distribution

Citrate, bicarbonate and potassium are not bound to protein. Citrate is mainly in the blood, bicarbonate can distribute to the whole body, and potassium is mainly found in muscle and the skeleton and it is also present in high concentrations in the blood, central nervous system, intestine, liver, lung and skin.

Elimination

Citrate, bicarbonate and potassium are excreted in urine mainly. Citrate, under its trivalent form, is filtered freely through the renal glomerulus. In stomach, bicarbonate neutralises gastric acid with the production of carbon dioxide that is eliminated by the respiratory route. The 90% potassium is excreted via the kidneys, and 10% is eliminated in the faeces and small amounts may also be excreted in sweat.

At physiological blood pH (7.4), citrate is entirely ionised under its trivalent form as the salt citrate. The citrate ion undergoes oxidative metabolic breakdown to carbon dioxide or bicarbonate. Bicarbonate and potassium are not metabolised.

Dose proportionality and time dependencies

Based on the PD study, the urine pH level is higher in the subjects with a higher dose of ADV7103. It indicates the exposure is dose dependent; however, the dose proportionality is unknown. At steady state (Day 4 - 5), the pre-dose levels were higher than placebo, supporting the dose regimen of 12 hours.

Special populations

Based on the diminished renal elimination of potassium, ADV7103 is not recommended for patients with moderate to severe renal impairment. No effect of sex and race on PK or PD profiles of alkalising agents or potassium supplements have been reported. The body weight is a factor and therefore ADV7103 is recommended based on the body weight (same as immediate release alkalising agents). Younger patients need a higher dose of alkalising agents, same as the finding in phase III study of ADV7103.

Pharmacokinetic interaction studies

No DDI studies have been conducted for ADV7103. Based on experiences with other potassium containing medicines and on literature, potassium salts should not be given to patients receiving potassium-sparing diuretics/aldosterone antagonists because they diminish renal potassium excretion. Concurrent use of potassium citrate with digitalis glycosides may increase the risk of hyperkalaemia in digitalised patients and potentiate the arrhythmogenic effect of the cardiac glycosides. The administration of potassium-containing salts with drugs that increase serum potassium concentrations such as angiotensin converting enzyme (ACE) inhibitors, heparin, NSAIDs or potassium-sparing diuretics should generally be avoided. The SmPC 4.5 includes an appropriate statement in this regard.

2.4.3. Pharmacodynamics

Mechanism of action

Sibnayal is a fixed-dose combination of potassium citrate and potassium hydrogen carbonate (also known as potassium bicarbonate) as prolonged release granules.

The pharmacological properties of Sibnayal are directly linked to the capacity of potassium citrate and potassium hydrogen carbonate to maintain electrolyte balance. Both act as alkalising agents and buffer the metabolic acidosis. Sibnayal provides a source of potassium to correct hypokalaemia. In addition, citrate acts also as a calcium chelating agent.

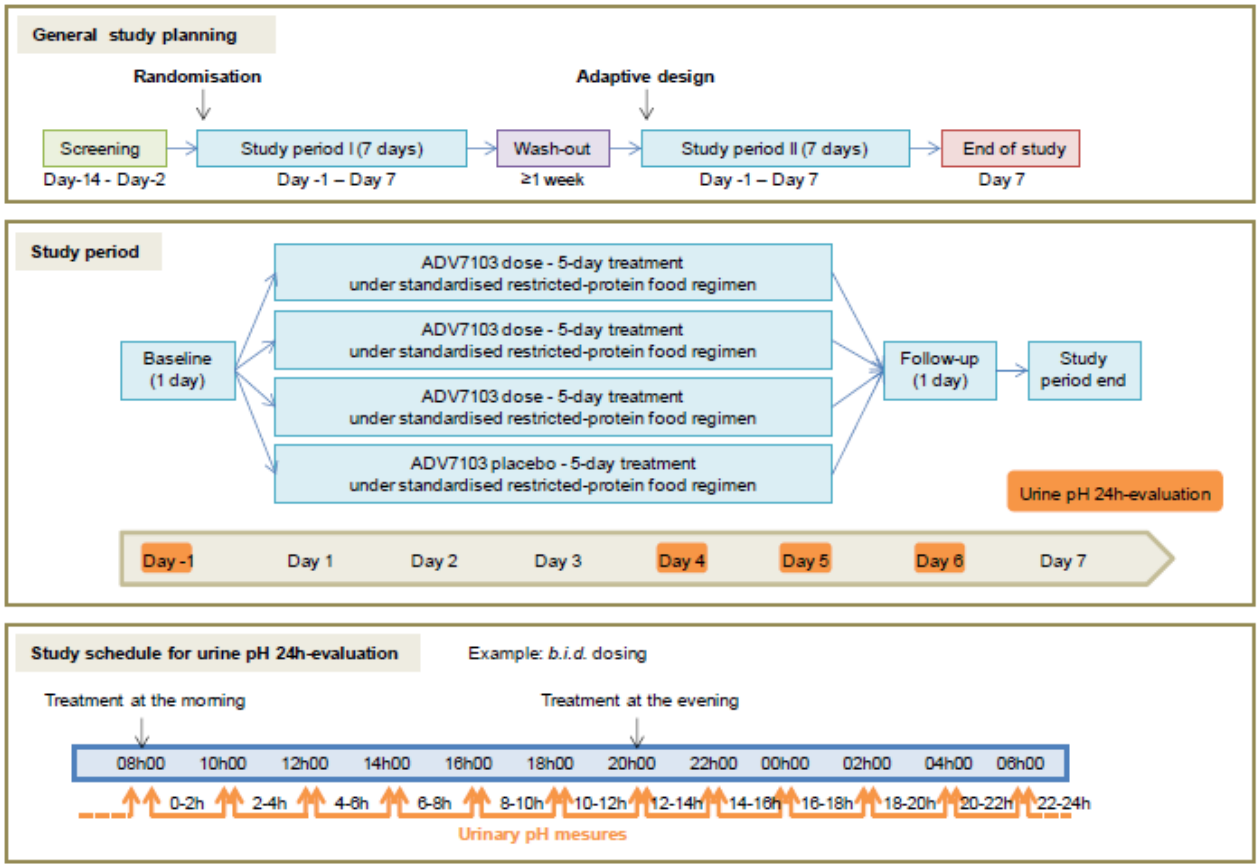
Primary and Secondary pharmacology

Phase I PD/ proof of concept and safety study (B03CS)

Study B03CS was a double blind, placebo controlled, two-period, incomplete crossover Phase I study conducted in 16 healthy subjects to investigate the pharmacodynamics, safety and tolerability of repeated doses of ADV7103 for 5 days.

A schematic diagram of the study design is presented below in Figure 4:

Figure 4*: Study design*



The eligible healthy subjects were to be included in a balanced manner to one of the four possible treatment sequences, as detailed in the table below:

Table 2*: Study treatment sequences*

Treatment sequence (number of subjects)	Study Period I	Study Period II
1 (n = 4)	placebo	ADV7103 dose X
2 (n = 4)	ADV7103 low dose CK/BK: 17/34 mg/kg *b.i.d.*	ADV7103 dose Y
3 (n = 4)	ADV7103 medium dose CK/BK: 33/66 mg/kg *b.i.d.*	placebo
4 (n = 4)	ADV7103 high dose CK/BK: 50/100 mg/kg *b.i.d.*	ADV7103 dose Z

Table 3*: Summary of the doses ADV7103 administered*

	Range of doses of CK/BK g/intake	Range of doses of CK/BK g/day	Dose ADV7103 mEq/kg/intake	Dose ADV7103 mEq/kg/day	Range of dose of ADV7103 mEq/intake	Range of doses of ADV7103 mEq/day
Period I						
Low dose CK/BK: 17/34 mg/kg *b.i.d.*	0.984/1.967 – 1.164/2.326	1.967/3.935 – 2.329/4.652	0.49	0.98	29.28 - 34.64	58.56 - 69.27
Medium dose CK/BK: 33/66 mg/kg *b.i.d.*	2.074/4.127 – 2.295/4.573	4.148/8.255 – 4.590/9.145	0.95	1.90	61.54 - 68.15	123.07 - 136.29
High dose CK/BK: 50/100 mg/kg *b.i.d.*	2.656/5.297 – 3.433/6.839	5.313/10.594 – 6.865/13.678	1.44	2.88	78.92 - 101.92	157.84 - 203.85
Period II						
Dose X CK/BK: 41.5/83.0 mg/kg *b.i.d.* midday and bedtime	2.650/5.277 – 3.292/6.553	5.299/10.544 – 6.584/13.106	1.19	2.38	78.66 – 97.69	157.31 – 195.38
Dose Y CK/BK: 41.5/83.0 mg/kg *b.i.d.* morning and evening	2.409/4.792 – 2.850/5.676	4.818/9.584 – 5.701/11.352	1.19	2.38	71.45 – 84.60	142.90 – 169.21
Dose Z CK/BK: 33/66 mg/kg morning and 50/100 mg/kg evening	Morning 1.753/3.496 – 2.201/4.386 Evening 2.656/5.297 – 3.339/6.646	4.409/8.793 – 5.540/11.033	Morning 0.95 Evening 1.44	2.38	Morning 52.09 – 65.37 Evening 78.92 – 99.08	131.01 – 164.45

In period II, ADV7103 doses X, Y and Z and regimens were determined after the end of period I.

The primary objective was to assess the PD effect on urine pH of oral doses of ADV7103 versus placebo after 5 days of treatment (Day 4, 5 and Day 6). Secondary objectives included assessment of the relationship between oral doses of ADV7103 and urine pH after 5 days of treatment, the PD effects on other urine biomarkers after 5 days of treatment, the residual effect on urine pH after treatment discontinuation over a 24- hour period, safety and tolerability.

All doses administered demonstrated a statistically significant increase of pH over 24 hours (pooled from day 4 and 5) as compared to placebo ($p<0.05$ and in multiple occasions $p<0.0001$, See Figure 5 and Table 9).

Figure 5*: Means (+/-SE) urine pH over time per treatment (Period I on the upper panel and period I and II on the lower panel)*

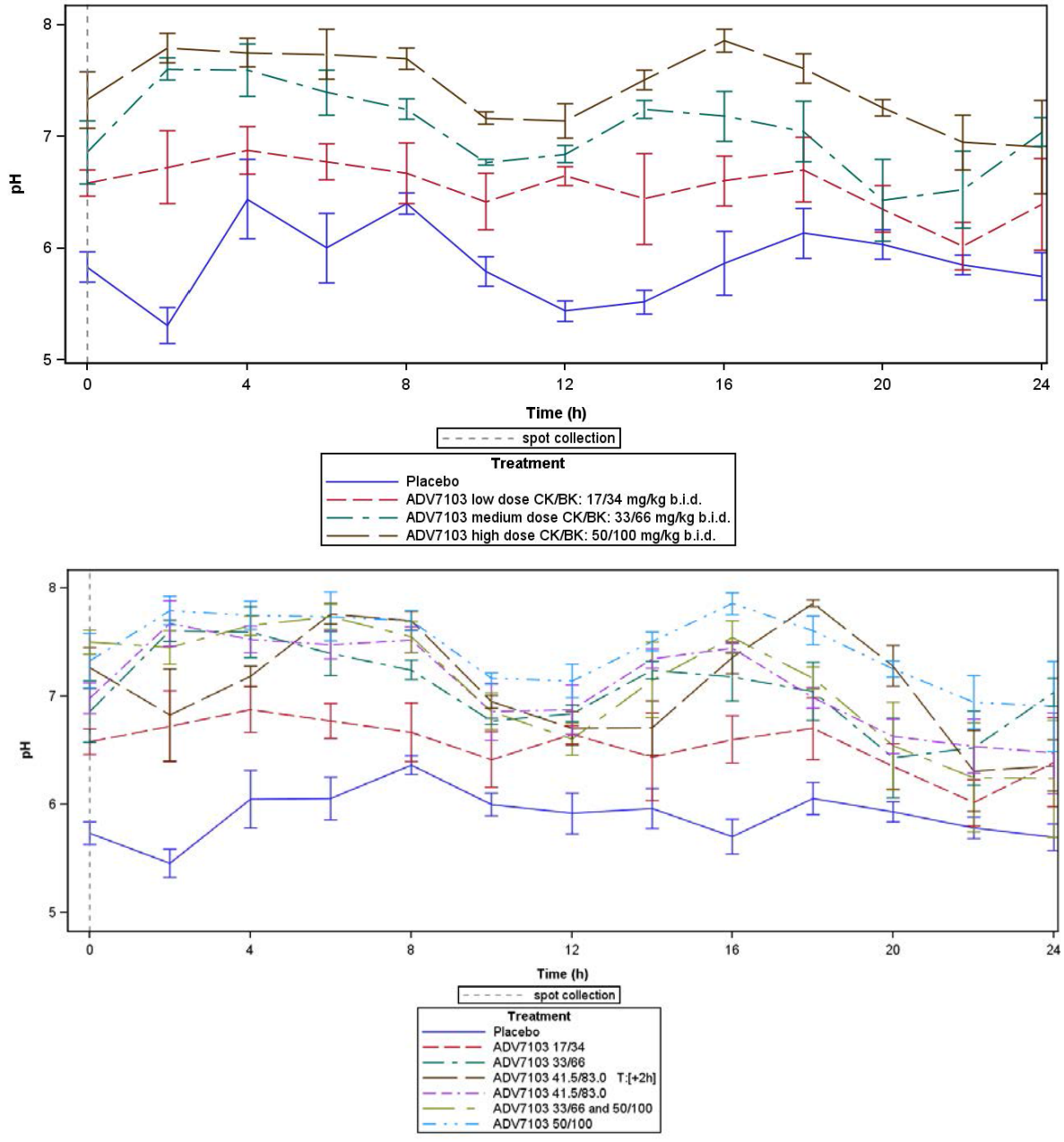
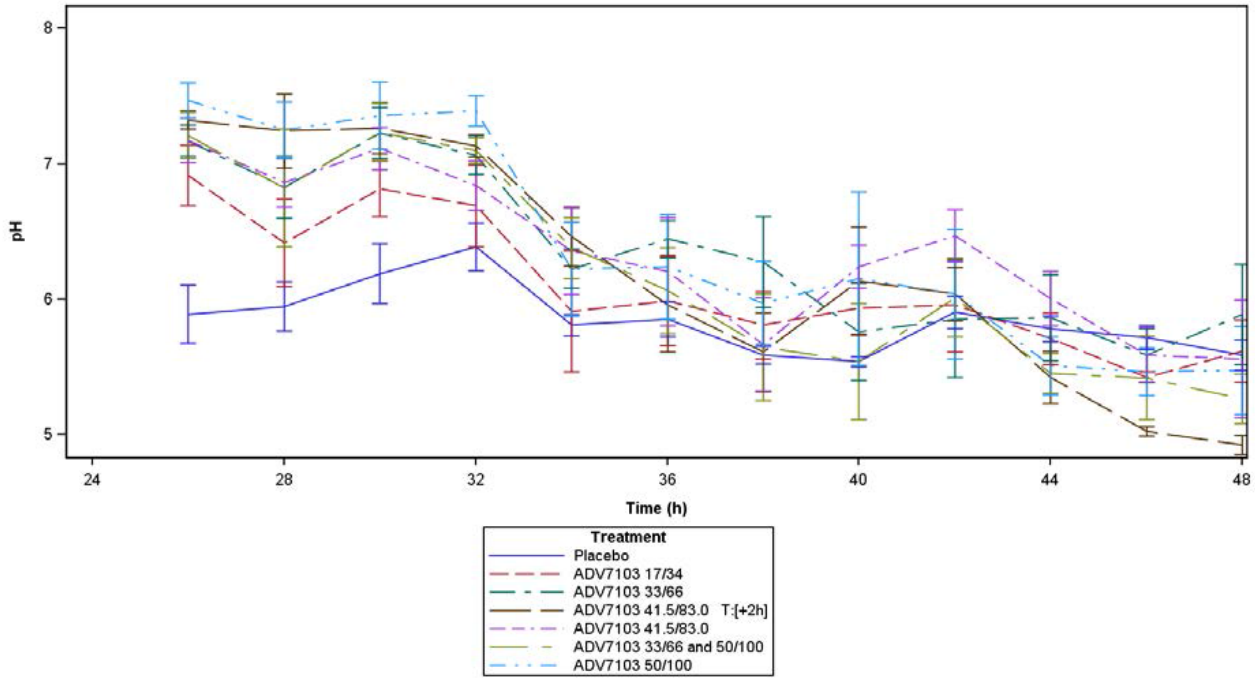


Table 4*: Treatment comparison of urine pH endpoints: ANCOVA model - Pharmacodynamic set*

Endpoint: pH in the first morning and predose urines on Day 4						
			____Comparison to placebo_____			
Treatment	**Lsmeans**	**(95% CI)**	**Comparator**	**Difference**	**(95% CI)**	**p-value**
ADV7103 41.5/83.0 T:[+2h]	7.281	(6.655 ; 7.908)	Placebo	1.611	(1.025 ; 2.196)	<.0001
ADV7103 33/66 and 50/100	7.674	(7.159 ; 8.189)	ADV7103 33/66	0.948	(-0.030 ; 1.925)	0.0562
			Placebo	2.003	(1.393 ; 2.613)	<.0001
ADV7103 50/100	7.324	(6.806 ; 7.842)	ADV7103 17/34	0.818	(0.226 ; 1.409)	0.0098
			ADV7103 33/66	0.598	(-0.008 ; 1.204)	0.0527
			ADV7103 33/66 and 50/100	-0.350	(-1.030 ; 0.331)	0.2984
			ADV7103 41.5/83.0	0.186	(-0.642 ; 1.015)	0.6401
			Placebo	1.653	(1.039 ; 2.267)	<.0001
ADV7103 41.5/83.0	7.138	(6.626 ; 7.650)	ADV7103 17/34	0.631	(-0.051 ; 1.314)	0.0682
			ADV7103 33/66	0.412	(-0.563 ; 1.387)	0.3755
			ADV7103 41.5/83.0 T:[+2h]	-0.143	(-0.752 ; 0.465)	0.6258
			Placebo	1.467	(0.862 ; 2.072)	<.0001
ADV7103 33/66	6.726	(6.104 ; 7.348)	ADV7103 17/34	0.220	(-0.370 ; 0.809)	0.4412
			Placebo	1.055	(0.469 ; 1.641)	0.0015
ADV7103 17/34	6.507	(5.999 ; 7.014)	Placebo	0.836	(0.242 ; 1.429)	0.0087
Placebo	5.671	(5.368 ; 5.974)				

As shown in Figure 6, the return to urine pH baseline values is reached within 24 hours after the last administration of ADV7103 regardless the dose.

Figure 6*: Means (+/-SE) urine pH over time per treatment - Pharmacodynamic set Day: 6*



Secondary pharmacodynamics endpoints

Citraturia: mean change from baseline of the values pooled across the 2 days.

All doses administered demonstrated a statistically significant increase of citraturia as compared to placebo ($p<0.05$ and $p<0.0001$ for the highest dose). The lowest dose (17/36 mg/kg CK/BK) was statistically significantly different from the highest dose (50/100 mg/kg CK/BK) administered ($p<0.0447$).

Table 5*: Endpoint: Mean change from baseline of citraturia values pooled across Day 4 and Day 5 - Pharmacodynamic set*

			Comparison to placebo			
Treatment	**Lsmeans**	**(95% CI)**	**Comparator**	**Difference**	**(95% CI)**	**p-value**
ADV7103 41.5/83.0 T:[+2h]	1.704	(0.413 ; 2.994)	Placebo	2.001	(0.730 ; 3.271)	0.0037
ADV7103 33/66 and 50/100	1.332	(0.228 ; 2.436)	ADV7103 33/66	-1.211	(-3.247 ; 0.825)	0.2234
			Placebo	1.629	(0.367 ; 2.892)	0.0141
ADV7103 50/100	2.660	(1.577 ; 3.743)	ADV7103 17/34	1.283	(0.033 ; 2.532)	0.0447
			ADV7103 33/66	0.117	(-1.144 ; 1.378)	0.8486
			ADV7103 33/66 and 50/100	1.328	(-0.255 ; 2.911)	0.0960
			ADV7103 41.5/83.0	1.632	(-0.143 ; 3.408)	0.0695
			Placebo	2.957	(1.705 ; 4.210)	<.0001
ADV7103 41.5/83.0	1.028	(-0.077 ; 2.133)	ADV7103 17/34	-0.349	(-1.918 ; 1.219)	0.6490
			ADV7103 33/66	-1.516	(-3.506 ; 0.475)	0.1247
			ADV7103 41.5/83.0 T:[+2h]	-0.675	(-2.017 ; 0.666)	0.3061
			Placebo	1.325	(0.049 ; 2.601)	0.0426
ADV7103 33/66	2.544	(1.261 ; 3.826)	ADV7103 17/34	1.166	(-0.093 ; 2.425)	0.0675
			Placebo	2.841	(1.566 ; 4.116)	0.0002
ADV7103 17/34	1.377	(0.293 ; 2.461)	Placebo	1.674	(0.421 ; 2.928)	0.0115
Placebo	-0.297	(-0.923 ; 0.329)				

2.4.4. Discussion on clinical pharmacology

No PK study has been performed for ADV7103 due to the difficulties of measuring the actual exposure of the active substances considering that they are endogenous compounds and regulated by homeostatic system. Considering the complexity of the formulation of ADV7103 (i.e. fixed combination medicinal product and prolonged release) the applicant could have provided a single dose study measuring potassium/bicarbonate in healthy subjects or at least compare with immediate release formulation of potassium citrate and potassium bicarbonate (as monotherapies).

Nevertheless, as the active substances (potassium citrate and potassium bicarbonate) are well-known endogenous compounds, literature was reviewed to describe the PK of potassium citrate and potassium bicarbonate. *In vitro* tests and clinical PD studies have been conducted that can be used to support the dose regimen of the twice daily of ADV7103. Therefore, the absence of PK studies can be accepted.

Overall, literature data are sufficient to describe the PK of potassium citrate and potassium bicarbonate. Interactions between the two active substances are not expected. Drugs that can increase the concentration of potassium or decrease the excretion of potassium should be avoided or monitored depending on the patients' experiences. This is appropriately labelled in the SmPC. Based on literature and study data the urine pH level will be increased due to alkalising agents treatment. However, because the patients with dRTA have already alkaline urine (pH 6.5 – 7.2), the further increase in urine pH due to the treatment was in a relatively small extent, (e.g. pH increased by 0.4 – 0.7 in literature). Patients with dRTA have alkaline urine due to their proton secretion defect. This may impact the excretion of medications into the urine (such as an increase of the elimination of salicylates, tetracyclines, and barbiturates and a decrease in the elimination of quinidine) or reduce the effectiveness of methenamine. As Sibnayal may further increase urine pH to a small extent, the interaction of alkaline urine with these medications may be enhanced. This was added to 4.5 of the

SmPC the applicant does not expect ADV7103 increases intragastic pH (due to bicarbonate) because of its prolonged-release profile limiting the release of alkalising agents in stomach and raising of gastric pH, which is agreed.

A double blind, placebo controlled, two-period, incomplete crossover Phase I study (B03C) was conducted to investigate the PD, safety and tolerability of repeated doses of ADV7103 for 5 days. The relevance of the current study for the proof of concept may be limited due to the inclusion of healthy volunteers, who are effectively able to correct metabolic acidosis, in contrast to the diseased dTRA population. The urine pH levels were measured at Day 4, 5 and 6, for which steady state of ADV7103 can be expected. Nevertheless, the urine pH at steady state could reflect a correction of blood pH based on alkali supplementation. In this respect, some information on duration of the alkalising effect could be derived from the current study with the primary and secondary objectives.

Based on doses of 0.98 mEq/kg/day to 2.38 mEq/kg/day during period I and a determined dose of 2.88 mEq/kg/day during period II, a dose dependent statistically significant treatment effect in urine pH values compared to placebo (up to pH 7 versus pH 5.5) in period I and in periods I and II was observed. The proportion of urine samples with urine pH >7.0 was about 60% between 33/66mg and 33/66 plus 50/100 mg and increased to 90% with the highest dose. Although the urine pH levels start to drop at approximately 8 hours after ADV7103 administration, the increased overall pH levels appear to reflect coverage of effect during the 12 h period. Because dTRA patients are expected to have an alkaline urine, whether the change of the urine pH level in healthy subjects would also apply to dTRA patients is not clear. It can be agreed that all doses administered demonstrated a statistically significant increase of citraturia as compared to placebo. No large differences in citraturia were observed between high and low doses.

2.4.5. Conclusions on clinical pharmacology

The PK of ADV7103 has been described with minimum data. Nevertheless, the absence of PK studies can be accepted because of the clear PD effects of ADV7103.

A proof of concept study in dTRA has not been provided. A study in 16 healthy volunteers was conducted with the administration of the product during two 5 days periods. By measuring the urine pH (over 2 days) the alkalising effect of ADV7103 can indirectly be examined due to normal physiological effects. Despite that a somewhat prolonged and dose dependent effect could be observed with ADV7103, it can be questioned whether this would also apply to dTRA patients because of abnormal physiological functioning but as patients in the phase 3 study are titrated based on effect and based on reaching normalised levels, the PD studies are superseded by the provided efficacy data.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

The Applicant has submitted no dose response studies within this application.

2.5.2. Main study

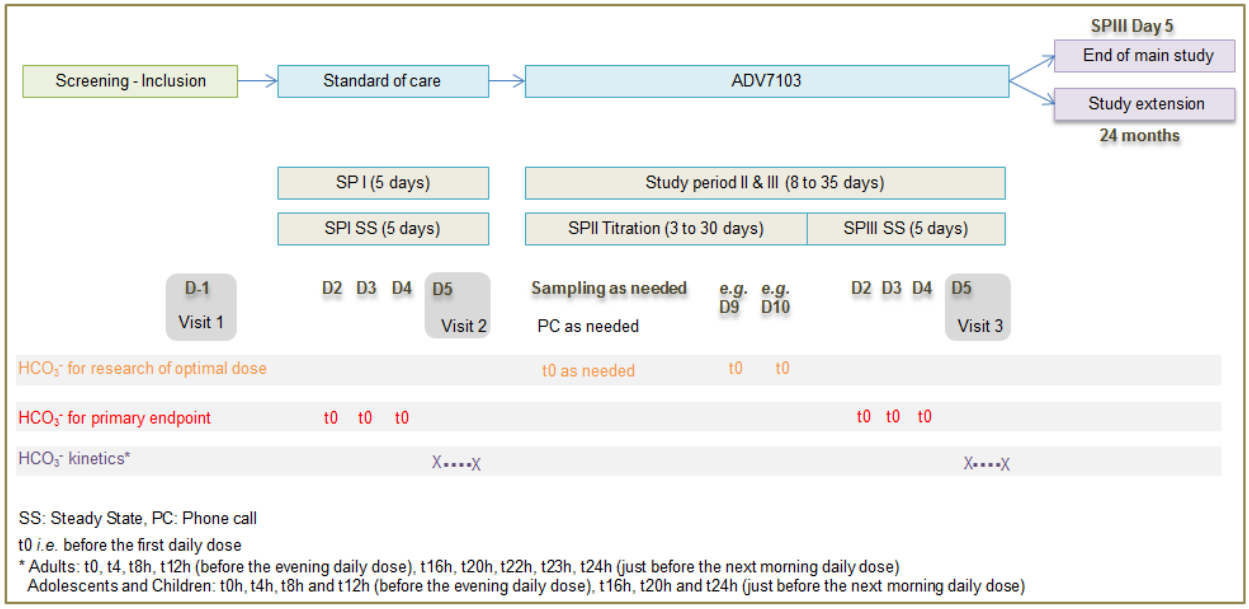
Phase II/III pivotal study (B21CS)

A multicentre, open-label, non-inferiority, sequential study, evaluating the efficacy, safety, tolerability and acceptability of ADV7103 compared to standard of care (SoC) in paediatric and adults patients with dRTA.

Methods

A schematic diagram of the study design is presented below in Figure 7:

Figure 7*: Study design*



Three study phases

The study included three study phases (SP). Enrolled patients were to continue their SoC (without modification or prior titration phase) during SP I (5-day period), and subsequently received ADV7103 via oral administration during SP II (titration phase; variable duration period up to 30 days) and SP III (5-day period). Treatment at each SP was as follows:

- SP I: Patients were to receive their usual SoC for 5 days.
- SP II: At the beginning of this period, patients switched from SoC to ADV7103. Patients were to receive ADV7103 twice a day for up to 30 days; titration was performed to determine the optimal dose based on patients' bicarbonataemia.
- SP III: Patients were to receive ADV7103 twice a day for 5 days at the fixed optimal dose identified during SP II.

Study Participants

Up to 32 patients were to be enrolled in order to have 24 patients fully evaluable, with at least 4 patients in each of the subsets as detailed below.

The 24 patients were to be divided into 4 subsets based on their age:

- Subset 1: adults of age ≥ 18 years (full fluctuation evaluation)

- Subset 2: adolescents of age between 12 and 17 years inclusive (fluctuation evaluation).
- Subset 3: children of age between 4 and 11 years inclusive (fluctuation evaluation if feasible).
- Subset 4: infants and children of age between 6 months and 3 years inclusive (fluctuation evaluation if feasible).

Enrolment was performed using a staggered approach. At least a total of 4 patients of Subsets 1 and 2 had to have completed the study before starting the enrolment of patients of Subset 3. At least 4 patients of Subset 3 had to have completed the study before starting the enrolment of patients of Subset 4.

Key inclusion criteria

The subjects had to fulfil the following key inclusion criteria:

- Patients who had a diagnosis of dRTA (acquired or inherited form) with metabolic acidosis, male or female, including children aged between 6 months and 17 years old and adults aged ≥ 18 years old and ≤55 years old.

Key exclusion criteria

Key exclusion criteria were subjects

- who presented associated proximal tubular signs (i.e. presenting for example hypophosphoraemia, urinary betamicroglobulin, hyponatremia),
- who presented a kalaemia (i.e. plasma potassium concentration) >5.0 mmol/L,
- who had a severe or moderate renal impairment (creatinine clearance <45 mL/min/1.73 m^2 according to Schwartz formula for the children and both Cockcroft & Gault and modification of diet in renal disease formulas for adults),
- who had any previous or concurrent medical condition or any laboratory or clinical findings or any other condition that in the opinion of the Investigator would have been negatively affected by the study medication or that would have affected the study medication or that precluded participation, e.g. uncontrolled diabetes mellitus, adrenal insufficiency, cardiac impairment, repeated infections, metabolic alkalosis, chronic diarrhoea, or who took or could not stop (last dose on Day 1) potassium sparing diuretics, angiotensin converting enzymes inhibitors, angiotensin II receptor antagonists, tacrolimus, potassium desodic salts,
- who were pregnant or breast-feeding,
- who received any medication within the 4 weeks before the inclusion in the study that could interfere with the study treatment,
- who had a history of difficult access to the oral administration route and/or conditions that may have hampered compliance and/or absorption of the study treatment (e.g. any difficulty of swallowing, mal-absorption, delayed gastric emptying, oesophageal compression, intestinal obstruction or other chronic gastrointestinal disease).

Treatments

Study medications

Patients received SoC (the patient's usual alkalising treatment) during SP I followed by ADV7103 in SP II and SP III. Both SoC and ADV7103 were administered orally.

- The SoC was the alkalising treatment normally used by the patient. These alkalising treatments were compounded drugs with different possible active principles and immediate release pharmaceutical forms (e.g. capsules or powder diluted in water, including sodium bicarbonate, sodium citrate, potassium bicarbonate or potassium citrate, alone or in combination).
- ADV7103 was a combination of a ratio of 1/3 potassium citrate and 2/3 potassium bicarbonate prolonged-release granules

Administration

The daily dose of SoC was taken as usual by the patient during SP I for five days. This dose was fixed at inclusion and the dose regimen was the same all throughout SP I, with at least one dose in the morning.

ADV7103 was administered twice per day (in the morning and in the evening). ADV7103 could be taken orally before a meal or with some semi-liquid foods for the youngest children. The morning dose was taken between 7 and 8 AM, and the evening dose between 7 and 9 PM.

Selection of Doses in the Study

The Applicant stated that the doses of SoC taken during SP I were the patients' usual doses.

The doses of ADV7103 were defined for each patient by the Investigator. At the start of SP II the dose was half of the daily dose of the patient's SoC for the patients in age subsets 1 and 2. For patients belonging to subset 3, the initial dose could be re-evaluated using the first results about the equivalence between ADV7103 and SoC observed in the first 4 older patients by the Data Safety Monitoring Board (DSMB), with the overall goal of limiting the length of the titration period. Similarly, for patients belonging to subset 4, the first dose could be re-evaluated after the inclusion of the first 4 patients of subset 3. During SP II, the dose increments could vary between 0.5, 1.0 and 1.5 mEq/kg/day, depending on the needs and treatment responses of the patients.

During SP III, the identified optimal daily dose of ADV7103 was to be taken for 5 days.

The maximum possible dose of ADV7103 in this study was 10 mEq/kg/day. This was selected based both on the fact that doses higher than 6 to 8 mEq/kg/day are generally prescribed to treat the proximal, rather than distal forms, of RTA and that to obtain an equivalent alkali effect, higher doses of ADV7103 (a prolonged-release formulation) may be needed compared to the usual immediate release formulations, such as described for other medications (e.g. propranolol). This dose is considered safe, even in infants. Nevertheless, it appears that for similar single doses of ADV7103 and of immediate release formulations (approximately 60 mEq) a prolonged alkalising effect of the urine pH is provided by ADV7103 compared to the other forms in healthy subjects.

Titration

During the titration phase of SP II, evaluations were planned and performed at regular intervals (e.g. every 2 days) between the Investigator and the patient to decide whether a dose increment/adjustment was needed or whether the optimal dose of ADV7103 had been reached, after obtaining the bicarbonataemia results, e.g. on Day 2, Day 4, Day 6 and Day 8 t0 before the first daily dose. The length of these steps could be between 2 and 10 days.

The increased doses (if needed) were determined by the Investigator with dose increments based on the bicarbonataemia data. The length of each step of dose increment was also defined by the Investigator. The Investigator either adjusted the treatment (e.g. by adding one or more 0.25 mEq/kg mono-doses morning and evening) or maintained the same dosage. The daily dose was increased by increments of 0.5, 1.0 or 1.5 mEq/kg/day up to the target dose, which was the dose required to reach a bicarbonataemia within the normal range of values, as defined by the local laboratory, without

exceeding a total dose of 10 mEq/kg/day. The dose of ADV7103 was increased if necessary, after control of the pre-morning dose bicarbonataemia, at a dose determined by the Investigator. Intolerable side effects could lead to termination of the titration, a decrease to the previously well-tolerated dose, or an adaptation of the dose regimen.

Optimal Dose

A soon as a normal value of bicarbonataemia was reached, a second control of bicarbonataemia was performed 24 hours following the first control and before the first following daily dose. If the bicarbonataemia of the second control confirmed the value of the first control, the optimal dose was considered as reached, SP II was thus considered as completed and the patient proceeded with the SP III steady state period on the following day. If the bicarbonataemia of the second control did not confirm the value of the first control, the dose increment continued until confirmation of the optimal dose by the same process. The titration period was not planned to last more than 30 days, and was expected to be reached in less than 7 days.

The optimal dose was validated after control of bicarbonataemia stability during at least 2 subsequent days, the first day being the day when the bicarbonataemia had reached a normal value, as defined by the local laboratory the first time, and the second day being the following day. For example, if the third increased daily dose resulted in a normal value of bicarbonataemia, then this dose would be maintained on Day 8 for the evening dose and control of bicarbonataemia would be performed again on Day 9 t0. If the bicarbonataemia value remained normal, the SP II titration phase ended on Day 9 after administration of the dose (morning and evening). The third increased daily dose would thus be considered as the optimal dose.

Bicarbonataemia was locally measured until the optimal dose was found.

Diet

Patients were required to eat meals at regular times, as a balanced standard diet as recommended by the dietician of the investigator site, have a similar diet on Day 5 of SP I and SP III (protein proportions as agreed by the Coordinating Investigator), not consume bicarbonate drinks and foods (e.g. soft drinks, Vichy water), have a limited intake of milk or dairy product, with standardised intake only (diet questionnaire at study inclusion), complete a diary book (for the patient/parents to record the investigational medicinal product intakes, times of blood samples, intake of proteins, any potential AEs and concomitant treatment).

Objectives

Primary Objective

The primary objective was to evaluate the relative efficacy of ADV7103 and SoC on correcting metabolic acidosis as measured by pre-morning dose blood bicarbonate levels (bicarbonataemia) during 3 days of treatment at steady state (Day 2 to Day 4).

Secondary Objectives

- To compare the efficacy on other blood bicarbonate-derived parameters of ADV7103 to standard of care given after 5 days of treatment at steady state.
- To evaluate the efficacy on the reduction of hypercalciuria, hypocitraturia of ADV7103 as compared to standard of care after 4 to 5 days of treatment at steady state.
- To evaluate the safety and tolerability including the gastrointestinal tolerability of ADV7103 as compared to standard of care during 5 days of treatment at steady state.

- To evaluate the acceptability (palatability, swallowing, ease of administration) of ADV7103 as compared to standard of care for 5 days of treatment at steady state.
- To evaluate the compliance to ADV7103 as compared to standard of care during 5 days of treatment at steady state.

Outcomes/endpoints

Primary efficacy endpoint

The primary efficacy endpoint of the study was: average bicarbonate blood level during 3 days of treatment at steady state with ADV7103 and SoC (Day 2 to Day 4, before the first daily dose, of SP III and SP I, respectively).

Secondary efficacy endpoints

To assess the efficacy of ADV7103 compared to SoC based on other blood bicarbonate-derived parameters after 4 days of treatment at steady state (SP III and SP I, respectively) the following endpoints were addressed.

• Categorical secondary endpoints:

  - Number/proportion of patients with abnormal bicarbonataemia value (i.e. patients with at least one value of bicarbonataemia below the lower normal range, on Day 2 t0, Day 3 t0 or Day 4 t0).
  - Number/proportion of non-responders (i.e. patients with all three values of bicarbonataemia below the lower normal range, on Day 2 t0, Day 3 t0 and Day 4 t0).
  - Number/proportion of non-responder patients with abnormally low bicarbonataemia value (i.e. patients with a mean blood bicarbonate value below the lower normal value on Day 2 t0, Day 3 t0 or Day 4 t0).

• Continuous secondary endpoints:

  - The area under the curve from t0 to t12h (AUC0-12h), AUC from t0 to t24h (AUC0-24h), minimum concentration (Cmin) over 24 h, fluctuation (maximum minus minimum concentrations) over 24 h on Day 5.

• Other secondary endpoints:

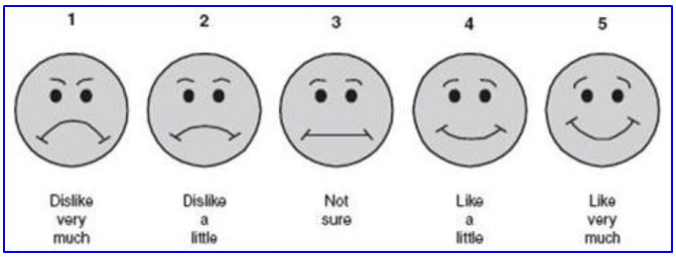
  - Number of patients with a hypokalaemia, hypercalciuria and hypocitraturia after 4 to 5 days of treatment at steady state.
  - Number of patients with abnormally high urine calcium/citrate (UCa/UCi) ratio (expressed in mg/mg) and with UCa/UCi expressed in mmol/mmol above the risk threshold for lithogenesis after 4 to 5 days of treatment at steady state (post-hoc analyses).

Further, acceptability was analysed on palatability, ease of swallowing and ease of administration on SP I and SP III Day 5, and the rate of compliance was determined in SP I and SP III.

Acceptability assessment was performed using a 100mm Visual Analogue Scale (VAS) or a 5- point facial hedonic scale (FHS) (Figure 6). Both scales are commonly used and widely accepted in clinical trial settings (with the FHS used more specifically in children aged between 4 and 12) and considered as valuable tools.

Adults and adolescents had to answer using VAS for which a score of '0' meant '*I dislike very much*' and a score of '100' meant '*I like very much'*. The VAS was also used for infants by the same parent at each of the visits, based on infant's behaviour or possible words. Children had to use the FHS with the help of their parents where necessary, to select the appropriate face to indicate their preference.

Figure 8*: Facial Hedonic Scale for palatability evaluation*



To allow a consolidated assessment with VAS results, linkage between VAS and FHS scorings was predefined in the CSP.

Table 6 *Linkages between VAS and Hedonic Face Scale*

VAS	Facial Hedonic Scale	Severity of the Event
0 to < 20 mm	Face 1	Dislike very much
20 to < 40mm	Face 2	Dislike a little
40 to < 60 mm	Face 3	Not sure
60 to <80 mm	Face 4	Like a little
80 to 100mm	Face 5	Like very much

Sample size

The sample size was planned to be 32 patients, to ensure that there would be at least 24 fully evaluable patients in the Per Protocol (PP) set, with at least 4 patients in each age subset. Approximately 12 patients were required to follow a fluctuation evaluation.

The sample size calculation was determined by mean difference in bicarbonate levels of ADV7103 and SoC after 4 days of treatment. The sample size was based on the number of patients required to achieve at least 80% power for the primary non-inferiority efficacy analysis. The calculation was performed by means of a one-sided paired-t-test at the 2.5% significance level with an SD of 4.1 mmol/L and a non-inferiority margin of -2.5 mmol/L for the mean difference in bicarbonate levels between ADV7103 and SoC.

The non-inferiority margin was selected in line with recommendations by the 2005 EMA guideline on the choice of the non-inferiority margin (EMEA/CPMP/EWP/2158/99). The -2.5mmol/L margin was thus selected based on literature data (Domrongkitchaiporn S et al. dosage of potassium citrate in the correction of urinary abnormalities in paediatric distal renal tubular acidosis patients. American Journal of Kidney Diseases 2002(a) 39(2): 383-391.)

2002a), statistical calculation and clinical experts' input, and judged acceptable by PDCO.

It is also important to note that although the 21-29 mmol/L reference value range is usually used, it is acknowledged there exist physiological differences between infants (17-25 mmol/L), children (18-29 mmol/L) and adults (>22 mmol/L), as reported by Mayo Clinic Laboratories (mayocliniclabs.com).

Randomisation

Not applicable; the study had a sequential design.

Blinding (masking)

The study was designed as an open-label study.

Statistical methods

Primary analyses set

Intent-To-Treat (ITT) Analysis Set: all patients receiving at least one dose of the study drug at steady state (SP I/SP III) and with at least one efficacy assessment.

PP Set: all patients who completed the study with no major protocol deviations having an impact on efficacy. In case of any missing bicarbonate blood concentration data on Day 2 t0, Day 3 t0 or Day 4 t0, the protocol deviation was not to be considered major if a mean value for the primary endpoint in the period could be calculated according to a specific replacement algorithm.

Efficacy analysis

Primary efficacy analysis

The primary endpoint was the average measure of bicarbonate blood levels during 3 days of treatment at steady state with ADV7103 and SoC.

The individual differences (ADV7103 – SoC) in the mean of the 3 pre-morning dose blood bicarbonate levels on Day 2 (t0), Day 3 (t0) and Day 4 (t0) were analysed. Non-inferiority (and superiority) of ADV7103 vs. SoC was to be declared when the lower, one-sided 97.5% confidence limit on the mean difference laid entirely on the positive side of the non-inferiority margin equal to – 2.5 mmol/L.

Secondary efficacy analyses

- Bicarbonataemia-related endpoints after 4-5 days of treatment during SP I and SP III
    - Categorical secondary endpoints. Proportions of non-responder patients.
    - Continuous secondary endpoints. The mean differences (ADV7103 – SoC) for AUC0-12h, AUC0-24h, Cmin and fluctuation was analysed
- Hypokalaemia, hypercalciuria, hypocitraturia, abnormally high UCa/UCi: Proportions of patients and kalaemia, calciuria, citraturia, UCa/UCi (in mg/mg) data were summarised by and compared between treatments separately.

Acceptability analysis

For each parameter (palatability, ease of swallowing, and ease of administration), the scale scores on Day 5 of SP I and SP III were analysed. The palatability, ease of swallowing and ease of administration data were summarised by and compared between treatments separately.

Compliance analysis

Compliance was determined during SP I and SP III. For each day or period, a patient was compliant if he/she took at least 80% and no more than 125% of all planned total dose in that day or period, respectively. The compliance of ADV7103 as compared with SoC during 5 days of treatment at steady state (SP I and SP III) was evaluated, and the proportion/number of compliant patients was analysed.

Safety analysis

Safety data were summarised descriptively by treatment, and listed by age subgroup, patient, treatment period and timepoint, as applicable.

Subgroup analyses

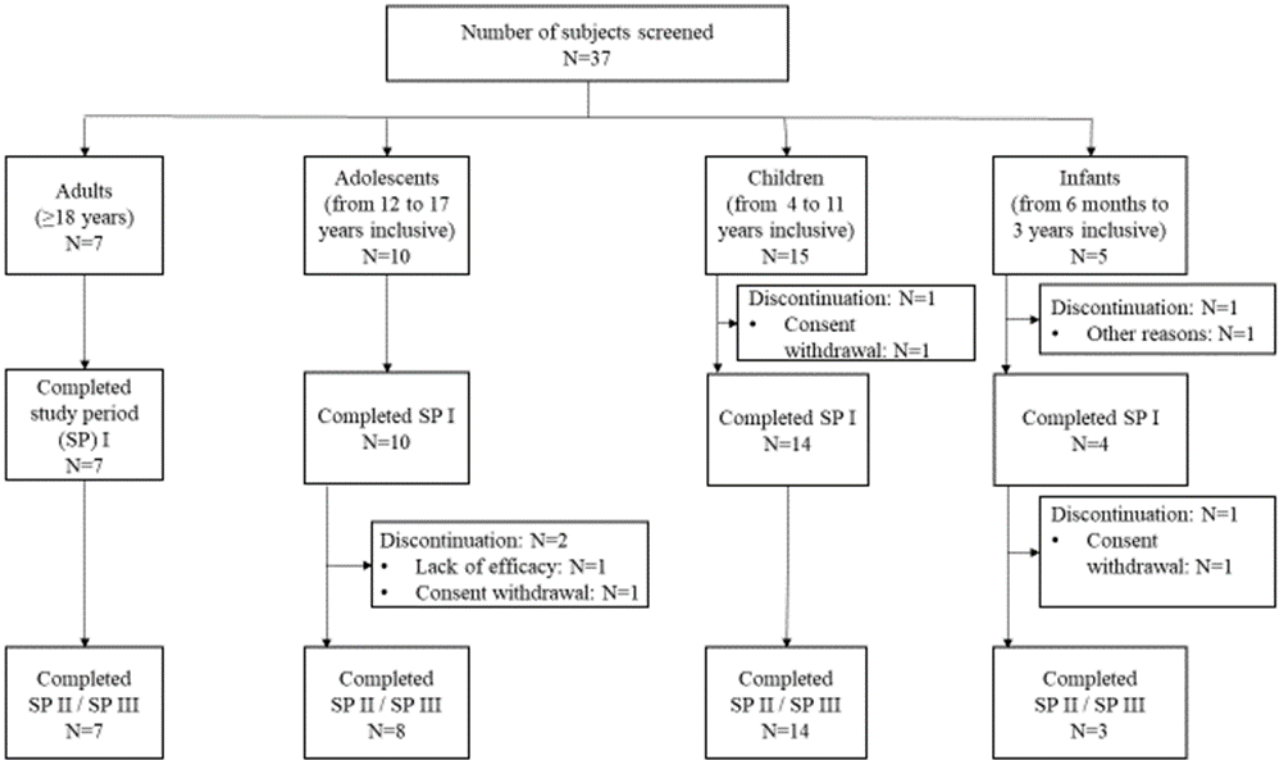
All variables were summarised in their respective analysis sets by treatment for each age subset separately. The primary and secondary efficacy variables were summarised by treatment of SoC type.

Results

Participant flow

The participant flow is presented in the following flow diagram. Of the 37 subjects screened, 37 patients were randomised. Thirty patients completed the study.

Figure 9*: Disposition of study patients (all enrolled patients)*



Recruitment

A total of 13 centres in 3 countries participated in the study: 11 centres in France, 1 in Slovakia and 1 in Serbia.

First patient first visit: 24 Sep 2014

Last patient last visit: 20 May 2016

Conduct of the study

A total of 2 (5.4%) patients, both children, had major protocol deviations. These patients were excluded from the PP set.

All patients had minor protocol deviations. Minor deviations included missing data, examination not done, protocol procedure deviation, visit window not respected, time-point not respected, inclusion/exclusion criteria not respected, diet not followed or treatment schedule not fully respected.

Table 7*: Major protocol deviations*

Patient	Number of major protocol deviations	Description	Study period
XXXXXXXX	1	Treatment schedule not respected	SP III
YYYYYYYY	3	Examination not done	SP I
	1	Schedule timepoint not respected	
	2	Missing data	SP III
	2	Schedule timepoint not respected	

In Study B21CS, compliance was defined by the patient who took at least 80% and no more than 125% of all planned treatments in that period. Using this definition, 34 of the 37 patients (91.9%) were compliant during SPI, and 31 of the 32 patients (96.9%) during SPIII. Results were similar in the different age subsets. Cases of non-compliance were mainly due to sparse intakes forgotten or error of dosing.

Baseline data

Demographics

Overall, the majority of patients were female (23 [62%] females vs. 14 [38%] males). More females (ranging from 60% to 80%) were enrolled in all age subsets, except for the infant category in which 4 (80%) patients were male. Overall, the mean age of the patients was 11.5 years (range: 1-46 years). In particular, the mean age of adults, adolescents, children and infants was 23.3 years, 14.0 years, 7.3 years and 2.6 years, respectively.

Table 8*: Demographic summary and key baseline characteristics*

Patients Characteristics	Adults (>18 yrs) (n=7)	Adolescents (12 - <18 yrs) (n=10)	Children (4 - <12 yrs) (n=15)	Infants (6 mths - < 4 yrs) (n=5)	Total (n=37)
Age[a] (years)					
Mean (SD)	23.3 (9.92)	4.0 (1.69)	7.3 (2.40)	2.6 (1.05)	11.5 (8.15)
Median	19.3	13.6	7.4	3.0	11.5
Range	19-46	12-17	5-12	1-4	1-46
Gender (n;%)					
Female	5 (71)	8 (80)	9 (60)	1 (20)	23 (62)
Male	2 (29)	2 (20)	6 (40)	4 (80)	14 (38)
Weight[b] (kg)					
Mean (SD)	69.1 (22.59)	43.7 (7.64)	26.5 (12.50)	13.4 (3.78)	37.4 (22.30)
Median	60.5	41.9	23.3	12.5	39.0
Range	51-114	32-57	12-54	9-19	9-114
Height[b] (cm)					
Mean (SD)	160.3 (7.52)	156.6 (9.97)	119.8 (16.50)	90.9 (11.05)	133.5 (27.79)
Median	164.0	157.0	117.0	94.0	139.0
Range	149-168	139-170	91-154	75-102	75-170
BMI (kg/m^2)					
Mean (SD)	26.6 (7.11)	17.8 (2.63)	17.5 (3.68)	16.0 (1.39)	19.1 (5.43)
Median	23.8	16.7	15.9	15.9	16.8
Range	20-41	15-23	13-24	14-18	13-41
Type of dRTA					
Acquired (n;%)	1 (14.3)	-	-	-	1 (2.7%)
Inherited (n;%)	6 (85.7)	10 (100)	14 (93.3%)	5 (100)	35 (94.6%)
Not specified (n;%)	-	-	1 (6.7%)	-	1 (2.7%)
Hearing impairment					
No	1(14)	4 (40)	7 (46.7)	2 (40)	14 (37.8)
Yes	6 (85.7)	6 (60)	8 (53.3)	3 (60)	23 (62.2)
Short stature (adults)					
No	5 (83.3)	N/A	N/A	N/A	5 (16.7)
Yes	1 (16.7)	N/A	N/A	N/A	1 (3.3)
Growth impairment (adolescents, children, infants)					
No	N/A	10 (100.0)	14 (92.3)	2 (40)	26 (86.7)
Yes	N/A	-	1 (6.7)	3(60)	4 (13.3)
Nephrocalcinosis					
No	1(14.3)	2 (20.0)	1 (6.7)	1 (20)	5 (13.5)
Yes	6 (85.7)	8 (80.0)	14 (93.3)	4 (80)	32 (86.5)
Nephrolithiasis					
No	6 (85.7)	8 (80)	14 (93.3)	4 (80)	32 (86.5)
Yes	1(14.3)	2 (20)	1 (6.7)	1 (20)	5 (13.5)

dRTA

The vast majority (35 [94.6%]) of patients had the inherited form of dRTA and 1 patient had an acquired form of dRTA concomitant to Sjögren syndrome. For 1 patient the type of dRTA was unknown, although an inherited dRTA was suspected, as the diagnosis was done 2 months after birth based on acidosis and nephrocalcinosis. The first diagnostic of dRTA was done early for most patients: at 3 years of age in average for the inherited dRTA cases (at 0.6, 5.3, 1.1 and 0.5 years of age, in adults, adolescents, children and infants, respectively), and at 38 years of age for the acquired dRTA case. Common dRTA symptoms were: nephrocalcinosis (in n=32 [86.5%]), hearing impairment (n=23 [62.2%]), nephrolithiasis (n=5 [13.5%]), growth impairment (n=4 [10.8%]).

Biochemistry Parameters

The overall mean (SD) venous blood bicarbonate was 23.18 (3.41) mmol/L (within the normal range), and generally similar across age subsets: 25.11 (3.69) mmol/L in adults, 21.65 (3.15) mmol/L in adolescents, 23.82 (3.09) mmol/L in children and 21.84 (3.41) mmol/L in infants.

The overall mean (SD) plasma potassium was 3.55 (0.485) mmol/L (low but within the median normal range), and generally similar across age subsets: 3.50 (0.852) mmol/L in adults, 3.46 (0.475) mmol/L in adolescents, 3.66 (0.394) mmol/L in children and 3.55 (0.071) mmol/L in infants.

Mean (SD) UCa/UCr was 0.28 (0.243) overall, and slightly higher in adolescents and children (0.32 [0.416] and 0.32 [0.135], respectively) than in adults and infants (0.21 [0.186] and 0.24 [0.243], respectively). Mean (SD) UCi/UCr ratio was 0.13 (0.210) overall, and higher in infants and children (0.30 [0.415] and 0.18 [0.204], respectively) than in adults and adolescents (0.03 [0.021] and 0.03 [0.015], respectively)

Diet

Most dRTA patients (30 [81.1%] patients) did not follow a specific diet before enrolment in the study. The remaining patients (7 [18.9%]) followed a specific diet:

- Diet normal in protein and low in salt for 3 (8.1%) patients
- Diet normal in protein, hypocaloric, without soft drinks or balanced standard diet, each for 1 (2.7%) patient.

Of the 6 patients who completed the study and followed a diet, 2 of them were fully compliant, 3 were moderately compliant (i.e. they were mainly not compliant on Day 5 of SP I and SP III) and one was not compliant.

Dose

In the table below, the daily dose of SoC and ADV7103 are presented. Mean doses in mEq/kg/day were highest in the infant subset and decreased with age.

Table 9*: Extent of Optimal Exposure in SP I and SP III of B21CS study by age subset and overall (SA set)*

	SP I SoC at a steady state dose for 5 days		SP III ADV7103 at a steady state dose for 5 days	
	Daily dose in mEq/day	**Daily dose in mEq/kg/day**	**Daily dose in mEq/day**	**Daily dose in mEq/kg/day**
Adults, ≥18 years old				
n	7		7	
Mean (SD)	118.72 (72.743)	1.99 (1.537)	108.39 (44.329)	1.74 (1.047)
Min-Max	38.8 -235.0	0.4 – 4.6	78.3 – 204.0	0.8 – 4.0
Adolescents, from 12-17 years inclusive				
n	10		8	
Mean (SD)	93.28 (55.204)	2.20 (1.408)	124.25 (79.194)	2.79 (1.737)
Min-Max	26.7 – 178.2	0.7 – 4.5	53.0 – 291.0	0.9 – 6.0
Children, from 4-11 years inclusive				
n	15		14	
Mean (SD)	64.79 (25.938)	2.70 (1.231)	96.46 (59.957)	3.80 (1.150)
Min-Max	33.0 – 124.6	1.5 – 6.1	30.5 – 272.0	1.9 – 6.0
Infants, from 6 months-3 years old inclusive				
n	5		3	
Mean (SD)	63.31 (18.213)	5.27 (2.535)	90.00 (25.519)	6.11 (2.262)
Min-Max	42.4 – 80.0	2.3 – 8.0	61.2 – 109.8	4.0 – 8.5
Overall				
n	37		32	
Mean (SD)	82.49 (49.107)	2.78 (1.808)	105.41 (59.151)	3.31 (1.810)
Min-Max	26.7 – 235.0	0.4 – 8.0	30.5 – 291.0	0.8 – 8.5

Regarding titration to the optimal dose, the majority of patients (25 [73.5%] patients) received a titration of ADV7103. Overall, nine patients (26.5%) did not need dose increments following the initial dose.

The mean increment of titration overall, regardless of age, was 0.72 mEq/kg/day (equivalent to an increment in the absolute total daily dose of 23.27 mEq). The increase was dependent on the age group with a higher increment in mEq/kg/day seen with decreasing age group (0.38, 0.64, 0.73 and 1.0 mEq/kg/day in adults, adolescents, children and infants, respectively). As dosing is weight-based this does not translate into a corresponding increase in an absolute total daily dose which was 28.16, 27.89, 21.67 and 15.03 mEq/day across the age groups.

The duration of the titration period ranged from 4 to 25 days. For those patients that were titrated, the median titration period was 10 days. Duration of the titration period was similar across age subsets, except for the infants who had a longer titration (17 days) in order to avoid too clustered blood samplings. The mean number of days between dose increments was of 4.19 overall, and of 3.33 for adults and adolescents, and longer for children and infants (4.65 and 5.13, respectively).

Table 10*: Titration dose increments of ADV7103 – Study B21CS*

SPII - ADV7103 titration	Increments of dose in mEq/day	Increments of dose in mEq/kg/day	Number of days per dose increment	No increment
Adults, ≥18 years old (N = 7)				
n	3			4
Mean (SD)	28.16 (1.94)	0.38 (0.14)	3.33 (0.58)	
Min – Med – Max	25.5 – 28.5 – 30.15	0.25 – 0.375 – 0.50	3.0 – 3.0 – 9.5	
Adolescents, from 12-17 years inclusive (N = 10)				
n	6			4
Mean (SD)	27.89 (9.77)	0.64 (0.23)	3.33 (1.97)	
Min – Med – Max	15.5 – 26.25 – 48.0	0.5 – 0.5 – 1.0	2.0 – 2.50 – 9.0	
Children, from 4-11 years inclusive (N = 14)				
n	13			1
Mean (SD)	21.67 (17.20)	0.73 (0.31)	4.65 (2.59)	
Min – Med – Max	5.0 – 13.8 – 74.4	0.2 – 0.5– 1.5	1.0 – 4.0 – 10.0	
Infants, from 6 months-3 years old inclusive (N = 3)				
n	3			0
Mean (SD)	15.03 (5.62)	1.0 (0.46)	5.13 (3.04)	
Min – Med – Max	6.0 – 16.75 – 23.0	0.5 – 1.0 – 2.0	3.0 – 4.0 – 12.0	
Overall (N= 34)				
n	25			9
Mean (SD)	23.27 (13.48)	0.72 (0.33)	4.19 (2.45)	
Min – Med – Max	5.0 – 20.5 – 74.4	0.2 – 0.5 – 2.0	1.0 – 3.0 – 12.0	

SoC treatment

The number (%) of patients by SoC type is summarised by age subset and overall, for all patients.

At study entry, SoC treatment included a variety of alkalising treatments. Almost 50% of the patients took 2 alkali agents. The most common SoCs were compounded formulations of potassium citrate with sodium bicarbonate (in 9 [24.3%] patients), potassium citrate (in 8 [21.6%] patients) and sodium bicarbonate (in 7 [18.9%] patients). The SoC brought a mean (standard deviation [SD]) daily load of sodium of 1.08 (0.56) g for 22 (59.5%) of the patients (ranging from 0.28 to 2.3 g). The SoC brought a mean (SD) daily dose of potassium of 63.9 (58.54) mmol for 81% of the patients, including also potassium supplementation for 8.1% of the patients. About 87% of the patients took at least 3 intakes of SoC a day (and up to 6 intakes a day). Approximately 27% of the patients, particularly children and infants, took SoC during the night.

Table 11*: SoC treatment*

Type	Adults (≥18 yrs) N=7	Adolescents (from 12-17 yrs old inclusive) N=10	Children (from 4-11-yrs old inclusive) N=15	Infants (from 6 mths-3 yrs old inclusive) N=5	Total N=37
SoC type					
1 product	5 (71.4%)	6 (60%)	5 (33.3%)	3 (60%)	19 (51.4%)
PB – N (%)	-	2 (20.0%)	1 (6.7%)	-	3 (8.1%)
PC – N (%)	4 (57.1%)	3 (30.0%)	1 (6.7%)	-	8 (21.6%)
SB – N (%)	1 (14.3%)	1 (10.0%)	2 (13.3%)	3 (60.0%)	7 (18.9%)
Modified Shohl's solution[a] N (%)	-	-	1 (6.7%)	-	1 (2.7%)
2 products	2 528.6%)	4 (40%)	10 (66.7%)	2 (40%)	18 (48.6%)
PB+PC – N(%)	-	1 (10.0%)	2 (13.3%)	-	3 (8.1%)
PB+SB – N(%)	1 (14.3%)	-	3 (20.0%)	1 (20.0%)	5 (13.5%)
PC+SB – N(%)	1 (14.3%)	2 (20.0%)	5 (33.3%)	1 (20.0%)	9 (24.3%)
Modified Shohl's solution[a] + SB – N (%)	-	1 (10.0%)	-	-	1 (2.7%)
Daily load in sodium (mg/day)[b]					
Number of patients, n (%)	3 (42.9%)	4 (40.0%)	10 (66.7%)	5 (100%)	22 (59.5%)
Mean (SD)	912.2 (632.34)	1207.3 (926.49)	1045.8 (473.47)	1158.4 (504.17)	1082.5 (560.64)
Min-Max	(547.2-1642.4)	(275.9-2282.6)	(551.8-2188.6)	(410.4-1643.6)	(275.9-2282.6)
Daily load in potassium (mmol/day – mEq/day)[b]					
Number of patients, n (%)	7 (100%)	8 (80%)	12 (80%)	3 (60%)	30 (81.1%)
Mean (SD)	105.2 (72.91)	89.7 (61.65)	33.5 (24.26)	20.1 (12.62)	63.9 (58.54)
Min-Max	(15.0-205.5)	(14.7-178.2)	(9.0-98.7)	(5.9-30.0)	(5.9-205.5)
Patients with potassium supplement	1 (14.3%)	1 (10%)	0 (0%)	1 (20%)	3 (8.1%)
Number of daily intakes[b]					
Mean (Min-Max)	3.0 (1c – 4)	3.1 (2 – 4)	3.5 (2 – 6)	3.6 (3 – 4)	3.3 (1[c] – 6)
Number of intakes ≥ 3 per day, n (%)	6 (85.7%)	8 (80%)	13 (86.7%)	5 (100%)	32 (86.5%)
Intake during night[d], n (%)	1 (14.3%)	2 (20%)	5 (33.3%)	2 (40%)	10 (27.0%)

Numbers analysed

Table 12: *Number (%) of patients in the analysis sets (All patients)*

	Adults (≥18 yrs) N = 7 n (%)	Adolescents (from 12-17 yrs old inclusive) N = 10 n (%)	Children (from 4-11 yrs old inclusive) N = 15 n (%)	Infants (from 6 mths – 3 yrs old inclusive) N = 5 n (%)	Total N=37 n (%)
Screened	7 (100%)	10 (100%)	15 (100%)	5 (100%)	37 (100%)
SA set[a]	7 (100%)	10 (100%)	15 (100%)	5 (100%)	37 (100%)
ITT set[b]	7 (100%)	10 (100%)	15 (100%)	5 (100%)	37 (100%)
PP set[c]	7 (100%)	8 (80%)	12 (80%)	3 (100%)	30 (81%)
AA set[d]	7 (100%)	10 (100%)	15 (100%)	5 (100%)	37 (100%)

Outcomes and estimation

Primary efficacy endpoint - bicarbonataemia

The applicant stated that non-inferiority of ADV7103 vs. SoC was demonstrated in the PP set in terms of pre-morning dose average blood bicarbonate levels from Day 2 to Day 4. Indeed, the lower, one sided 97.5% confidence limit on the mean difference between treatments laid entirely on the positive side of the non-inferiority margin of -2.5 mmol/L: the mean difference (95% confidence interval [CI]) between treatments was 1.42 (0.41, 2.43) mmol/L, p<0.0001.

By age subset, in the PP set, mean (SD) blood bicarbonate levels were higher with ADV7103 than with SoC in the paediatric subsets, and similar for both products in the adults. In addition, less variability was observed for adults and infants.

The applicant reported furthermore that the mixed effect ANOVA in the ITT set, which was originally planned as sensitivity analysis, was showed superiority of ADV7103 to SoC with an adjusted mean difference (95% CI) of 1.64 (0.67, 2.60) mmol/L, p=0.0008. The analysis of mean blood bicarbonate

levels using the PP set provided additional support for the superiority evaluation of ADV7103 compared to SoC as significance was also achieved (p=0.0037) Table 18 .

Figure 10*: Primary endpoint results: Bicarbonataemia – B21CS (ITT set)*

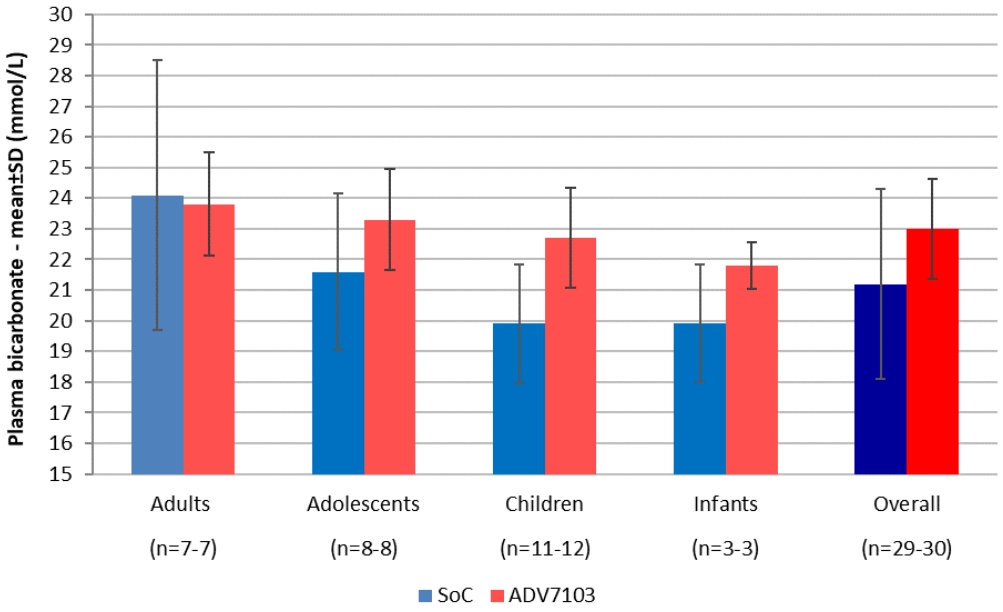


Table 13*: Summary of average blood bicarbonate levels (pre-dose Day 2 to Day 4) after SoC and ADV7103 treatment (PP and ITT sets)*

mmol/L	PP set		ITT set	
	SP I (SoC)	SP III (ADV7103)	SP I (SoC)	SP III (ADV7103)
Adults, ≥18 years old	N=7		N=7	
n Mean (SD) Min-Max	7 24.1 (4.39) 18-29	7 23.8 (1.69) 21-27	7 24.1 (4.39) 18-29	7 23.8 (1.69) 21-27
Adolescents, from 12-17 years inclusive	N=8		N=10	
n Mean (SD) Min-Max	8 22.5 (1.42) 21-25	8 23.3 (1.64) 20-25	10 21.6 (2.54) 16-25	8 23.3 (1.64) 20-25
Children, from 4-11 years inclusive	N=12		N=13	
n Mean (SD) Min-Max	11 19.9 (2.04) 17-25	12 22.8 (1.66) 19-25	12 19.9 (1.95) 17-25	13 22.7 (1.62) 19-25
Infants, from 6 months-3 years old inclusive	N=3		N=5	
n Mean (SD) Min-Max	3 20.0 (1.32) 19-21	3 21.8 (0.76) 21-23	5 19.9 (1.92) 17-22	3 21.8 (0.76) 21-23
Overall	N=30		N=35	
n Mean (SD) Min-Max	29 21.7 (3.06) 17-29	30 23.1 (1.62) 19-27	34 21.2 (3.11) 16-29	31 23.0 (1.62) 19-27

Table 14*: Non-inferiority and superiority analyses on blood bicarbonate level (PP and ITT sets)*

	PP Set		ITT set	
	SoC	ADV7103	SoC	ADV7103
n	29		34	31
Mean difference (SD) [PP set] – LS mean [ITT set]	1.4195 (2.647)		1.636	
95% CI	(0.4128, 2.4263)		(0.6679, 2.6034)	
Non-inferiority p-value	<0.0001			
Superiority p-value	0.0037		0.0008	

Secondary efficacy endpoints

- *(Non-)responders*

The efficacy of ADV7103 vs. SoC was supported by the analyses of patients who presented with blood bicarbonate levels below the lower limit of normal as defined by the local laboratories. A higher number of patients with on ADV7103 treatment (90%; 26/29) vs patients on SoC treatment (45%; 13/29) were responders based on the definition of a mean level above normal blood bicarbonate range (derived from the table below). This was 75% vs 38% (non-responders defined as one measurement below normal range) and 97% vs 76% (non-responders defined as all non-missing measurements below normal level) for ADV7103 and SoC

Table 15*: Non-responder patients (n [%]) presenting the mean value of blood bicarbonate below the normal lower limit on Day 2 t0, Day 3 t0 and Day 4 t0 (PP and ITT sets)*

PP Set			ITT Set		
SoC	ADV7103	n/N (%)	SoC	ADV7103	n/N (%)
No	No	13/29 (45%)	No	No	13/30 (43%)
Yes	No	13/29 (45%)	Yes	No	14/30 (47%)
No	Yes	0 (0.0%)	No	Yes	0 (0.0%)
Yes	Yes	3/29 (10%)	Yes	Yes	3/30 (10%)
p-value[a]		<0.001	p-value[a]		<0.001

In all cases, the McNemar's test determined that there was a statistically significant difference between the two treatments, indicating a greater probability of non-responders occurring with SoC.

- *24 hours analyses of blood bicarbonate*

Blood bicarbonate parameters of Day 5 were measured at t0h, t4h, t8h, t12h (before the evening daily dose), t16h, t20h, t22h, t23h t24h (just before the next morning daily dose) for adults and t0h, t4h, t8h, t12h (before the evening daily dose), t16h, t20h, t24h (just before the next morning daily dose) for adolescents and children.

No meaningful differences were observed for each age subset. The analyses of mean differences between ADV7103 and SoC for AUC0-12h, AUC0-24h, Cmin, and fluctuation did not achieve statistical significance in the PP set and the ITT set (see table below).

AUC0-12h: mean difference (95% CI) between treatments: 1.5 (-14.32, 17.32) mmol.h/L in favour of ADV7103 (N=15), p=0.8418 (PP set).

AUC0-24h: mean difference (95% CI) between treatments: -0.44 (-33.01; 32.12) mmol.h/L in favour of SoC (N=5), p=0.9718 (PP set).

Cmin: mean difference (95% CI) between treatments: -0.68 (-2.11, 0.75) mmol/L in favour of SoC (N=23), p=0.3370 (PP set).

Fluctuation over 24 h: mean difference (95% CI) between treatments: 0.4870 (-0.97, 1.94) mmol/L in favour of SoC (N=23), p=0.4949 (PP set)

Table 16*: Venous blood bicarbonate Day 5 parameters (PP and ITT sets)*

	PP Set		ITT Set	
	SP I (SoC)	SP III (ADV7103)	SP I (SoC)	SP III (ADV7103)
Overall	N=24		N=26	
AUC_{0-12h} (mmol.h/L)	n=21	n=17	n=23	n=17
Mean (SD)	270.9 (39.71)	270.6 (27.26)	266.6 (40.86)	270.6 (27.26)
Min-Max	201-345	229-326	201-345	229-326
AUC_{0-24h} (mmol.h/L)	n=14	n=7	n=16	n=7
Mean (SD)	567.9 (71.67)	536.8 (44.45)	550.6 (83.40)	536.8 (44.45)
Min-Max	433-687	458-586	384-687	458-586
C_{min} (mmol/L)	n=24	n=23	n=26	n=23
Mean (SD)	20.4 (3.30)	19.8 (3.72)	20.1 (3.43)	19.8 (3.72)
Min-Max	14-26	13-25	14-26	13-25
Fluctuation (mmol/L)	n=24	n=23	n=26	n=23
Mean (SD)	4.3 (1.76)	4.8 (2.69)	4.2 (1.73)	4.8 (2.69)
Min-Max	2-10	1-10	2-10	1-10

- *Potassium levels and proportion of patients with hypokalaemia.*

The average pre-morning dose plasma potassium levels (Day 2 to Day 4) at steady state, at SP I (SoC) and SP III (ADV7103) are summarised in Table 22 by age subset for the PP. Overall, the normalisation of blood potassium was achieved with both ADV7103 and SoC, with a slightly higher mean average blood potassium level for ADV7103.

Figure 11*: Kalaemia (pre-dose Day 2-4) – B21CS (PP Set)*

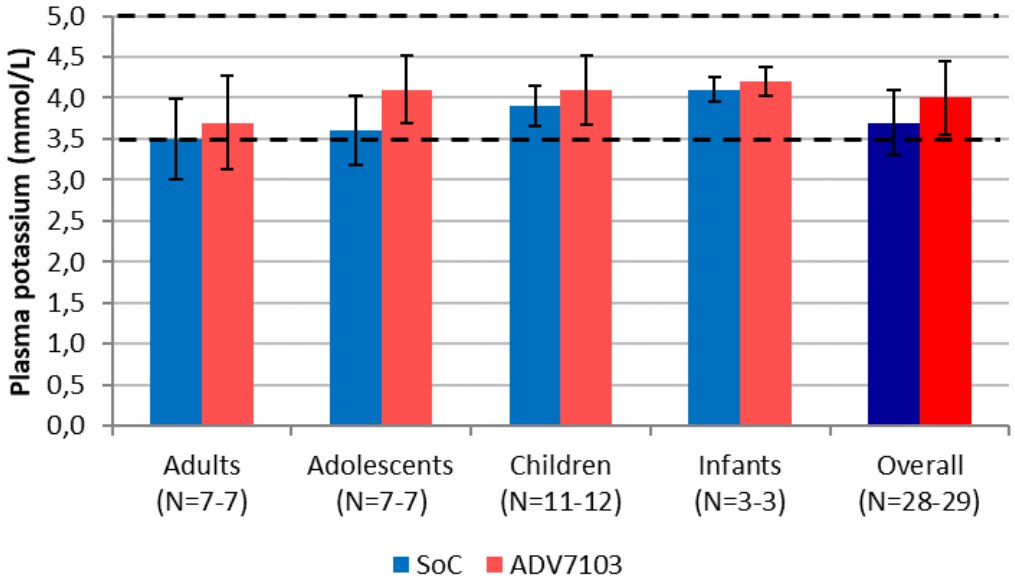


Table 17*: Summary of average plasma potassium levels (mmol/L) (pre-dose Day 2 to Day 4) after SoC and ADV7103 treatment (PP and ITT sets)*

	PP set		ITT set	
	SP I (SoC)	SP III (ADV7103)	SP I (SoC)	SP III (ADV7103)
Adults, ≥18 years old	N=7		N=7	
n Mean (SD) Min-Max	7 3.5 (0.49) 3.0-4.0	7 3.7 (0.57) 3.0-5.0	7 3.5 (0.49) 3.0-4.0	7 3.7 (0.57) 3.0-5.0
Adolescents, from 12-17 years inclusive	N=7		N=9	
n Mean (SD) Min-Max	7 3.6 (0.42) 3.0-4.0	7 4.1 (0.41) 4.0-4.0	9 3.7 (0.53) 3.0-4.0	7 4.1 (0.41) 4.0-4.0
Children, from 4-11 years inclusive	N=12		N=13	
n Mean (SD) Min-Max	11 3.9 (0.25) 3.0-4.0	12 4.1 (0.42) 3.0-5.0	12 3.9 (0.27) 3.0-4.0	13 4.1 (0.40) 3.0-5.0
Infants, from 6 months-3 years old inclusive	N=3		N=5	
n Mean (SD) Min-Max	3 4.1 (0.15) 4.0-4.0	3 4.2 (0.18) 4.0-4.0	5 4.2 (0.18) 4.0-4.0	3 4.2 (0.18) 4.0-4.0
Overall	N=30		N=34	
n Mean (SD) Min-Max	28 3.7 (0.40) 3.0-4.0	29 4.0 (0.45) 3.0-5.0	33 3.8 (0.44) 3.0-4.0	30 4.0 (0.44) 3.0-5.0

Responder rates of normalisation of potassium levels were similar between SoC and ADV8103 as can be derived from the table below (82% (23/28) for both).

Table 18*: Patients with hypokalaemia after 4 to 5 days of SoC and ADV7103 treatment (PP and ITT sets)*

Study product		PP Set	ITT Set
SoC	ADV7103	n/N (%)	n/N (%)
No	No	21/28 (75%)	22/29 (76%)
Yes	No	2/28 (7.1%)	2/29 (6.9%)
No	Yes	2/28 (7.1%)	2/29 (6.9%)
Yes	Yes	3/28 (11%)	3/29 (10%)
p-value[a]		1.000	1.000

- *Urine parameter: Hypercalciuria (expressed by urine calcium/creatinine ratio value above the normal ranges) (post-hoc analysis)*

Overall, only 3 patients presented hypercalciuria, 1 after SoC, 1 after ADV7103 and 1 after both treatments, representing for each case 3.6% of the patients in the PP set and 3.3% of the patients in the ITT set.

Table 19*: Patients (n [%]) with hypercalciuria after 4 to 5 days of treatment, in SP I and in SP III – urine spot (PP set and ITT set)*

PP Set			ITT Set		
Paediatric population					
SoC	ADV7103	n/N (%)	SoC	ADV7103	n/N (%)
No	No	18/21 (86%)	No	No	20/23 (87%)
Yes	No	1/21 (4.8%)	Yes	No	1/23 (4.3%)
No	Yes	1/21 (4.8%)	No	Yes	1/23 (4.3%)
Yes	Yes	1/21 (4.8%)	Yes	Yes	1/23 (4.3%)
p-value[a]		1.000	p-value[a]		1.000
Whole population (post-hoc analysis)					
SoC	ADV7103	n/N (%)	SoC	ADV7103	n/N (%)
No	No	25/28 (89%)	No	No	27/30 (90%)
Yes	No	1/28 (3.6%)	Yes	No	1/30 (3.3%)
No	Yes	1/28 (3.6%)	No	Yes	1/30 (3.3%)
Yes	Yes	1/28 (3.6%)	Yes	Yes	1/30 (3.3%)
p-value[a]		1.000	p-value[a]		1.000

- *Urine parameter: Hypocitraturia (expressed by urine citrate/creatinine value below the normal ranges) (post-hoc analysis)*

The proportion of non-responder patients lacking normalisation of citraturia after SoC treatment relative to ADV7103 treatment (41% versus 5.9% in ITT set).

Table 20*: Patients (n [%]) with hypocitraturia after 4 to 5 days of treatment, in SP I and in SP III – urine spot (PP and ITT sets)*

PP Set			ITT Set		
Paediatric population					
SoC	ADV7103	n/N (%)	SoC	ADV7103	n/N (%)
No	No	0 (0%)	No	No	0 (0%)
Yes	No	4/11 (36%)	Yes	No	5/12 (42%)
No	Yes	0/0 (0.0%)	No	Yes	0/0 (0.0%)
Yes	Yes	7/11 (64%)	Yes	Yes	7/12 (58%)
p-value[a]		NA[b]	p-value[a]		NA[b]
Whole population (post-hoc analysis)					
SoC	ADV7103	n/N (%)	SoC	ADV7103	n/N (%)
No	No	0 (0%)	No	No	0 (0%)
Yes	No	6/16 (38%)	Yes	No	7/17 (41%)
No	Yes	1/16 (6.3%)	No	Yes	1/17 (5.9%)
Yes	Yes	9/16 (56%)	Yes	Yes	9/17 (53%)
p-value[a]		0.125	p-value[a]		0.070

- *Abnormally high UCa/UCi value (expressed in mg/mg) and with UCa/UCi value (expressed in mmol/mmol) above the risk threshold for lithogenesis (post-hoc analysis)*

The number of patients with normal UCa/UCi values was higher for the ADV7103 with 11/19 (58%) patients compared to 3/19 (16%) patients in the SoC treatment group.

Table 21*: Patients (n [%]) with UCa/UCi values abnormally high and at risk of lithogenesis on Day 4 t0 and Day 5 t0, in SP I and in SP III (PP and ITT sets) – Post-hoc analyses*

PP Set			ITT Set		
UCa/UCi value abnormally high					
SoC	ADV7103	n/N (%)	SoC	ADV7103	n/N (%)
No	No	1/19 (5.3%)	No	No	2/20 (10%)
Yes	No	9/19 (47%)	Yes	No	9/20 (45%)
No	Yes	1/19 (5.3%)	No	Yes	1/20 (5.0%)
Yes	Yes	8/19 (42%)	Yes	Yes	8/20 (40%)
p-value[a]		0.021	p-value[a]		0.021
UCa/UCi value considered as risk of lithogenesis (>3 mmol/mmol)					
SoC	ADV7103	n/N (%)	SoC	ADV7103	n/N (%)
No	No	2/19 (11%)	No	No	3/20 (15%)
Yes	No	9/19 (47%)	Yes	No	9/20 (45%)
No	Yes	1/19 (5.3%)	No	Yes	1/20 (5.0%)
Yes	Yes	7/19 (37%)	Yes	Yes	7/20 (35%)
p-value[a]		0.021	p-value[a]		0.021

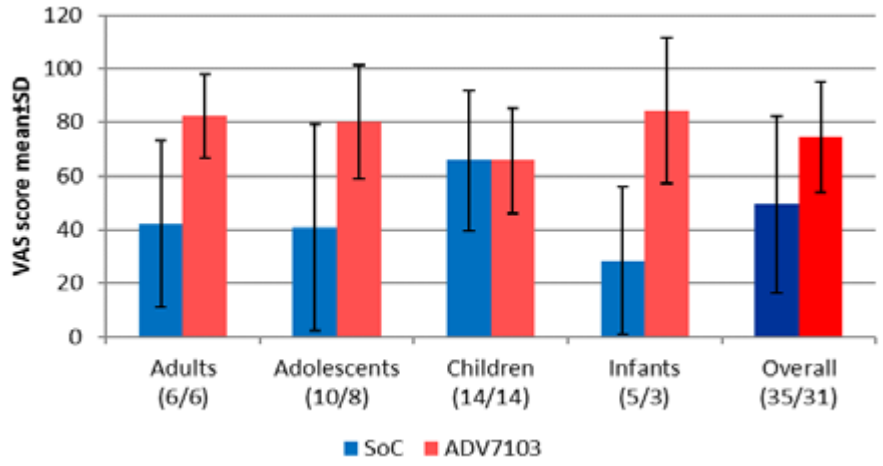
Acceptability analysis

Palatability, ease of administration and ease of swallowing were evaluated by VAS score.

Palatability

Overall, palatability was better with ADV7103 than with SoC, with mean (SD) scores of 74.4 (20.60) mm vs. 49.3 (33.00) mm. This was similar across age subsets, except for children (from whom palatability was similar for the two treatments) (Figure 12).

Figure 12*: Palatability (AAS)*

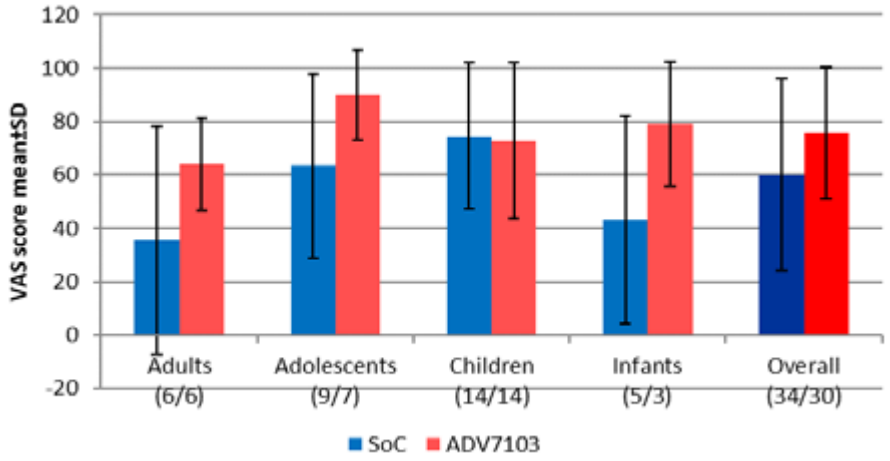


The mixed model showed a superiority of ADV7103 vs. SoC in terms of palatability (mean difference: 24.961 mm [95% CI: 10.6818, 39.2406]). The overall pattern of response shifted to a more favourable profile once patients were taking ADV7103. With their SoC, 40.00% of patients (14/35) expressed at least some degree of dislike for the taste of their medication whereas vs. only 3.23% of patients (1/31) with ADV7103. Conversely, the proportion of patients who showed to like the taste of their medication to some extent was 37.14 % (13/35) with SoC vs. 67.74% (21/31) with ADV7103. Overall, 61.3% of patients (19/31) exhibited a rating improvement ≥1 category and 48.4% of patients (15/31) ≥2 categories.

Ease of Administration

Overall, mean (SD) ease of administration was greater with ADV7103 than SoC, without reaching statistical significance: 75.7 (24.71) mm vs. 60.1 (35.89) mm (mean difference: 15.477 mm [95% CI -0.8782, 31.8329]), consistent across age subsets, except for children (for whom ease of administration was similar for the two treatments) (Figure 13).

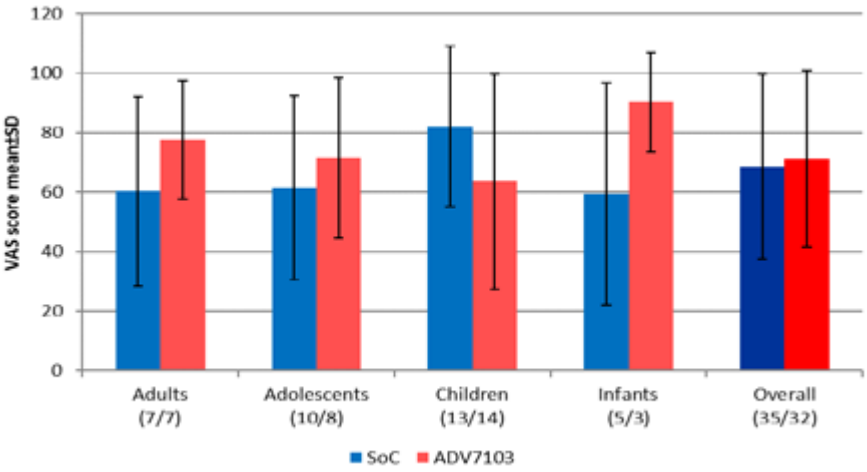
Figure 13*: Ease of administration (AAS)*



Ease of Swallowing

Overall, mean (SD) ease of swallowing was similar to ADV7103 and SoC: 71.2 (29.70) mm and 68.6 (30.98) mm, respectively. Adults, adolescents and infants reported easier swallowing with ADV7103 than with SoC, while children reported easier swallowing with SoC than with ADV7103. Acceptability of the alkalising salts was significantly improved with ADV7103 compared to SoC (Figure 14)

Figure 14*: Ease of swallowing (AAS)*



Ancillary analyses

Sensitivity analysis on primary efficacy endpoint - bicarbonataemia

The sensitivity analysis (two-sample t test for in the PP and ITT sets for the comparison vs. historical baseline data in untreated patients) showed that there were differences between the treatment groups (ADV7103 and reference), with an estimated difference (95% CI) of 6.96 (5.60, 8.32) mmol/L for the

PP set and of 6.92 (5.56, 8.27) mmol/L for the ITT set, confirming the robustness of the non-inferiority analysis.

Table 22*: Sensitivity analyses on blood bicarbonate level, two sample t-test (PP and ITT sets)*

	PP Set	ITT set
N Reference / ADV7103	18 / 30	18 / 31
Mean (SD) Reference / ADV7103	16.10 (2.50) / 23.060 (1.625)	16.10 (2.5) / 23.015 (1.617)
LS Mean difference	6.960	6.915
95% CI	(5.6033, 8.3167)	(5.5632, 8.2669)

Subgroup analyses by type of SOC treatment

Subgroup analyses of the primary endpoints were conducted by comparing ADV7103 treatment with SoC treatment based on bicarbonate, combination citrate + bicarbonate, or citrate or comparison to SoC treatment based on sodium or potassium.

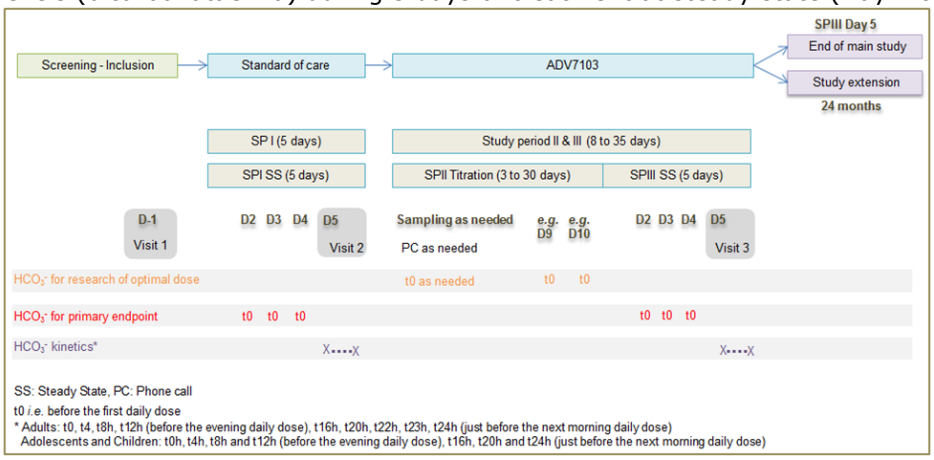
The mean difference (95% CI) between treatments was 2.28 (0.72; 3.84) mmol/L, p<0.0001 versus bicarbonate, 2.14 (0.42; 3.85) mmol/L, p<0.0001 versus combination citrate + bicarbonate, and -0.07 (-2.39; 2.26) mmol/L, p=0.0212 versus citrate. Similar results were obtained in the ITT set. Statistically significant superiority was not shown.

The mean difference (95% CI) between treatments was 0.33 (-1.35, 2.01) mmol/L, p=0.0018 versus potassium, 2.73 (1.25, 4.21) mmol/L, p<0.0001 versus potassium+sodium, and 1.90 (-1.04, 4.84) mmol/L, p=0.0071 versus sodium. Non-inferiority was demonstrated versus all SoC types in the PP and ITT sets, and superiority of ADV7103 over SoC was demonstrated versus potassium+sodium SoC in the PP and ITT sets. Similar results were obtained in the ITT set.

Summary of the main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 23*: Summary of efficacy for trial B21CS*

Title: Multicentre, open-label, non-inferiority sequential study, evaluating the efficacy, safety, tolerability and acceptability of ADV7103 compared to standard of care in distal renal tubular acidosis patients.	
Study identifier	B21CS
Design	This was a multicentre, open-label, non-inferiority, sequential Phase II/III study to compare the efficacy, safety, tolerability and acceptability of ADV7103 with SoC. The study included three study phases (SP): • SP I: patients were to receive their usual SoC. • SP II: patients switched from SoC to ADV7103, titration phase to optimal dose • SP III: patients were to receive ADV7103 twice a day at the fixed optimal dose identified during SP II. Patients' bicarbonataemia and other defined parameters were assessed. Primary objective was to evaluate the relative efficacy of ADV7103 and SoC on correcting metabolic acidosis as measured by pre-morning dose blood bicarbonate levels (bicarbonataemia) during 3 days of treatment at steady state (Day 2 to Day 4). 
	Duration of main phase: — Maximum of 40 days Screening — 1 Day SP I (SoC) — 5 days with SoC SP II (titration phase) — 3 up to 30 days with ADV7103 SP III — 5 days with ADV7103
Hypothesis	The calculation was performed by means of a one-sided paired-t-test at the 2.5% significance level with an SD of 4.1 mmol/L and a non-inferiority margin of -2.5 mmol/L for the mean difference in bicarbonate levels between ADV7103 and SoC.

Treatments groups	Subset 1		Adults of age ≥ 18 years (full evaluation; at least N=4) Enrolment following a staggered approach. At least a total of 4 patients of subsets 1 and 2 had to have completed the study before starting the enrolment of patients of Subset 3. At least 4 patients of Subset 3 had to have completed the study before starting the enrolment of patients of Subset 4
	Subset 2		Adolescents of age between 12 and 17 years inclusive (full evaluation; at least N=4)
	Subset 3		Children of age between 4 and 11 years inclusive (full evaluation if feasible; at least N=4)
	Subset 4		Infants and children of age between 6 months and 3 years inclusive (full evaluation if feasible; at least N=4)
Endpoints and definitions	Primary endpoint	BC level at steady state	Average bicarbonate blood level during 3 days of treatment at steady state with ADV7103 and SoC (Day 2 to Day 4, before the first daily dose, of SP III and SP I, respectively).
	Secondary efficacy endpoints	Number/proportion of patients with abnormal BC level	Number/proportion of non-responder patients with abnormally low bicarbonataemia value (i.e. patients with a mean blood bicarbonate value below the lower normal value on Day 2 t0, Day 3 t0 or Day 4 t0).
		AUC0- 12h AUC0-24h Cmin Fluctuation	Area under the curve from t0 to t12h (AUC0-12h) on Day 5 AUC from t0 to t24h (AUC0-24h) on Day 5 Minimum concentration (Cmin) over 24 h on Day 5. Fluctuation: Maximum minus minimum concentrations over 24 h on Day 5
		Number of patients with hypokalaemia	Number of patients with a hypokalaemia after 4 to 5 days of treatment at steady state.
		Number of patients with hypercalciuria	Number of patients with a hypercalciuria after 4 to 5 days of treatment at steady state.
		Number of patients with hypocitraturia	Number of patients with a hypocitraturia after 4 to 5 days of treatment at steady state.

		Number of patients with abnormal UCa/UCi ratio at steady state	Number of patients with abnormally high urine calcium/citrate (UCa/UCi) ratio (expressed in mg/mg) and with UCa/UCi expressed in mmol/mmol above the risk threshold for lithogenesis after 4 to 5 days of treatment at steady state (post-hoc analyses).
Database lock	-		
Results and Analysis			
Analysis description	**Primary Analysis - Efficacy**		
Analysis population and time point description	PP Set: all patients who completed the study with no major protocol deviations having an impact on efficacy. In case of any missing bicarbonate blood concentration data on Day 2 t0, Day 3 t0 or Day 4 t0, the protocol deviation was not to be considered major if a mean value for the primary endpoint in the period could be calculated according to a specific replacement algorithm. Data have been shown below with PP set. ITT Analysis Set: all patients receiving at least one dose of the study drug at steady state (SP I/SP III) and with at least one efficacy assessment.		

Descriptive statistics and estimate variability	Treatment group	ADV7103	SoC	
	Number of subjects	N=30	N=30	
	Bicarbonate level at steady state (mean (SD))	23.1 (1.62)	21.7 (3.06)	Mean difference (SD) (95% CI) 1.4195 (2.647) (0.4128, 2.4263) Non-inferiority value <0.0001
	Number/proportion of patients with abnormal Bicarbonate level (n/N (%))	3/29 (10%)	16/29 (55%)	p=<0.001
	AUC0- 12h (mean (SD))	270.6 (27.26)	270.9 (39.71)	p=0.8418
	AUC0-24h	536.8 (44.45)	567.9 (71.67)	p=0.9718
	Cmin	19.8 (3.72)	20.4 (3.30)	p=0.3370
	Fluctuation	4.8 (2.69)	4.3 (1.76)	p=0.3370
	Number of patients with hypokalaemia (n/N (%))	5/28 (18%)	5/28 (18%)	p=1.000

	Number of patients with hypercalciuria (n/N (%))	2/28 (7%)	2/28 (7%)	p=1.000
	Number of patients with hypocitraturia (n/N (%))	10/16 (63%)	15/16 (94%)	p=0.125
	Number of patients with abnormal UCa/UCi ratio at steady state (n/N (%))	8/19 (42%)	16/19 (84%)	p=0.021

Analysis performed across trials (pooled analyses and meta-analysis)

No analysis performed across trials were provided.

Clinical studies in special populations

No clinical studies in special populations were provided.

Supportive study

Open label extension Study B22CS

A multicentre, open-label (OLE), extension study, evaluating the safety and tolerability and the efficacy of ADV7103 at long term in distal renal tubular acidosis patients. Patients completing Study B21CS were allowed to enter the OLE study (Study B22CS) and continue their treatment with ADV7103 at the optimal dose determined during Study B21CS (and further adapted if needed) for at least 24 months (M24). The dose could be readjusted if the Investigator considered it necessary according to the laboratory results of the patient.

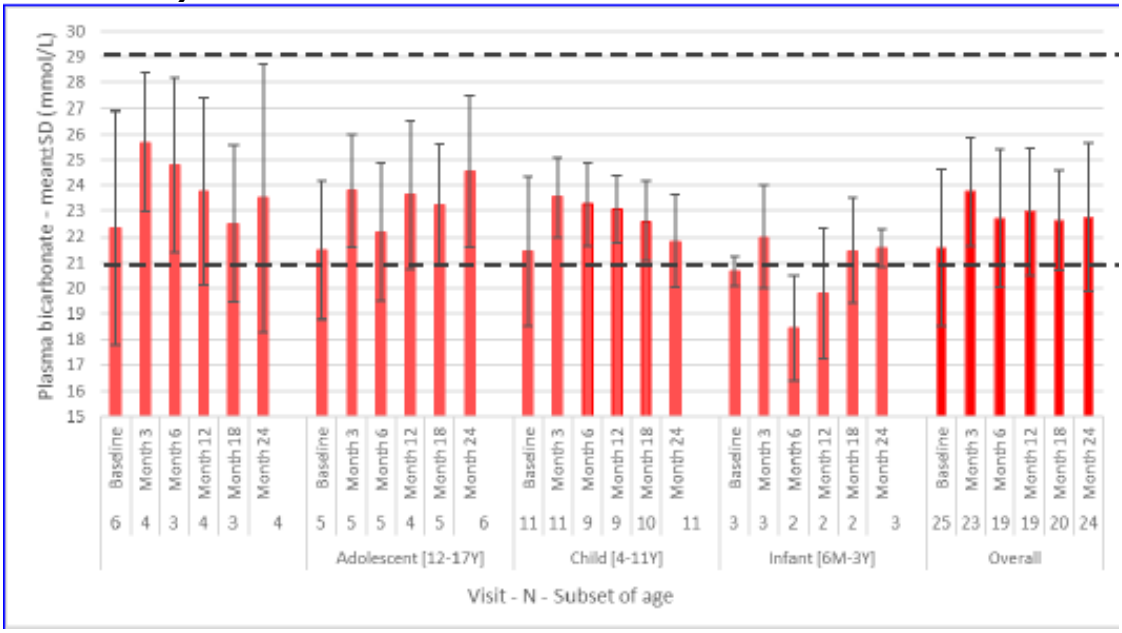
The primary objective of the study was to evaluate the long-term safety and tolerability of ADV7103 as measured by AEs. The secondary objectives of this study were to evaluate the long-term efficacy of ADV7103 on correcting metabolic acidosis as measured by bicarbonataemia, hypocitraturia, hypercalciuria and crystalluria, the long-term paraclinical and biological safety of ADV7103, the long-term compliance to ADV7103, and the long-term effects of ADV7103 on kalaemia, hyperphosphaturia, hypermagnesuria. Further, the long-term effects of ADV7103 on nephrocalcinosis, nephrolithiasis, bone remodelling, rickets and osteomalacia, respectively in the paediatric and adult population, growth in the paediatric study population and on pubertal maturity in the relevant paediatric study population and on QoL, and the long-term treatment acceptability of ADV7103 were examined as exploratory endpoints.

A total of 30 patients (six adults, eight adolescents, 13 children and three infants) entered the OLE study and 29 of these had data collected up to M24. One adult withdrew from the study after M12 for personal reasons.

- Long-term Effects of ADV7103 on Correcting Metabolic Acidosis as Measured by Bicarbonataemia

The applicant reported that overall, when blood tests were done before study drug intake, 13 patients (52.0%) at baseline, 21 patients (91.3%) at M3, 12 patients (63.2%) at M6, 15 patients (78.9%) at M12, 17 patients (85.0%) at M18 and 15 patients (62.5%) at M24 had plasma bicarbonate levels in the normal range (Figure 15).

Figure 15*: Mean (SD) plasma bicarbonate over time, by subset of age and overall - B22CS Study*

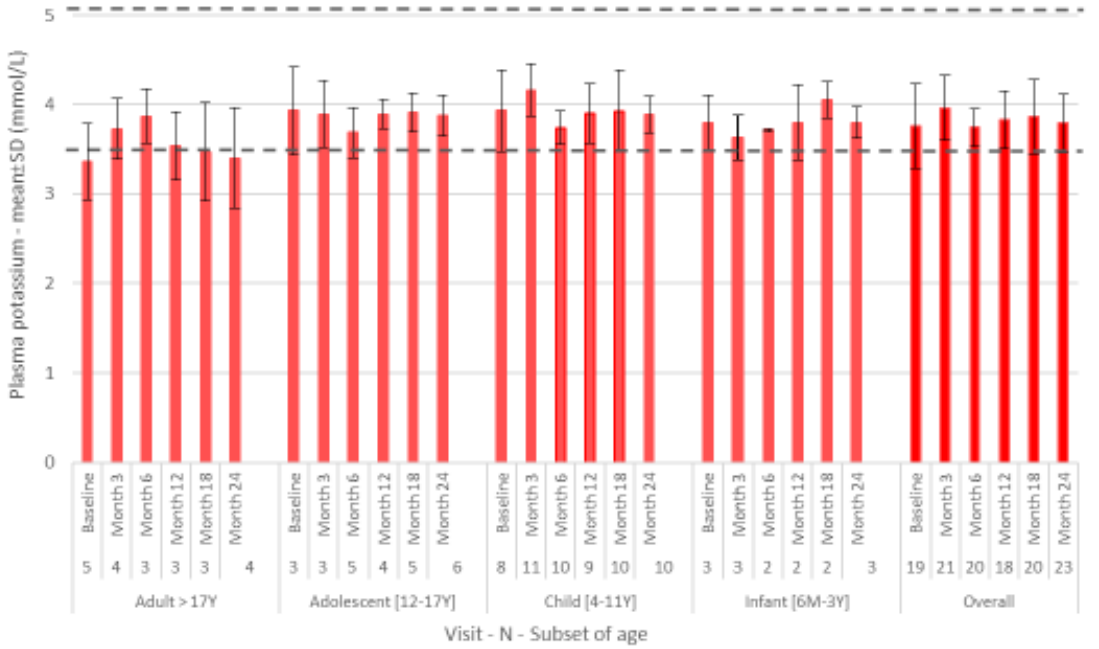


There was a small mean±SD increase from baseline in plasma bicarbonate of 1.96±3.55 mmol/L at M3, 1.31±4.16 mmol/L at M6, 1.78±3.07 mmol/L at M12, 0.99±3.47 mmol/L at M18 and 0.96±3.20 mmol/L at M24 overall, with the highest increase in the adult group. The adolescent and infant groups were the only groups showing a decrease at some visits.

- Potassium levels

Overall, for non-haemolysed blood samples from blood tests done before study drug intake, 16 patients (84.2%) at baseline, 20 patients (95.2%) at M3, 19 patients (95.0%) at M6, 17 patients (94.4%) at M12, 18 patients (90.0%) at M18 and 21 patients (91.3%) at M24 had clinically normal plasma potassium levels.

Figure 16*: Mean (SD) plasma potassium over time, by subset of age and overall - B22CS Study (EAS)*



Three patients overall (15.8%) had abnormally low plasma potassium at baseline and this figure was reduced at M3, M6, M12, M18 and M24 (4.8%, 5.0%, 5.6%, 10.0% and 8.7%, respectively).

- Citraturia

Overall, compared to B21CS Study where 7 (41.0%) of the patients had normal UCi/UCr after ADV7103 treatment, 7 patients (35.0%) had citraturia (UCi/UCr) in the normal ranges at baseline, 10 patients (52.6%) at M3, 9 patients (40.9%) at M6, 7 patients (29.2%) at M12, 14 patients (51.9%) at M18 and 10 patients (41.7%) at M24.

- Calciuria

- Urine calcium/creatinine ratio

All patients had UCa/UCr within the normal range at all visits, except for one to two patients who presented abnormally high values at M3 and subsequent visits.

- Urine calcium/citrate ratio

Compared to B21CS Study where 11 (55.0%) of the patients had UCa/UCi values in the normal range after ADV7103 treatment; in B22CS Study, overall 9 patients (45.0%) at baseline, 11 patients (57.9%) at Month 3, 9 patients (47.4%) at Month 6, 10 patients (43.5%) at Month 12, 10 patients (38.5%) at Month 18 and 9 patients (37.5%) at Month 24 had UCa/UCi in the normal range.

- Other parameters

Twenty-five patients (92.6%) overall had UPh/UCr in the normal range at baseline, and this was stable during the study. Most patients overall had UMg/UCr in the normal range from M1 to M24, with fluctuations of one to 4 patients with levels above normal range during follow-up.

- Crystalluria

Thirteen patients overall (50.0% of the 26 assessed, including 3 adults, 4 adolescents, 5 children and 1 infant) had a positive result for crystalluria at M24. Crystal species reported were amorphous

carbonated calcium phosphate (ACCP) in 7 cases (53.8%), ammonium hydrogen urate in 3 cases (23.1%) and brushite, calcium oxalate and struvite, each in 1 case (7.7%).

The majority of patients overall had urine pH between 7.0 and 8.0 ranging from 64% to 76%.

- Treatment compliance

Overall, 18 of the 29 patients (62.1%) remaining in the study at M24 had compliance of >90%, 5 patients (17.2%) had compliance of 75-90%, 6 patients (20.7%) had compliance of 50-74%, and there were no patients with compliance of <50%. Compliance was in the adult and child groups (with a compliance ≥75% in 100% and 84.6% of patients, respectively), and good in the adolescent and infant groups (with a compliance ≥75% in 62.5% and 66.7% of patients, respectively).

- Nephrocalcinosis

Overall, most patients presented with nephrocalcinosis at both baseline (25 patients; 86.2%) and M24 (28 patients; 96.6%). Two patients (one adolescent and one infant) developed nephrocalcinosis during the 24 months of follow-up, while they were not always fully compliant to the treatment.

- Nephrolithiasis

Overall, nephrolithiasis was only seen in small numbers of patients, and the proportion of patients presenting with this condition was similar at baseline (six patients; 20.7%) and M24 (five patients; 17.2%).

- Bone Remodelling

Bone alkaline phosphatase levels in the normal range fluctuated from 75% to 95%, phosphorus levels in the normal range from 83% to 100% and blood calcium levels in the normal range from 93% to 100% during the study period. Hydroxy-vitamin D levels in the normal range ranged from 43% to60% and thus considerable proportion had low Hydroxy-vitamin D levels. Some patients (17/30; 56.7%) received doses of 25-dihydroxy-vitamin D at some time points during the study. For 1α,25-dihydroxy-vitamin D 80% to 100% were in the normal range during the study. For parathyroid hormone 88% to 100% were in the normal range during the study. For calcitonin levels 83% to 100% were in the normal range. The majority of patients had normal Z-scores (above -2.0) at both baseline and M24 for BMD in the spine region, hip region and whole-body region. No adults presented with osteomalacia and one infant presented with rickets, at baseline. By M24, no patients presented with either osteomalacia or rickets.

- Growth in Children

The majority of patients in all age groups and at all visits were in the ±2SD range and in the ±3SD range for weight, height and BMI.

- Growth velocity

Considering adolescents, growth velocity decreased from M3-M1 to M24-M18. Growth velocity for children and infants remained relatively constant during the study. Growth velocity was normal for the majority of patients overall (17 patients; 70.8%) at M3, with seven patients (one adolescent, four children and two infants) having a low value. By M24, all patients had normal (18 patients) or low (six patients) growth velocity. The six patients reported with low values comprised two adolescents, three children and one infant.

- Pubertal Maturity

Incidences of early pubertal maturity/growth regarding pubic hair were reported in one patient at M1, two patients at M3, one patient at M6, two patients at M12, three patients at M18 and one patient at

M24. Additionally, late pubertal maturity/growth was reported in one patient at each visit from M12. Incidences of early pubertal maturity/growth regarding penis/breast were reported in two patients at M1, two patients at M3, one patient at M6, one patient at M12, three patients at M18 and one patient at M24. Almost all the cases of abnormal pubertal maturity/growth occurred in the adolescent group, except for early pubertal maturity/growth (both parameters) in one patient in the child group at each visit from M18.

- Treatment Acceptability

At the end of the study (M24), the question asked to the patient (or to the caregiver) and repeated for each topic was *"As compared to your previous alkalinising treatment, what is/are the reason(s) for which you prefer keep ADV7103 rather than your previous alkalinising product?"*

Overall, high mean VAS scores were obtained for improvement in efficacy (91.2%), improvement in safety (72.2%), more appropriate formulation (83.9%), more convenient number of daily dose intakes (90.2%) and improvement in taste (68.6%).

All patients had an improved efficacy score of ≥50% and all but two patients (8.7%), both children, had an improved efficacy score ≥75%. An improved safety score of ≥50% was reported for 22 patients (75.9%) overall and a score of ≥75% in 19 patients (65.5%). The same trend was seen in the individual groups by age, except for infants, where all patients had a safety score ≥75%. More appropriate formulation scores ≥50% were obtained for all children and infants, all but one adolescent (i.e. seven patients (87.5%)) and three adults (60.0%). The same results were observed for scores ≥ 75% for adults and adolescents, and all but one of the children (12 patients; 92.3%) and infants (two patients; 66.7%) reached this score. More convenient number of daily dose intake scores were ≥50% for all adults, adolescents and infants, and 11 children (84.6%). Considering the higher threshold, all adults and infants had scores ≥75%, as did seven adolescents (87.5%) and ten children (76.9%).

Better taste scores of ≥50% were obtained for all infants (all scores also ≥75%), ten children (76.9%) half of adolescents (four patients; 50.0%) and four adults (80.0%). Scores ≥75% were also obtained for eight children (61.5%), three adolescents (37.5%) and three adults (60.0%).

- Quality of Life

The change of alkalising treatment from their SoC to ADV7103 led to an average improvement in their QoL using a 100-mm VAS of 80.7% at M6 and 88.9% at M24 (98.6% in the adult group, 84.6% in the adolescent group, 86.5% in the child group and 94.7% in the infant group at M24).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

ADV7103 (Sibnayal) is a FCMP of prolonged release granules of potassium citrate and potassium hydrogen bicarbonate (2 different sachets of 8 mEq and 24 mEq). The effect of ADV7103 has been evaluated in the B21CS study, a multicentre, open-label, non-inferiority, sequential phase II/III study and aimed to evaluate the efficacy, safety, tolerability and acceptability of ADV7103 twice daily compared to SoC (variety of use of salts 3 to 6 times a day) in dRTA patients from different age categories of 6 months to adulthood. In this respect, SoC treatment cannot be exactly defined as no guidance on the preferred treatment exists and different medications have thus been used. The study included three study phases (SP) as follows: enrolled patients were to continue their SoC without modification during a 5-day period (SP1), and were subsequently crossed-over and titrated with ADV7103 to an optimal dose for up to 30 days (SP II) to control their bicarbonate levels, followed by a

5 days steady state period (SPIII) once stable control was reached. Effect of treatment was compared based on the steady state of SoC (SPI) versus steady state of ADV7103 (SPIII).

Although the study design complied generally with earlier CHMP/SAWP and EMA/PDCO advices (February 2013 (EMA/CHMP/SAWP/69792/2013); EMA Decision: P/0355/2018)), several issues to the study design are noticed that may limit conclusions on any potential non-inferiority and superiority claim. The assumption is made that patients were on an optimal SoC dose based on their long-term usual care without any interference during the 5 days follow-up. However, a titration phase (up to 30 days) for ADV7103 has been applied to establish the optimal dose, which could inappropriately favour ADV7103 in comparison to SoC. Secondly, the sequential cross-over design between SoC and ADV7103 further limits evaluation and interpretation for direct comparison of SoC with ADV7103.

Considering the rarity of the disease, a limited number up to 32 patients were planned to be enrolled in the study. The proposed sample size consisted of at least 24 dRTA patients fully evaluable and stratified in 4 subsets of age, with at least 4 subjects in each of the 4 sub-sets and the staggered approach starting with older paediatric populations. The sample size was discussed and agreed in the CHMP/SAWP (EMA/CHMP/SAWP/69792/2013) and PIP (EMA Decision: P/0355/2018), and based on the assumptions, the sample size calculation is correct.

The primary endpoint, the difference between average bicarbonate levels for ADV7103 and SOC at steady state, allows for evaluation of short-term correction of metabolic acidosis, and is acceptable. This is compared with a one-sided t-test, with non-inferiority declared if the corresponding CI was above the non-inferiority margin. For setting the non-inferiority margin, the guidelines were followed, using statistical reasoning and clinical judgement. The statistical reasoning is based on limited data present, which may lead to uncertainties. Nevertheless, the margin of 2.5 mmol/L can be accepted as it falls within the standard variability of bicarbonate in these patients and was judged adequate in a survey in key opinion leaders and by the PDCO. Although, limitations to the study design, as discussed, may limit a conclusion on any potential non-inferiority claim the CHMP considers a clinically relevant therapeutic effect of the product.

Similar limitations in design to conclude on any non-inferiority claim are also applicable for any potential superiority claim.

Secondary endpoints of responder analysis are helpful in the further interpretation of the data. A 24-hour evaluation on Day 5 of steady state could be helpful to interpret the 24-hour coverage of metabolic acidosis control. Evaluation of other electrolytes likely to be dysregulated in dTRA including hypokalaemia, hypercalciuria and hypocitraturia are also relevant. The endpoint on acceptability is important for assessment of the formulation and its advantages on taste, daily dosing intervals etc. These secondary categorical endpoints using 2x2 tables and McNemar's test and continues endpoints using t-tests are both considered standard and acceptable. However, no multiplicity-adjustments were considered for the secondary endpoints; therefore, they are regarded as descriptive and no conclusions based on statistics can be drawn.

Generally, the inclusion criteria of a diagnosis of dRTA (acquired or inherited form) with metabolic acidosis, male or female, including children aged between 6 months and 17 years old and adults aged ≥ 18 years old and ≤55 years old reflects the intended population of patients suffering from dRTA and represents all relevant age groups. Exclusion criteria were planned to exclude patients with possible other reasons such as presentation of proximal tubular signs, kalaemia >5.0 mmol/L, or other reasons that could potentially jeopardise study conduct and completion, which is supported.

Those patients completing the pivotal B21CS study could be included in study B22CS, a multicentre, open-label, extension study and was intended to evaluate the safety and tolerability and the efficacy of ADV7103 over a longer term of 24 months in dRTA patients. The study provided more long-term

information on treatment with ADV7103 in support of the pivotal study in terms of maintenance of treatment effect and longer-term evaluation of safety. The main exploratory endpoints were nephrocalcinosis and lithiasis, bone remodelling, growth, long-term treatment acceptability and QoL, endpoints which are relevant for long term disease progression and which could not be evaluated in the pivotal short-term study.

Efficacy data and additional analyses

B21CS (pivotal) study

The number of patients who discontinued the study were limited to 5 (14%). Two of those patients discontinued during the SoC treatment period (SPI) due to withdrawal of consent (children category), and one patient due to difficulty in swallowing (infants' category). Three patients discontinued during the titration and/or steady state phase during treatment with ADV7103 due to lack of efficacy (n=1, adolescent) or consent withdrawal (1 adolescent, 1 infant) and one patient for other reasons. However, from the more specific data provided in the clinical study report, it appears that these patients discontinued due to issues with treatment acceptability (difficulty in swallowing) during the titration period SP II and one patient had the age of 1 year, when enrolled in the study. Treatment in patients below one year of age has not been evaluated and the single patient of one year of age treated discontinued treatment due to issues with treatment acceptability. Therefore, the CHMP questioned the appropriateness for use of Sibnayal in very young patients also because the current sachets cannot be applied in case of the presence of a feeding tube. It was acknowledged by the committee that intake of such granules depends on the maturity of the individual child and infant for swallowing but agreed with the applicant to amend the to be treated patient population to patients aged one year and older.

The number of major protocol deviations were limited and are therefore not expected to majorly impact the study results. No concerns have been identified on recruitment or compliance. Non-compliance was not based on tolerability or safety reasons. However, according to the study protocol, patients were required to follow certain diet requirements, but over 80% of the patients did not follow a diet. Moreover, from the 7 patients following a diet and completed the study (n=6), only 2 completely complied to their diet. However, no pattern could be obtained from the different diets and the outcome on the plasma bicarbonate levels.

Included adults were relatively young with a mean of 23 years of age, while the age ranged from 1 year to 46 years of age. Patients ≤1 year were not included, the applicant agreed therefore to exclude patients ≤1 year from the claimed indication. In line with inclusion criteria, almost all patients had genetically confirmed dRTA with only one patient having an acquired type of dRTA, but it is considered that a treatment effect of Sibnayal will be similar for patients with acquired or inherited dTRA. The condition of dRTA is further confirmed by associated symptoms of hearing impairment, nephrocalcinosis, and nephrolithiasis.

SoC treatment included a variety of alkalising treatments, and thus any precise definition of SoC is complicated, also complicating several aspects of comparison of study results to ADV7103 treatment. Almost 50% of the patients took 2 alkali agents. The most common SoCs were combined formulations of potassium citrate with sodium bicarbonate (in 9 [24.3%] patients), or one product of potassium citrate (in 8 [21.6%] patients) or sodium bicarbonate (in 7 [18.9%] patients).

At screening, bicarbonate levels seem well controlled within normal range (>22 mmol/L) for adults (25.1 mmol/L) and children (23.8 mmol/L) and just below normal range for adolescents (21.7 mmol/L) and infants (21.8 mmol/L) with use of SoC treatment based on one measurement. A more precise measurement during SPI including mean levels on day 2 to 4 identified slightly different results with only adults (24.1 mmol/L) being well controlled and adolescents (21.6 mmol/L), children (19.9

mmol/L) and infants (19.9 mmol/L) below normal range. Consequently, infants, children and adolescents were most in need for titration to reach normal blood carbonate levels. During the titration phase, a lower increment in mEq/kg/day was seen with increasing age group with dose increases performed in 3/3 patients (mean increase 1.0 mEq/kg/day per 5.1 days), 13/14 patients (0.73 mEq/kg/day per 4.7 days), 6/10 patients (0.64 mEq/kg/day per 3.3 days) and 3/7 patients (mean increase 0.38 mEq/kg/day per 3.3 days), respectively. Accordingly, following the titration phase (SPII) a higher mean level with ADV7103 at steady state compared to SoC (6.1 vs 5.3; 3.8 vs 2.7 and 2.8 vs 2.2 mEq/kg/day) was found, and slightly lower levels were needed for adults (1.7 vs 2.0 mEq/kg/day). Increased blood bicarbonate levels with ADV7103 appear mainly attributed to the paediatric patients, with normal levels being reached for all age groups, although normal levels could still not be reached for infants (21.8 mmol/L). Adults blood bicarbonate levels were comparable in both treatment groups, already being at normal levels on SoC. Whether closer follow-up and titration for SoC would also have yielded comparable results in control of bicarbonate levels remains an unanswered question and importantly invalidates the non-inferiority and superiority claim, in addition to other mentioned limitations of the study design. Nevertheless, the primary endpoint of a non-inferior treatment effect in blood bicarbonate levels with ADV7103 as compared to treatment with SoC was met with a mean difference (95% CI) between treatments of 1.42 (0.41, 2.43) mmol/L, $p<0.0001$. Further, superiority was also reached with an adjusted mean difference (95% CI) of 1.64 (0.67, 2.60) mmol/L, $p=0.0008$. This was also shown for the PP data set ($p=0.0037$). The primary efficacy findings on bicarbonate levels generally showed consistent effect with the overall effect when comparing ADV7103 to the subgroups of SoC treatment with, bicarbonate (2.28 mmol/L) combination citrate + bicarbonate (2.14 mmol/L), and comparison to sodium (1.90 mmol/L), potassium (0.33 mmol/L) or both of them (2.73 mmol/L). The CHMP considers a clinically relevant therapeutic effect of the product. However, SoC treatment with citrate appeared to demonstrate slightly better results than ADV7103 (-0.07 mmol/L).

Secondary endpoints generally supported the primary endpoint findings. A higher number of patients on ADV7103 (90%; 26/29) vs SoC (45%; 13/29) were responders defined as a mean level above normal blood bicarbonate range. Other definitions of responders supported these results with 75% vs 38% (non-responders defined as one measurement below normal range) and 97% vs 76% (non-responders defined as all non-missing measurements below normal level), respectively Further, continuous monitoring (roughly every 2 hours) of the bicarbonate at steady state showed comparable results between ADV7103 and SoC for AUC0-12h (mean (SD) 270.6 (27.26) vs 270.9 (39.71) mmol.h/L), AUC0-24h (536.8 (44.45) vs 567.9 (71.67) mmol.h/L), Cmin (19.8 (3.72) vs. 20.4 (3.30) mmol/L), and fluctuation range (4.8 (2.69) vs. 4.3 (1.76) mmol/L), suggesting comparable 24 hour coverage of effect of the FCMP (of citrate for the first three hours after intake and of bicarbonate after passing the stomach about twelve hours after intake), which would then allow for a more consistent and complete alkalising effect over the twelve hours for twice-daily dosing, than each individual mono-component could achieve.

Further analyses, linked to the dRTA indication, have been provided on potassium levels, urine calcium, and urine citrate, however, any comparison is limited by the different compounds used in the SoC, e.g. whether citrate was part of the SoC treatment. Nevertheless, potassium levels were just above normal range for all age groups (3.50 mmol/L in adults, 3.46 mmol/L in adolescents, 3.66 mmol/L in children and 3.55 mmol/L in infants) at baseline and achievement of normal potassium levels remained comparable during the study with for both SoC and ADV7103 treatments (3.8 mmol/L vs 4.0 mmol/L). For incidences of hypokalaemia, which is a major symptom for patients with dRTA, no large differences have been observed between the two treatment groups during the study (17% each). Sodium-based alkalising agents increase renal excretion of calcium. However, no meaningful differences have been observed between the two treatment groups with respect to hypercalciuria. Two patients each with SoC and ADV7103 had hypercalciuria. One of the mechanisms to compensate low blood pH is endogenous citrate, which is reabsorbed from the renal tubules into the blood and

decreases the levels of citrate in the urine (e.g. hypocitraturia). Addition of citrate would be expected to reduce this effect. A post-hoc analysis on hypocitraturia showed a lower proportion of patients with hypocitraturia for ADV7103 (10/16 (62.5%)) vs SoC (15/16 (94%)). Further, the number of responders with normal UCa/UCi values was higher for ADV7103 (11/19 (58%)) than for SoC (3/19 (16%)) which may suggest a lower risk to lithogenesis

Acceptability

About 87% of the patients took at least 3 intakes of SoC a day (and up to 6 intakes a day), and approximately 27% of the patients, particularly children (5, 33%)) and infants (2 (40%)), took SoC during the night. It could reasonably be assumed that 2 times dosing a day with the FCMP would improve treatment adherence and convenience. Overall, this appears to be generally confirmed with improved palatability (mean (SD) scores of 74.4 (20.60) mm vs. 49.3 (33.00) mm), mean and improved ease of administration (75.7 (24.71) mm vs. 60.1 (35.89) mm) for ADV7103 vs SoC. Ease of swallowing appears similar with ADV7103 and SoC: 71.2 (29.70) mm and 68.6 (30.98) mm. Yet, overall, 61.3% of patients (19/31) exhibited a rating improvement ≥1 category and 48.4% of patients (15/31) ≥2 categories. Although this was not that clear for the children category (4-11 years, with similar results for palatability, ease of administration and lower for ease of swallowing, also with a within analysis, probably based on heterogeneity of the rater and the lack of sensitivity of the evaluation scale). Of note, current sachets cannot be applied in case of the presence of a feeding tube, while this is often applied in infants, which is currently adequately reflected in the SmPC.

Patients generally remained compliant to therapy during the additional 24 months of therapy in the open label B22CS study (75-90%), and only one patient discontinued at 12 months.

Long term effect on bicarbonate levels could generally be maintained as levels were generally above the normal range, however, high variability between each visit could be observed in each age group. This may likely be (partly) explained by the single measurement at each time point, variation in timepoint (hours after intake), treatment compliance and time of dose adjustment. Although, the responder rates were slightly lower (56-92%) during the 24 months as compared to the initial period as evaluated in the pivotal B21CS study (75-97%) but appears comparable to SoC (38-76%).

Further, normal plasma potassium levels could be maintained (84% vs 82% in B21CS study), although some variability exists especially observed in the adults. A similar observation applies to data on citraturia, calciuria and urine calcium/citrate ratio. The number of patients with phosphaturia or magnesuria is low with ~10% and incidentally observed and were generally stable over time. ACCP crystals were the main reported type of crystalluria in the study and are generally also mostly found in clinical practice in dRTA patients due to their high urine pH, hypercalciuria and/or hypocitraturia, and hyperphosphaturia.

Explorative findings

Any beneficial impact of ADV7103 on several disease characteristics could not be clearly observed. Nephrocalcinosis increased from 86% to 97% (i.e. one patient developed nephrocalcinosis during the B22CS trial). No impact has been observed for nephrolithiasis, bone alkaline phosphatase, phosphorus, vitamin D, calcium, parathyroid hormone, and calcitonin. Seven patients have shown a negative change in Z-score of the BMD from baseline to the end of the study, but this may inherent to the underlying disease. Further, no impact has been seen on stature and growth, or pubertal maturity.

Also, during long term therapy, exploratory evaluation showed improved perception of efficacy (91.2%), safety (72.2%), taste (68.6%) and more appropriate formulation (83.9%), and more convenient number of daily dose intakes (90.2%). However, these data should be taken with caution due to potential bias (e.g. recall bias) and the way questions were perceived which tend to be suggestive in favour of ADV7103 (e.g. *"As compared to your previous alkalinising treatment, what*

is/are the reason(s) for which you prefer keep ADV7103 rather than your previous alkalinising product?").

During assessment the applicant was asked to clarify the contribution of each component (potassium citrate and potassium hydrogen carbonate) to the overall effect of the fixed combination medicinal product and the rationale for the combination. The bicarbonate component of Sibnayal has been developed to provide minimal release of bicarbonate in the stomach and the proximal part of the Gastrointestinal (GI) tract to avoid a loss of active substance due to the production of CO_2 by the bicarbonate and gastric acid and possible side effects of gastric gas accumulation. Thereafter gradual release is taken place, which therefore provides a 12-hour coverage after a single intake for twice-daily dosing. It is consequently assumed that there is a limited (clinical) effect of the bicarbonate component alone in the first three hours after each intake. Therefore, the rationale of the addition of the potassium citrate component, developed as a 'short' oral prolonged-release dosage form, is to fill the gap of the delay in release of bicarbonate by the release of this citrate in the first hours. The combination of the citrate (for the first three hours) and the bicarbonate (after passing the stomach to twelve hours after intake) would then allow for a more consistent and complete alkalising effect over the twelve hours for twice-daily dosing, than each individual mono-component could achieve.

This was supported by *in-vitro* dissolution profiles, as approximately 90% of the citrate component is released within the first three hours, while the bicarbonate is released gradually over a time-frame of about twelve hours, with overall a higher release effect in the first three hours of the Sibnayal FCMP formulation, compared to the profile of the potassium bicarbonate component alone. Due to the simple direct alkalising effect of both components, it can be assumed that the clinical effect would follow a similar pattern as for the *in-vitro* dissolution data. Furthermore, urine pH data over twelve hours, as evaluated in study B03CS in healthy subjects, reasonably match with this assumption for the overall effect of the FCMP with a steep rise in effect already at the first two hours post-dose (at steady state) and an almost consistent coverage of effect for twelve hours.

The CHMP considered this sufficient to support the scientific principle for a FCMP of the contribution of each individual component to the desired effect, in particular in the context of absence of any clear increased safety issues identified when combining both components, the relative straightforward mechanism of action.

2.5.4. Conclusions on the clinical efficacy

An overall treatment effect of normalising blood bicarbonate levels as well as normalisation of potassium was observed in adults, adolescents and children >1 year of age with dRTA during 24 months of treatment with Sibnayal. Despite that a non-inferior and a superior treatment effect, as compared to SoC treatment, was reached for achieving appropriate bicarbonate levels, limitations to study design and conduct preclude to make such claims especially for the sequential design and a titration phase lacking for SoC treatment. Similar limitations apply to other secondary endpoints such as evaluation of urine calcium and urine citrate.

A two times daily dosing intended for the ADV7103 is generally favoured over 3 up to 6 times dosing with current SoC, which is generally supported by the acceptability data.

2.6. Clinical safety

The safety database includes all patients with dRTA having taken at least one dose of ADV7103 (from up to 40 days to up to 24 months) during the pivotal short term study B21CS and the extension study

B22CS. Safety data generated with the Phase I study (B03CS) in 16 healthy subjects who received ADV7103 for 5 or 10 days, were presented separately as supportive safety data.

Patient exposure

Fifty subjects have been exposed to ADV7103, of which 16 were healthy subjects and 34 were patients with dRTA. Daily doses of ADV7103 were titrated on an individual basis. Study drug exposure through the studies is summarised in the table below.

Table 24*: Study drug exposure through the studies*

Study	ADV7103 dose range (mEq/day)	Duration	Number of subjects	Total number of subjects
B21CS SPII	92.00	4 days	1	34 dRTA patients [a]
	30.50 – 204.00	9 days	4	
	28.50 – 158.00	10 days	11	
	46.50 – 124.00	11 days	2	
	30.00 – 90.46	13 days	2	
	27.40 – 110.00	14 days	3	
	39.00 – 272.00	15 days	2	
	49.00 – 135.00	16 days	4	
	46.00 – 61.20	17 days	1	
	45.80 – 109.80	18 days	2	
	146.00- 292.00	22 days	1	
	87.00	25 days	1	
B21CS SPIII	30.50 – 291.00	5 days	32	32 dRTA patients [a]
B22CS	32.00 – 288.00	1 month	30	30 dRTA patients [a]
	32.00 – 312.00	3 months	30	
	32.00 – 288.00	6 months	30	
	32.00 – 288.00	12 months	30	
	32.00 – 336.00	18 months	29	
	32.00 – 336.00	24 months	29	
B03CS Treatment period 1	58.56 – 69.27	5 days	4	16[a] healthy subjects [b]
	123.07 – 136.29	5 days	4	
	157.84 – 203.85	5 days	4	
B03CS Treatment period 2	157.31 – 195.38	5 days	4	
	142.90 – 169.21	5 days	4	
	131.01 – 164.45	5 days	4	

Table 25*: Study Product Exposure with the daily dose in mEq/kg/day, by subset of age and overall, in B22CS Study*

Visit	Statistics	Adult [≥18Y] (N=6)	Adolescent [12-17Y] (N=8)	Child [4-11Y] (N=13)	Infant [6M-3Y] (N=3)	Overall (N=30)
Month 1 (inclusion)	N	6	8	13	3	30
	Mean±SD	2.008±0.923	2.729±1.649	3.773±1.115	5.909±1.934	3.355±1.677
	SEM	0.377	0.583	0.309	1.117	0.306
	Min/Med/Max	1.47/1.581/3.82	1.11/2.142/5.88	2.40/3.529/6.40	4.18/5.545/8.00	1.11/3.228/8.00
Month 3	N	6	8	13	3	30
	Mean±SD	2.152±1.107	2.753±1.669	3.639±1.114	5.712±1.772	3.313±1.619
	SEM	0.452	0.590	0.309	1.023	0.296
	Min/Med/Max	1.45/1.687/4.33	1.35/2.043/6.15	2.31/3.333/6.40	3.86/5.895/7.38	1.35/3.182/7.38
Month 6	N	6	8	13	3	30
	Mean±SD	2.177±1.164	2.744±1.532	3.513±1.069	5.554±1.646	3.245±1.533
	SEM	0.475	0.542	0.297	0.950	0.280
	Min/Med/Max	1.49/1.669/4.48	1.33/2.260/5.75	2.23/3.288/6.12	3.93/5.517/7.22	1.33/3.038/7.22
Month 12	N	6	8	13	3	30
	Mean±SD	2.221±1.129	2.693±1.584	3.422±1.178	5.668±2.453	3.212±1.654
	SEM	0.461	0.560	0.327	1.416	0.302
	Min/Med/Max	1.48/1.716/4.39	1.26/2.095/5.89	2.10/3.368/6.24	3.56/5.091/8.36	1.26/2.813/8.36
Month 18	N	5	8	12	3	28
	Mean±SD	2.205±1.277	2.576±1.628	3.473±1.347	5.101±1.860	3.165±1.630
	SEM	0.571	0.575	0.389	1.074	0.308
	Min/Med/Max	1.46/1.714/4.48	1.16/1.901/5.89	1.98/3.169/6.05	3.28/5.022/7.00	1.16/3.101/7.00
Month 24	N	5	7	13	3	28
	Mean±SD	2.260±1.299	2.606±1.728	3.413±1.297	4.806±2.002	3.155±1.587
	SEM	0.581	0.653	0.360	1.156	0.300
	Min/Med/Max	1.47/1.736/4.57	1.06/1.821/5.79	1.86/2.972/5.84	3.08/4.341/7.00	1.06/2.938/7.00

Adverse events

Treatment Emergent Adverse Events (TEAEs) in the overall study population

Study B21CS

In Study B21CS, information on AEs is summarised in the table below. Overall, a total of 24 (64.9%) patients experienced TEAEs during the study. This was 7 (18.9%) patients during SP I (SoC steady state) and 6 (18.8%) patients during SP III (ADV7103 steady state). TEAEs were reported in 19 (55.9%) patients during the ADV7103 titration period (SP II).

Only 1 patient reported serious TEAEs in Study B21CS. No AEs leading to treatment discontinuation have been reported.

Table 26*: TEAEs in the overall patient population – B21CS (Safety Set)*

Overall	SP I[a] n (%) N=37	SP II[b] n (%) N=34	SP III[c] n (%) N=32	Total n (%) N=37
AEs	7 (18.9%)	19 (55.9%)	6 (18.8%)	24 (64.9%)
Serious TEAEs	-	1 (2.9%)	-	1 (2.7%)
Treatment-related TEAEs	4 (10.8%)	9 (26.5%)	1 (3.1%)	11 (29.7%)
Severe TEAEs	-	1 (2.9%)	-	1 (2.7%)
TEAEs leading to discontinuation	-	-	-	-
Death	-	-	-	-

Abbreviations: TEAE= treatment-emergent adverse event, N=total number of patients, n=number of patients with at least one TEAE in the category, SP=study period
[a]SoC steady state
[b]ADV7103 titration
[c]ADV7103 steady state

Study B22CS

In study B22CS, where patients have received ADV7103 for up to 24 months, overall, a total of 27 (90.0%) patients experienced at last one AE. All but one of the AEs were judged as TEAEs. Among these TEAEs, 5 (16.7%) patients were reported with treatment-related TEAEs, 1 (3.3%) patient experienced a severe TEAE judged not-related to the treatment, 4 (13.3%) patients reported serious AEs, which were considered as not treatment related, was reported in 1 (2.7%) adolescent during SPII.

There were no TEAEs leading to discontinuation and no deaths during the study. No pattern was observed of increasing treatment-related events with increasing duration of exposure to ADV7103.

Table 27*: Summary of Adverse Events B22CS study– Safety Set*

	Adult [≥18Y] (N=6)		Adolescent [12-17Y] (N=8)		Child [4-11Y] (N=13)		Infant [6M-3Y] (N=3)		Overall (N=30)	
	n (%)	NAE	n (%)	NAE	n (%)	NAE	n (%)	NAE	n (%)	NAE
TEAEs	4 (66.7)	20	8 (100.0)	37	12 (92.3)	37	3 (100.0)	10	27 (90.0)	104
Related TEAEs	1 (16.7)	1	2 (25.0)	6	2 (15.4)	2	0	0	5 (16.7)	9
Serious AEs	1 (16.7)	1	2 (25.0)	2	0	0	1 (33.3)	1	4 (13.3)	4
Related SAEs	0	0	0	0	0	0	0	0	0	0
Severe TEAEs	0	0	0	0	0	0	1 (33.3)	1	1 (3.3)	1
TEAEs leading to study drug discontinuation	0	0	0	0	0	0	0	0	0	0
TEAEs leading to death	0	0	0	0	0	0	0	0	0	0

AE = adverse event; M = months; N, n = number of patients; NAE = number of adverse events; SAE = serious adverse event; TEAE = treatment emergent adverse event; Y = years.

Study B03CS

In Study B03CS, 6 (37.5%) healthy subjects were reported with 9 AEs, 8 of them were considered TEAEs. Among these TEAEs, 1/16 (6.3%) subject was reported with a treatment-related TEAE. There were no TEAEs severe, serious or leading to discontinuation and no deaths during the study.

Common Adverse Events

Study B21CS

Most frequently reported TEAEs (overall in >10% of patients in any SP) were from the Gastrointestinal Disorders (in 16 [43.2%] patients), General Disorders and Administration Site Conditions (in 8 [21.6%] patients) and Nervous System Disorders SOCs (in 7 [18.9%] patients). As expected, these TEAEs were reported more frequently in the titration period SP II than in the steady state periods SP I and SP III.

Table 28*: All TEAEs by SOC, PT, SP and age subset – Study B21CS, Safety analysis set*

SOC, PT n (%)	SPI SoC steady state	SPII ADV7103 titration	SPIII ADV7103 steady state	Total
Adults (≥18 years)	*N=7*	*N=7*	*N=7*	*N=7*
Patients with any TEAE	2 (28.6%)	5 (71.4%)	1 (14.3%)	6 (85.7%)
Gastrointestinal Disorders	**2 (28.6%)**	**4 (57.1%)**	**0 (0.0%)**	**5 (71.4%)**
Abdominal pain	1 (14.3%)	3 (42.9%)	0 (0.0%)	4 (57.1%)
Abdominal distension	1 (14.3%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
Abdominal pain upper	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (14.3%)
Diarrhoea	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (14.3%)
Nausea	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (14.3%)
Vomiting	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (14.3%)
Nervous System Disorders	**1 (14.3%)**	**4 (57.1%)**	**1 (14.3%)**	**4 (57.1%)**
Headache	1 (14.3%)	3 (42.9%)	1 (14.3%)	3 (42.9%)
Dizziness	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (14.3%)
General Disorders and Administration Site Conditions	**0 (0.0%)**	**1 (14.3%)**	**1 (14.3%)**	**2 (28.6%)**
Fatigue	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (14.3%)
Influenza like illness	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (14.3%)
Pyrexia	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (14.3%)
Musculoskeletal and Connective Tissue Disorders	**0 (0.0%)**	**1 (14.3%)**	**0 (0.0%)**	**1 (14.3%)**
Neck pain	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (14.3%)
Adolescents (12-17 years)	*N=10*	*N=10*	*N=8*	*N=10*
Patients with any TEAE	3 (30.0%)	7 (70.0%)	0 (0.0%)	8 (80.0%)
Gastrointestinal Disorders	**2 (20.0%)**	**4 (40.0%)**	**0 (0.0%)**	**5 (50.0%)**
Abdominal pain	2 (20.0%)	2 (20.0%)	0 (0.0%)	3 (30.0%)
Abdominal pain upper	0 (0.0%)	1 (10.0%)	0 (0.0%)	1 (10.0%)
Diarrhoea	0 (0.0%)	1 (10.0%)	0 (0.0%)	1 (10.0%)
Toothache	0 (0.0%)	1 (10.0%)	0 (0.0%)	1 (10.0%)
General Disorders and Administration Site Conditions	**0 (0.0%)**	**3 (30.0%)**	**0 (0.0%)**	**3 (30.0%)**
Fatigue	0 (0.0%)	2 (20.0%)	0 (0.0%)	2 (20.0%)
Asthenia	0 (0.0%)	1 (10.0%)	0 (0.0%)	1 (10.0%)
Metabolism and Nutrition Disorders	**0 (0.0%)**	**2 (20.0%)**	**0 (0.0%)**	**2 (20.0%)**
Decreased appetite	0 (0.0%)	1 (10.0%)	0 (0.0%)	1 (10.0%)
Dehydration	0 (0.0%)	1 (10.0%)	0 (0.0%)	1 (10.0%)
Infections and Infestations	**0 (0.0%)**	**1 (10.0%)**	**0 (0.0%)**	**1 (10.0%)**
Gastroenteritis	0 (0.0%)	1 (10.0%)	0 (0.0%)	1 (10.0%)
Nervous System Disorders	**0 (0.0%)**	**1 (10.0%)**	**0 (0.0%)**	**1 (10.0%)**
Headache	0 (0.0%)	1 (10.0%)	0 (0.0%)	1 (10.0%)
Reproductive System and Breast Disorders	**1 (10.0%)**	**1 (10.0%)**	**0 (0.0%)**	**1 (10.0%)**
Dysmenorrhoea	0 (0.0%)	1 (10.0%)	0 (0.0%)	1 (10.0%)
Premenstrual pain	1 (10.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)
Children (4-11 years)	*N=15*	*N=14*	*N=14*	*N=15*
Patients with any TEAE	1 (6.7%)	5 (35.7%)	3 (21.4%)	6 (40.0%)
Gastrointestinal Disorders	**0 (0.0%)**	**5 (35.7%)**	**1 (7.1%)**	**5 (33.3%)**
Abdominal pain upper	0 (0.0%)	3 (21.4%)	0 (0.0%)	3 (20.0%)
Vomiting	0 (0.0%)	2 (14.3%)	0 (0.0%)	2 (13.3%)

SOC, PT n (%)	SPI SoC steady state	SPII ADV7103 titration	SPIII ADV7103 steady state	Total
Abdominal pain	0 (0.0%)	1 (7.1%)	1 (7.1%)	1 (6.7%)
Enterocolitis	0 (0.0%)	1 (7.1%)	0 (0.0%)	1 (6.7%)
Nausea	0 (0.0%)	1 (7.1%)	0 (0.0%)	1 (6.7%)
General Disorders and Administration Site Conditions	**0 (0.0%)**	**2 (14.3%)**	**0 (0.0%)**	**2 (13.3%)**
Fatigue	0 (0.0%)	1 (7.1%)	0 (0.0%)	1 (6.7%)
Pyrexia	0 (0.0%)	1 (7.1%)	0 (0.0%)	1 (6.7%)
Nervous System Disorders	**1 (6.7%)**	**2 (14.3%)**	**1 (7.1%)**	**2 (13.3%)**
Headache	1 (6.7%)	2 (14.3%)	1 (7.1%)	2 (13.3%)
Respiratory, Thoracic and Mediastinal Disorders	**0 (0.0%)**	**1 (7.1%)**	**1 (7.1%)**	**2 (13.3%)**
Epistaxis	0 (0.0%)	1 (7.1%)	0 (0.0%)	1 (6.7%)
Oropharyngeal pain	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (6.7%)
Blood and Lymphatic System Disorders	**0 (0.0%)**	**0 (0.0%)**	**1 (7.1%)**	**1 (6.7%)**
Lymphadenopathy	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (6.7%)
Infants (6 months-3 years)	*N=5*	*N=3*	*N=3*	*N=5*
Patients with any TEAE	1 (20.0%)	2 (66.7%)	2 (66.7%)	4 (80.0%)
Infections and Infestations	**0 (0.0%)**	**1 (33.3%)**	**1 (33.3%)**	**2 (40.0%)**
Ear infection	0 (0.0%)	1 (33.3%)	0 (0.0%)	1 (20.0%)
Myringitis bullous	0 (0.0%)	0 (0.0%)	1 (33.3%)	1 (20.0%)
Nasopharyngitis	0 (0.0%)	0 (0.0%)	1 (33.3%)	1 (20.0%)
Gastrointestinal Disorders	**1 (20.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (20.0%)**
Diarrhoea	1 (20.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
General Disorders and Administration Site Conditions	**0 (0.0%)**	**0 (0.0%)**	**1 (33.3%)**	**1 (20.0%)**
Pyrexia	0 (0.0%)	0 (0.0%)	1 (33.3%)	1 (20.0%)
Musculoskeletal and Connective Tissue Disorders	**0 (0.0%)**	**1 (33.3%)**	**1 (33.3%)**	**1 (20.0%)**
Pain in extremity	0 (0.0%)	1 (33.3%)	1 (33.3%)	1 (20.0%)
Overall	*N=37*	*N=34*	*N=32*	*N=37*
Patients with any TEAE	7 (18.9%)	19 (55.9%)	6 (18.8%)	24 (64.9%)
Gastrointestinal Disorders	**5 (13.5%)**	**13 (38.2%)**	**1 (3.1%)**	**16 (43.2%)**
Abdominal pain	3 (8.1%)	6 (17.6%)	1 (3.1%)	8 (21.6%)
Abdominal pain upper	0 (0.0%)	5 (14.7%)	0 (0.0%)	5 (13.5%)
Diarrhoea	1 (2.7%)	2 (5.9%)	0 (0.0%)	3 (8.1%)
Vomiting	0 (0.0%)	3 (8.8%)	0 (0.0%)	3 (8.1%)
Nausea	0 (0.0%)	2 (5.9%)	0 (0.0%)	2 (5.4%)
Abdominal distension	1 (2.7%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
Enterocolitis	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.7%)
Toothache	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.7%)
General Disorders and Administration Site Conditions	**0 (0.0%)**	**6 (17.6%)**	**2 (6.3%)**	**8 (21.6%)**
Fatigue	0 (0.0%)	3 (8.8%)	1 (3.1%)	4 (10.8%)
Pyrexia	0 (0.0%)	2 (5.9%)	1 (3.1%)	3 (8.1%)
Asthenia	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.7%)
Influenza like illness	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.7%)
Nervous System Disorders	**2 (5.4%)**	**7 (20.6%)**	**2 (6.3%)**	**7 (18.9%)**
Headache	2 (5.4%)	6 (17.6%)	2 (6.3%)	6 (16.2%)
Dizziness	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.7%)
Infections and Infestations	**0 (0.0%)**	**2 (5.9%)**	**1 (3.1%)**	**3 (8.1%)**
Ear infection	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.7%)
Gastroenteritis	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.7%)
Myringitis bullous	0 (0.0%)	0 (0.0%)	1 (3.1%)	1 (2.7%)
Nasopharyngitis	0 (0.0%)	0 (0.0%)	1 (3.1%)	1 (2.7%)
Metabolism and Nutrition Disorders	**0 (0.0%)**	**2 (5.9%)**	**0 (0.0%)**	**2 (5.4%)**
Decreased appetite	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.7%)
Dehydration	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.7%)

SOC, PT n (%)	SPI SoC steady state	SPII ADV7103 titration	SPIII ADV7103 steady state	Total
Musculoskeletal and Connective Tissue Disorders	**0 (0.0%)**	**2 (5.9%)**	**1 (3.1%)**	**2 (5.4%)**
Neck pain	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.7%)
Pain in extremity	0 (0.0%)	1 (2.9%)	1 (3.1%)	1 (2.7%)
Respiratory, Thoracic and Mediastinal Disorders	**0 (0.0%)**	**1 (2.9%)**	**1 (3.1%)**	**2 (5.4%)**
Epistaxis	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.7%)
Oropharyngeal pain	0 (0.0%)	0 (0.0%)	1 (3.1%)	1 (2.7%)
Blood and Lymphatic System Disorders	**0 (0.0%)**	**0 (0.0%)**	**1 (3.1%)**	**1 (2.7%)**
Lymphadenopathy	0 (0.0%)	0 (0.0%)	1 (3.1%)	1 (2.7%)
Reproductive System and Breast Disorders	**1 (2.7%)**	**1 (2.9%)**	**0 (0.0%)**	**1 (2.7%)**
Dysmenorrhoea	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.7%)
Premenstrual pain	1 (2.7%)	0 (0.0%)	0 (0.0%)	1 (2.7%)

Study B22CS

In study B22CS, overall, TEAEs were reported in a total of 27 (90.0%) patients. A summary of SOCs where TEAEs occurred in more than 1 patient during the 24 months of the study is provided in Table 34.

Table 29*: SOCs with > 1 patient reporting TEAE in Overall population – B22CS*

SOC Preferred term	Number of TEAEs	Number of patients	Percentage of patients
Metabolism and nutrition disorders	21	14	46.7
Vitamin D deficiency	15	12	40.0
Hypokalaemia	3	3	10.0
Gastrointestinal disorders	20	12	40.0
Abdominal pain	5	4	13.3
Vomiting	4	3	10.0
Diarrhoea	4	2	6.7
Upper abdominal pain	2	2	6.7
Infections and infestations	29	10	33.3
Ear infection	4	2	6.7
Bronchitis	3	2	6.7
Nasopharyngitis	2	2	6.7
Rhinitis	2	2	6.7
Tinea infection	2	2	6.7
Urinary tract infection	2	2	6.7
Musculoskeletal and connective tissue disorders	6	6	20.0
Back pain	2	2	6.7
Pain in extremity	2	2	6.7

Treatment related adverse events

Overall, 17 patients (50%) had at least an AE in the SOC 'Gastrointestinal disorders' that can be considered as an adverse drug reaction (ADR).

In particular, abdominal pain was 3 [8.1%] patients in SoC and 1 [3.1%] patient with ADV7103, respectively.

Table 30*: All treatment-related TEAEs by SOC, PT, SP and age subset – Study B21CS, Safety analysis set*

SOC, PT n (%)	SPI SoC steady state	SPII ADV7103 titration	SPIII ADV7103 steady state	Total
Adults (≥18 years)	*N=7*	*N=7*	*N=7*	*N=7*
Patients with any treatment-related TEAE	2 (28.6%)	3 (42.9%)	0 (0.0%)	4 (57.1%)
Gastrointestinal Disorders	**2 (28.6%)**	**3 (42.9%)**	**0 (0.0%)**	**4 (57.1%)**
Abdominal pain	1 (14.3%)	2 (28.6%)	0 (0.0%)	3 (42.9%)
Abdominal distension	1 (14.3%)	0 (0.0%)	0 (0.0%)	1 (14.3%)
Abdominal pain upper	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (14.3%)
Vomiting	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (14.3%)
Nervous System Disorders	**0 (0.0%)**	**1 (14.3%)**	**0 (0.0%)**	**1 (14.3%)**
Dizziness	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (14.3%)
Adolescents (12-17 years)	*N=10*	*N=10*	*N=8*	*N=10*
Patients with any treatment-related TEAE	2 (20.0%)	3 (30.0%)	0 (0.0%)	4 (40.0%)
Gastrointestinal Disorders	**2 (20.0%)**	**2 (20.0%)**	**0 (0.0%)**	**3 (30.0%)**
Abdominal pain	2 (20.0%)	2 (20.0%)	0 (0.0%)	3 (30.0%)
Diarrhoea	0 (0.0%)	1 (10.0%)	0 (0.0%)	1 (10%)
Metabolism and Nutrition Disorders	**0 (0.0%)**	**1 (10%)**	**0 (0.0%)**	**1 (10%)**
Decreased appetite	0 (0.0%)	1 (10%)	0 (0.0%)	1 (10%)
Children (4-11 years)	*N=15*	*N=14*	*N=14*	*N=15*
Patients with any treatment-related TEAE	0 (0.0%)	3 (21.4%)	1 (7.1%)	3 (20.0%)
Gastrointestinal Disorders	**0 (0.0%)**	**3 (21.4%)**	**1 (7.1%)**	**3 (20.0%)**
Abdominal pain upper	0 (0.0%)	2 (14.3%)	0 (0.0%)	2 (13.3%)
Abdominal pain	0 (0.0%)	1 (7.1%)	1 (7.1%)	1 (6.7%)
Vomiting	0 (0.0%)	1 (7.1%)	0 (0.0%)	1 (6.7%)
Infants (6 months-3 years)	*N=5*	*N=3*	*N=3*	*N=5*
Patients with any treatment-related TEAE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Overall	*N=37*	*N=34*	*N=32*	*N=37*
Patients with any TEAE	4 (10.8%)	9 (26.5%)	1 (3.1%)	11 (29.7%)
Gastrointestinal Disorders	**4 (10.8%)**	**8 (23.5%)**	**1 (3.1%)**	**10 (27.0%)**
Abdominal pain	3 (8.1%)	5 (14.7%)	1 (3.1%)	7 (18.9%)
Abdominal pain upper	0 (0.0%)	3 (8.8%)	0 (0.0%)	3 (8.1%)
Abdominal distension	1 (2.7%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
Vomiting	0 (0.0%)	2 (5.9%)	0 (0.0%)	2 (5.4%)
Diarrhoea	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.7%)
Metabolism and Nutrition Disorders	**0 (0.0%)**	**1 (2.9%)**	**0 (0.0%)**	**1 (2.7%)**
Decreased appetite	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.7%)
Nervous System Disorders	**0 (0.0%)**	**1 (2.9%)**	**0 (0.0%)**	**1 (2.7%)**
Dizziness	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.7%)

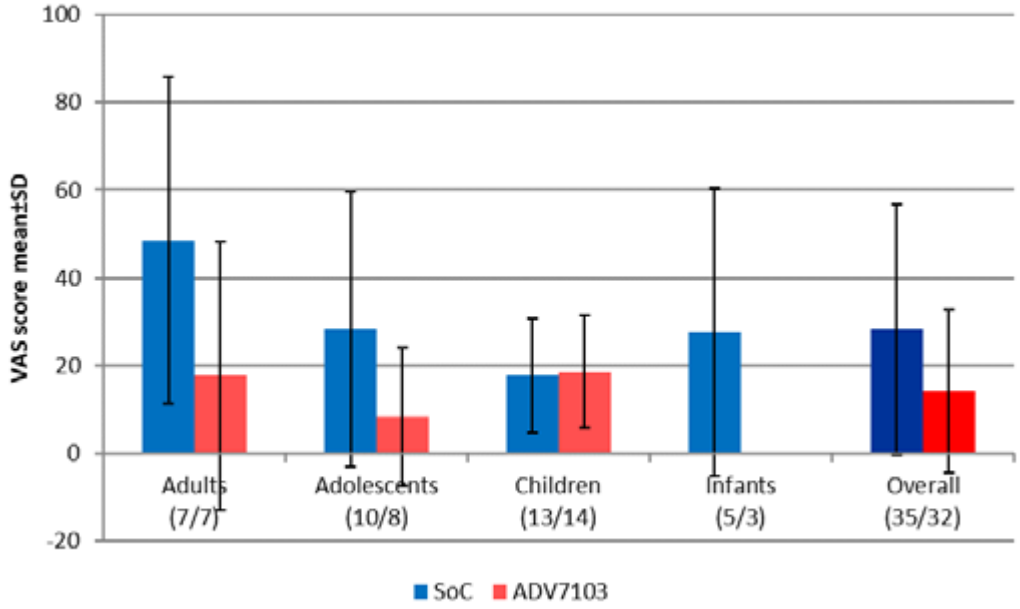
Table 31*: All treatment-related TEAEs by SOC, PT and age subset – Study B22CS, Safety analysis set*

SOC, PT n (%)	Adults (≥ 18 years) N=6	Adolescents (12-17 years) N=8	Children (4-11 years) N=13	Total N=30
Any treatment-related TEAE	**1 (16.7%)**	**2 (25.0%)**	**2 (15.4%)**	**5 (16.7%)**
Gastrointestinal Disorders	**1 (16.7%)**	**2 (25.0%)**	**2 (15.4%)**	**5 (16.7%)**
Abdominal pain			2 (15.4%)	2 (6.7%)
Upper abdominal pain		1 (12.5%)		1 (3.3%)
Diarrhoea		1 (12.5%)		1 (3.3%)
Dyspepsia	1 (16.7%)	0 (0.0%)		1 (3.3%)
Gastrointestinal disorder		1 (12.5%)		1 (3.3%)
Gastrointestinal pain		1 (12.5%)		1 (3.3%)

GI tolerability (based on VAS assessment)

Improved GI tolerability was reported for ADV7103 compared to SoC (Figure 15). The mixed model showed a statistically significant decrease in severity of the GI discomfort with ADV7103 compared to SoC, with a mean score difference of -14.237 mm (95% CI: -25.9196, -2.5545). Following the switch from SoC to ADV7103, the proportion of patients with rating category (including 5 grades 'Extremely severe/severe/moderate/mild/no complaint') improvement ≥1 and ≥2 were 38.7% (12/31) and 22.6% (7/31), respectively.

Figure 17*: Gastro-intestinal tolerability (Acceptability analysis set (AAS))*



Serious adverse event and deaths

Serious adverse events

In Study B21CS, one serious case of gastroenteritis was reported in one adolescent during the titration period (SPII). The event, which was of moderate intensity was not considered as related to the study drug and resolved within 24 hours without any corrective treatment. Treatment with ADV7103 was interrupted for a day since vomiting was associated to the gastroenteritis then reintroduced without dose change.

In Study B22CS, four SAEs were reported in four patients overall (13.3%), all considered unrelated to treatment. These SAEs were: renal colic (in an adult), gastritis and wisdom teeth removal (in adolescents) and gastroenteritis rotavirus (in an infant). All were due to a requirement or prolongation of hospitalisation, and all were resolved/recovered within the following days without ADV7103 dose change.

In Study B03CS, no serious TEAEs were reported.

Deaths

No death was reported during the clinical development of ADV7103.

Laboratory findings

Study B21CS

Overall, the assessed safety blood chemistry parameters of safety did not change in a clinically significant manner from screening to Day 5 of SPI and SPIII and from baseline to M24. The same trend was observed in each age subset.

There was only one isolated case of hyperkalaemia of 4.7 mmol/L (normal value range: 3.5- 4.5 mmol/L), reported in 1 child at Day 2 t0 of SPIII. The child did not present other episodes of hyperkalaemia during any of the 4 days remaining in SPIII, until the end of SPIII, with values of 4.1 on Day 3 t0, 4.2 on Day 4 t0 (normal value range: 3.5 4.5 mmol/L), and 3.47 on Day 5 t0 and 3.74 on Day 5 t12h. Overall, in this study population no trend for hyperkalaemia was observed, confirming the safe use of ADV7103 in the treatment of dRTA.

Safety in special populations

Elderly population

Since the upper age limit of inclusion was 55 years and the oldest patient recruited was aged 46 years, there were no elderly recruited in the study.

Renal impairment

Laboratory values for estimated Glomerular Filtration Rate (eGFR) included abnormal values for 6 patients who presented abnormally low eGFR values of grade 2 (i.e. eGFR mildly decreased, between 60 and 89 mL/min/1.73m^2). Five of them had abnormally low eGFR at a single time-point or for a limited time period, but one child had abnormally low eGFR values from Month 12 up to at least Month 24. There was no pattern in the decreased eGFR over time.

Hepatic impairment

Patients with hepatic impairment have not been included.

Immunological events

Not applicable. The components of Sibnayal (potassium, bicarbonate, and citrate) are endogenous substances.

Safety related to drug-drug interactions and other interactions

No specific DDI studies have been performed with ADV7103, however, the applicant provided a discussion related to potential interaction of ADV7103 with other active substances which may be concomitantly used by dRTA patients.

The proposed SmPC covers these concerns with regard to concomitant use of medicinal products that may increase potassium levels or induce hyperkalaemia (e.g. ACE inhibitors, potassium-sparing diuretics or ciclosporin), medicinal products affected by serum potassium disturbances (e.g. antiarrhythmics or corticosteroids) and alcohol, i.e. in the section 4.5 with one cross-reference to section 4.4. It includes among others an advice for monitoring of potassium plasma levels, serum potassium and ECG, and a recommendation to avoid an alcohol. For more details on DDIs please refer to the PD section.

Further, with regard to the method of administration and concomitant use of ADV7103 with hot food and alcohol, in the section 4.2 of proposed SmPC the following statement is presented: "In no instance granules must be mixed with hot food, hot liquid or alcohol or chewed as this can disrupt their prolonged release properties and may lead to large sudden release of alkalising agent that could affect product efficacy and safety." The package leaflet includes a similar statement. This is considered fully sufficient.

Discontinuation due to adverse events

No cases of study treatment discontinuation due to TEAE have been noted during the performed clinical studies.

Post marketing experience

There are no post-marketing data for ADV7103 at the time of this application.

However, ADV7103 is available in the frame of early access programs in Europe: named patient uses have been approved in Sweden from 11 April 2018, in France from 13 July 2018 and in Norway from 14 October 2019. At the cut-off date of 15 October 2019, prescriptions of ADV7103 have been delivered to 56 new dRTA patients. Overall, the duration of exposure has been from 1 to 13 months. Among these patients, four patients reported adverse events, two cases of diarrhoea, one case of stomach burning sensation, and one case of depressed mood and weight gain. In addition, two patients misused ADV7103 either by crunching some granules or by taking one sachet and a half.

2.6.1. Discussion on clinical safety

The safety database for treatment with the FCMP of ADV7103 is very limited due to the orphan nature of the disease. The safety results are based on the data from a short-term study in healthy volunteers, a short-term pivotal study including a titration phase of maximum 30 days and 5 days of steady state followed by a 24 months extension in dTRA patients. Fifty subjects have been exposed to ADV7103, of which 16 were healthy subjects and 34 were patients with dRTA. Longer term exposure data are available for only 29 patients with dTRA for 24 months. Doses used for ADV7103 were generally higher as for SoC, except for adults.

Due to the widespread use of both ingredients alone or in combination in patients with dRTA in clinical practice the safety profile has been widely established mainly including gastrointestinal disorders, such as nausea, vomiting, abdominal pain, dyspepsia or diarrhoea depending on citrate or hydrogen carbonate based therapy as labelled in section 4.8 of the SmPC.

Further, there is a potential risk for hyperkalaemia with potassium supplementation either used as a cation in the product or supplemented separately. For the current FCMP a coating has been used, and in that sense differs from existing therapies. However, the sequential study design, uncontrolled data and the limited number of patients limit the interpretation of the safety profile in comparison to existing therapies or placebo. Precautions have been included in the SmPC with contraindications in patients with hyperkalaemia and in case of renal impairment with GFR ≤ 44 mL/min/1.73m². and precautionary statements on conditions pre-disposing to hyperkalaemia such as monitoring of plasma potassium and risk of overdose as included in section 4.4, 4.5 and 4.9 of the SmPC. The package leaflet has been updated accordingly.

Overall, a high proportion of subjects (24 (64.9%)) experienced AEs during the B21CS study, but this was mainly due to the high frequency of AEs during the titration phase (19 (56%), while during SoC

treatment and steady state period with ADV7103 (SPIII period) frequency of AEs were 18.9% and 18.8%, respectively. A smaller proportion was considered treatment related, this was 4 (10.8%), 9 (26.5%) and 1 (3.1%) for SoC, titration phase of ADV7103 and steady state phase of ADV7103, respectively. Incidence of AEs during the titration phase has not caused limitations to optimal dosing. Due to the longer follow-up period in the OLE study more AEs were reported than during the short-term pivotal study (90% vs 65%), although treatment related events were also limited to 5 patients (16.7%).

In general, ADV7103 appears generally well tolerated, as no patients discontinued treatment due to AEs during 24 months of treatment. Furthermore, SAEs are limited, with one patient with gastroenteritis in an adolescent observed during the short-term pivotal study and resolved within 24 hours and 4 patients (13.3%) during the extension phase (renal colic (in an adult), gastritis and wisdom teeth removal (in an adolescent) and gastroenteritis rotavirus (in an infant)), but these were all considered unrelated to treatment, resolved within the following days and no dose changes were performed. Reassuringly, no deaths occurred during the studies.

As expected most common AEs were observed in the SOC of Gastrointestinal Disorders (16 patients [43.2%]), including abdominal pain (8 (21.6%)), upper abdominal pain ((5 (13.5%)), diarrhoea (3 (8.1%)), vomiting (3 (8.1%)), and nausea (2 (5.4%)) being mostly observed, mainly during the titration phase with ADV7103 13 (38.2%) vs 5 (13.5%) with SoC and 1 (3.1%) during steady state ADV7103. During steady state, only the abdominal pain AEs (3 (8.1%) with SoC, 1 (3.1%) with ADV7103) were considered treatment related. Another frequently reported AE was headache (2 (5.4%) with SoC; 2 (6.3%) during steady state ADV7103), but this was not considered related to treatment. The long-term study confirmed the high frequency of gastrointestinal AEs (12 (40%) including abdominal pain (3 (13.3%), vomiting (3 (10%)), diarrhoea (2 (7%)) and upper abdominal pain (2 (7%)). However, only for 5 patients (16.7%), GI symptoms were considered treatment related. Further, vitamin D deficiency (12 (40%)) and hypokalaemia (3 (10%)) were also frequently reported, likely associated with the underlying disease characteristics. Due to the low number of subjects for each age category no conclusion can be drawn for the individual AEs observed across these different age categories.

Overall, any risk for hyperkalaemia appears to be limited. Only one isolated case of hyperkalaemia of 4.7 mmol/L was reported in 1 child at Day 2 t0 of steady state ADV7103 treatment with no other episodes of hyperkalaemia during rest of treatment.

Four out of 56 patients reported AEs through the early access programs of ADV7103 use in Europe. All reported adverse events can be considered as isolated cases and no pattern could be identified. Therefore, no safety concern can be identified from the current available experience through early access programs in Europe.

ADV7103 has not been investigated in patients below 6 months of age or above 46 years of age. The safety profile for older patients could be different for those with decreased renal function. Therefore the precautionary wording in 4.4 of the SmPC recommends to the prescriber to take special care in elderly people in whom renal function can be decreased. In moderate to severe renal impairment a higher risk for hyperkalaemia may be expected. Accordingly, hyperkalaemia and renal impairment with GFR ≤ 44mL/min/1.73m² are contraindications. Furthermore, the "risk of hyperkalaemia when used in patients with comorbidities such as renal impairment" is listed as an important identified risk in the risk management plan (RMP).

2.6.2. Conclusions on the clinical safety

Sibnayal in paediatric, adolescent and adult subjects with dRTA was generally well tolerated with no patients who discontinued during a 24-month treatment period due to AEs. The main adverse drug events are gastro-intestinal events of which abdominal pain was dominantly reported. Any comparison with SoC or comparison between age groups is hampered by the small number of patients evaluated but in the context of the orphan nature of the disease and considering the widespread use of both ingredients alone or in combination in patients with dRTA in clinical practice an acceptable safety profile has been demonstrated. The current safety profile of ADV7103 does not suggest any difference to Standard of care (SoC) treatment.

2.7. Risk Management Plan

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk: Risk of hyperkalaemia, when used in patients with comorbidities such as renal impairment	SmPC section 4.2 SmPC section 4.4 SmPC section 4.6 SmPC section 4.9 PL section 2 (Warnings and precautions)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - Systems and processes that ensure that information about all suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible and appropriate manner according to system in place; - Preparation of reports for regulatory authorities; - Expedited adverse drug reaction (ADR) reports; - Periodic Safety Update Reports (PSURs); - Continuous monitoring of the safety profile of Sibnayal once approved including signal detection, issue evaluation, labelling update, and liaison with regulatory authorities where necessary; - Other requirements, as defined by local regulations.

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

Sibnayal is a new dose combination of potassium citrate/potassium hydrogen bicarbonate and the first product indicated specifically in the dRTA population. Therefore, the CHMP is of the opinion that a separate entry in the EURD list for Sibnayal is needed, as it cannot follow the already existing entry for potassium. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request the alignment of the new PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

A request of translation exemption of the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The Group accepted the proposal to have 4 different multilingual outer cartons and two different sachets (one in English only and one in French, German, Dutch and Italian). For both sachets, active substances are presented in English and Latin only due to space constraints.

The package leaflet will be translated in each national language. However, in Member States from groups 2, 3 and 4, the active substances will be included in English and Latin as well, so there will be a link between the package leaflet and the packaging.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Distal renal tubular acidosis (dRTA) is a condition characterised by a renal defect in hydrogen ion secretion (distal renal tubule localisation) and insufficient secretion of bicarbonate (HCO_3^-) into the blood (most important blood acid buffer) inducing a hyperchloremic metabolic acidosis (blood pH ≤ 7.35). Metabolic acidosis corresponds to a blood pH below 7.35 with a bicarbonate blood concentration lower than 22 mmol/L. Other symptoms are hypokalaemia, hypocitraturia and hypercalciuria. If metabolic acidosis is left untreated or poorly treated this can induce nephrocalcinosis or lithiasis of which may result in CKD (85% stage 2-4 in adults and 35% CKD stage ≥2 in children). Metabolic acidosis triggers bicarbonate and phosphate efflux from the bone in an attempt to buffer the acid blood pH. This results in bone softening manifestations such as osteomalacia in adults and rickets in children, and fractures. As blood pH homeostasis is essential for the secretion of growth hormone, particularly at night when its secretion is maximal, metabolic acidosis also induces restricted growth in children. Overall, if thus left untreated or mistreated, dRTA can thus lead to renal function impairment, weaken muscle strength, affect bone structure and result in adults of short stature. In some genetics forms, deafness, ocular abnormalities or mental retardation have been described

The disease can be of inherited origin (arising from a genetic mutation) most commonly observed in children, or of acquired origin due to an underlying autoimmune systemic disease, such as Sjögren syndrome, systemic lupus erythematosous or autoimmune hepatic diseases as usually observed in adults. dRTA was estimated to affect approximately 2.1 per 10,000 persons in the EU.

3.1.2. Available therapies and unmet medical need

In dRTA, lifelong alkali replacement therapy is given to correct metabolic acidosis. Potassium supplements are also be administered to maintain plasma potassium levels in the normal range as needed.

In dRTA adults, the patient may be started with a daily dose of 1 to 3 mEq/kg of alkali given in divided doses. Children with dRTA usually require higher doses (up to 5-8 mEq/kg/day in infants) of alkali due to growth associated increased metabolism and increased protein intake. The dose is titrated to raise bicarbonataemia and blood pH to normal. Night intakes of the current immediate release alkalising agents are also particularly necessary for children, since growth hormone is secreted mainly at night, but at physiological pH. To achieve appropriate bicarbonate levels is sometimes difficult to achieve, especially in younger children. To avoid renal complications, citrate is (sometimes) used as it is also chelator of calcium, but this is not always part of therapy, especially due to the occurrence of nausea.

Several alkalising salts have been authorised in the EU for indications that include metabolic acidosis, hypokalaemia or nephrolithiasis, but not in all countries, and hospital preparations are being used. These include, among others, potassium citrate, potassium bicarbonate, sodium bicarbonate, and sodium citrate each as a single active substance or in different product combinations. There is no preferred treatment and this likely depends on country availability and practice preference. All products are immediate-release formulations, except for Acalka (potassium citrate, authorised in Spain and Portugal), which is a modified release formulation. The immediate release products generally have a bitter taste if no coating is applied. GI adverse events are common but differ among patients and type

of product. Nausea and vomiting may be more observed with potassium citrate, while abdominal discomfort (due to gas (CO_2) production) may be more observed with carbonate-based therapy. Multiple daily intakes from 2 to 6 times a day are needed, especially in young children doses at night may be needed. Daily intakes of 4 times a day or more are particularly challenging as this likely includes dosing at night.

Sibnayal is a fixed combination medicinal product of prolonged-release granules of potassium citrate and potassium hydrogen carbonate (8 and 24 mEq sachets) for which the following therapeutic indication was proposed: "Sibnayal is indicated for the treatment of distal renal tubular acidosis (dRTA) in patients aged 6 months and older." Treatment in patients below one year of age had not been evaluated and the single patient of one year of age treated discontinued treatment due to issues with treatment acceptability. Therefore, the CHMP questioned the appropriateness for use of Sibnayal in very young patients also because the current sachets cannot be applied in case of the presence of a feeding tube. It was acknowledged by the committee that intake of such granules depends on the maturity of the individual child and infant for swallowing but agreed with the applicant to amend the to be treated patient population to patients aged one year and older.

Combining these two different alkalising agents (potassium citrate (CK) and potassium bicarbonate (BK)) gives ADV7103 the potential to control of metabolic acidosis and its consequences, while also providing potassium supplementation, and when combined in a prolonged-release formulation, a twice-daily (BID) administration would allow control throughout the day and night. Further, the formulation would also provide bad taste masking.

3.1.3. Main clinical studies

The pivotal study (B21CS) is a multicentre, open-label, non-inferiority, sequential study and aimed to evaluate the efficacy, safety, tolerability and acceptability of ADV7103 compared to SoC care in dRTA patients (n=34). The study included three study phases (SP) as follows: enrolled patients were to continue their SoC (possible variety of use of salts 3 to 6 times a day) without modification during a 5-days period (SPI), and were subsequently crossed-over and titrated with ADV7103 to an optimal dose for up to 30 days (SP II) to control their bicarbonate levels, followed by a 5 days steady state period (SPIII) once stable control was reached. Effect of treatment was compared based on the steady state of SoC (SPI) versus steady state of ADV7103 (SPIII).

This study was followed by an open-label extension study (B22CS) for longer-term (24 months) evaluation of safety, tolerability and efficacy of ADV7103 in those patients that rolled over from the pivotal study.

3.2. Favourable effects

With ADV7103 treatment, the primary endpoint showed that the mean (SD) plasma bicarbonate pre-dose levels during 3 days of treatment at steady state were 23.1 (1.62) mmol/L with 90% (26/29) of the patients achieving 3-day mean normal carbonate levels. This effect was generally maintained during 24 months of therapy, although some variability was observed with responder rate of 56-92%. Also, almost all patients (29 of 30) remained on therapy during the 24 months. The effect was demonstrated for age categories of children, adolescents and adults, although normal levels could still not be reached for infants (21.8 mmol/L). The mean plasma potassium level was well within the normal range (4.0 mmol/L) and was maintained during 24 months of therapy, with 82-84% of the patients within a normal range.

As far as comparison is allowed (see limitations below under section 5.3), the results with ADV7103 appears approximately comparable with SoC with a mean (SD) plasma bicarbonate pre-dose levels during 3 days of treatment at steady state of 21.7 (3.06) mmol/L with 45% (13/29) of the patients at target level, with only adults (24.1 mmol/L) being well controlled and adolescents (21.6 mmol/L), children (19.9 mmol/L) and infants (19.9 mmol/L) slightly below normal range. Potassium levels appear also comparable (mean 3.7 mmol/L; 82% at normal levels).

3.3. Uncertainties and limitations about favourable effects

Although non-inferiority was demonstrated (mean difference (95% CI) of 1.42 (0.41, 2.43) mmol/L, p<0.0001 for bicarbonate levels) and superiority was also reached with an adjusted mean difference (95% CI) of 1.64 (0.67, 2.60) mmol/L, p=0.0008 and confirmed with two imputation and a tipping point analyses, important limitations in the study design and conduct have been identified that limits conclusions on any non-inferiority and superiority claim, despite that the study design complied generally with earlier CHMP/SAWP and EMA/PDCO advices. Firstly, the assumption is made that patients were on an optimal SoC dose based on their long-term usual care without any interference during the 5 days follow-up. Further, a titration phase (up to 30 days) for ADV7103 has been applied to establish the optimal dose, which could inappropriately favour ADV7103 in comparison to SoC. Secondly, the sequential cross-over design further limits evaluation and interpretation for a direct comparison in time of SoC with ADV7103.

Treatment in patients below one year of age had not been evaluated and the single patient of one year of age treated discontinued treatment due to issues with treatment acceptability. Therefore, the CHMP questioned the appropriateness for use of Sibnayal in very young patients also because the current sachets cannot be applied in case of the presence of a feeding tube. It was acknowledged by the committee that intake of such granules depends on the maturity of the individual child and infant for swallowing but agreed with the applicant to amend the to be treated patient population to patients aged one year and older.

The primary efficacy findings on bicarbonate levels generally showed consistent effect with the overall effect when comparing ADV7103 to the subgroups of SoC treatment including bicarbonate (2.28 mmol/L), combination citrate + bicarbonate (2.14 mmol/L), and comparison to sodium (1.90 mmol/L), potassium (0.33 mmol/L) or both of them (2.73 mmol/L). However, SoC treatment with citrate appeared to demonstrate slightly better results than ADV7103 (-0.07 mmol/L).

Comparison for urinary endpoints showed a lower proportion with hypocitraturia for ADV7103 (10/16 (62.5%)) vs SoC (15/16 (94%)) and a higher responder proportion with normal UCa/UCi values for ADV7103 (11/19 (58%)) than for SoC (3/19 (16%). This did not translate in a clear beneficial impact of ADV7103 on several disease characteristics. Nephrocalcinosis increased from 86% to 97% (i.e. one patient developed nephrocalcinosis during the B22CS trial). Further, no impact has been observed for nephrolithiasis, bone alkaline phosphatase, phosphorus, vitamin D, calcium, parathyroid hormone, and calcitonin. Seven patients have shown a negative change in Z-score of the BMD from baseline to the end of the study, but this may inherent to the underlying disease. Further, no impact has been seen on stature and growth, or pubertal maturity.

During long term therapy exploratory evaluation showed improved perception of efficacy (91.2%), safety (72.2%), taste (68.6%) and more appropriate formulation (83.9%), and more convenient number of daily dose intakes (90.2%). However, these data should be taken with caution due to potential bias (e.g. information and recall bias) and the way questions were perceived which tend to be suggestive in favour of ADV7103 (e.g. *"As compared to your previous alkalinising treatment, what*

is/are the reason(s) for which you prefer keep ADV7103 rather than your previous alkalinising product?").

3.4. Unfavourable effects

Overall, during the short steady state period with ADV7103 (SPIII period) frequency of adverse events were 18.8%, with only 1 (3.1%) AE considered treatment related. Due to the longer follow-up period of 24 months in the OLE study more adverse events were reported than during the short-term pivotal study (90%), although treatment related events were limited to 5 patients (16.7%). The incidence of AEs was highest during the titration period with ADV7103 treatment with 19 (55.9%) AEs. For short-term SoC treatment, adverse events were reported for 18.9% and only 4 (10.8%) of AEs were treatment related.

In line with the currently known safety profile of the separate active substances of potassium citrate and potassium bicarbonate, most common adverse events were gastrointestinal disorders (16 patients (43.2%)), including abdominal pain (8 (21.6%)), upper abdominal pain ((5 (13.5%)), diarrhoea (3 (8.1%)), vomiting (3 (8.1%)), and nausea (2 (5.4%)) being mostly observed, mainly during the titration phase with ADV7103 13 (38.2%) vs 1 (3.1%) during steady state ADV7103 and 5 (13.5%) with SoC. During steady state, only the abdominal pain AEs (1 (3.1%) with ADV7103 and 3 (8.1%) with SoC) were considered treatment related. Another frequently reported adverse event was headache (2 (6.3%) during steady state ADV7103 and 2 (5.4%) with SoC), but this was not considered related to treatment. The long-term study confirmed the high frequency of gastrointestinal adverse events (12 (40%) including abdominal pain (3 (13.3%), vomiting (3 (10%)), diarrhoea (2 (7%)) and upper abdominal pain (2 (7%)). However, only in 5 patients (16.7%), GI symptoms were considered treatment related. Further, vitamin D deficiency (12 (40%)) and hypokalaemia (3 (10%)) were also frequently reported, likely associated with the underlying disease characteristics. The section 4.8 of the SmPC is therefore listing abdominal pain with a frequency very common and upper abdominal pain, diarrhoea, dyspepsia, gastrointestinal disorder, gastrointestinal pain, nausea and vomiting with a frequency common.

No patients discontinued treatment due to adverse events during 24 months of treatment with ADV7103.

Serious adverse events are limited, with one patient with gastroenteritis in an adolescent observed during the short-term pivotal study and resolved within 24 hours and 4 patients (13.3%) during the extension open label phase (renal colic (in an adult), gastritis and wisdom teeth removal (in an adolescents) and gastroenteritis rotavirus (in an infant)), but these were all considered unrelated to treatment, resolved within the following days and no dose changes were performed. Reassuringly, no deaths occurred during the studies.

Any risk for hyperkalaemia appears to be limited. Only one isolated case of hyperkalaemia of 4.7 mmol/L was reported in 1 child at Day 2 t0 of steady state ADV7103 treatment with no other episodes of hyperkalaemia during the rest of treatment. However, due to the severity of potential clinical consequences hyperkalaemia and renal impairment with GFR ≤ 44 mL/min/1.73m² are contraindications. Furthermore, the product information includes appropriate warning statements to use Sibnayal with caution in conditions pre-disposing them to hyperkalaemia as a further rise in plasma potassium may lead to cardiac arrest. In addition, the "risk of hyperkalaemia when used in patients with comorbidities such as renal impairment" is listed as an important identified risk in the risk management plan.

3.5. Uncertainties and limitations about unfavourable effects

The safety of ADV7103 has only been studied in 34 patients in the short-term and 30 patients during 24 months.

The incidence of AEs was highest during the titration period of ADV7103 (19 (56%), but this did not lead to limiting patients in reaching appropriate bicarbonate levels.

Due to the low number of subjects for each age category no conclusion can be drawn for the individual adverse events observed across these different age categories.

3.6. Effects Table

Effects Table for Sibnayal is a fixed-dose combination of prolonged-release granules of potassium citrate and potassium bicarbonate (data cut-off: 17 May 2018)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
BC level	Average bicarbonate blood level during 3 days of treatment at steady state with ADV7103 and SoC	mean (SD)	23.1 (1.62)	21.7 (3.06)	SoE: Primary endpoint; Non-inferiority value p<0.0001. Superiority value p=0.0037. Consistent effect across age groups and SoC types. Effect maintained during 24 months. Data supported by PK data.	Study B21CS
Abnormal BC level	Number/proportion of non-responder patients with abnormally low bicarbonataemia value (i.e. patients with a mean blood bicarbonate value below the lower normal value on Day 2 t0, Day 3 t0 or Day 4 t0).	n/N (%)	3/29 (10%)	16/29 (55%)	SoE: Secondary endpoint; Consistent effect across age groups and SoC types; p=<0.001.	
Hypercalciuria	Number of patients with a hypercalciuria after 4 to 5 days of treatment at steady state.	n/N (%)	2/28 (7%)	2/28 (7%)	SoE: Consistent effect across age groups and SoC types	Study B21CS

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Hypocitraturia	Number of patients with a hypocitraturia after 4 to 5 days of treatment at steady state.	n/N (%)	10/16 (63%)	15/16 (94%)		
Abnormal UCa/UCi	Number of patients with abnormally high urine calcium/citrate (UCa/UCi) ratio after 4 to 5 days of treatment at steady state	n/N (%)	8/19 (42%)	16/19 (84%)		
Unfavourable Effects						
Gastrointestinal disorders	SoC with most frequently reported AEs	N (%)	1 (3.1%)	5 (13.5%)	SoE: Expected event, inherent to mechanism of action. GI adverse events were higher during the titration phase (38% vs 3%).	Study B21CS
Treatment-related gastrointestinal disorders	SoC with most frequently reported treatment-related AEs	N (%)	1 (3.1%)	4 (10.8%)	SoE: Expected event, inherent to mechanism of action.	Study B21CS

Abbreviations: BC = bicarbonate, SoC = standard of care, UCa/UCi = urine calcium/citrate ratio

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Maintaining blood bicarbonate levels within the normal ranges in patients with dRTA is considered of important clinical relevance to correct metabolic acidosis and potentially reduce morbidity (nephrocalcinosis, lithiasis, bone remodelling and growth/development in children) and mortality, as best demonstrated for the separate active substances of these alkalising medicinal products. In the current study, a clinically relevant treatment effect has been observed of Sibnayal (ADV7103) prolonged-release granules, dosed twice daily, in the maintenance of blood bicarbonate levels, in adults, adolescents and children >12 months of age, remaining over a long-time period (24 months) without patient discontinuing their intended life-long treatment. Based on the known mechanism of action, this treatment effect was expected. dTRA generally presents with hypokalaemia. The use of potassium as cation shows that potassium levels were generally maintained at the lower site of the normal range, without an observed risk for hyperkalaemia.

It should however be mentioned, that a formal claim on non-inferiority and superiority cannot be made due to several issues on the robustness of the study design and conduct, such as the concerns found around a lack of titration for an optimal dose for SoC treatment, as comparator and the sequential study design.

The treatment effect, including a 24-hour effect coverage, has been obtained with twice-daily dosing of Sibnayal, which may waive the need for possible dosing at night with current therapies, which sometimes need a 3 to 6 times daily dosing. Although not fully demonstrated by clinical data, the combination of the citrate (for the first three hours) and the bicarbonate (after passing the stomach to about twelve hours after intake), as observed in *in-vitro* dissolution data, would allow for a more consistent and complete alkalising effect over the twelve hours for twice daily dosing, than each mono-component could achieve.

Any other beneficial impact of ADV7103 on several (longer term) disease characteristics including urine calcium and urine citrate, and nephrocalcinosis, nephrolithiasis, and bone parameters, stature and growth could not be clearly observed. This may likely be explained by the fact that patients were already (almost) controlled with SoC and no major improvement in bicarbonate control was seen with ADV7103. Also, any potential calcium chelating effect of potassium citrate may not be sufficiently effective when only a twice-a-day 3-4-hour effect is covered.

The safety profile of Sibnayal in patients with dRTA was comparable to that of SoC treatment. It is mainly characterised by gastrointestinal adverse events but seem not to compromise long term treatment as none of the patients discontinued treatment due to adverse events during 2 years of treatment. Frequencies of serious adverse events were limited and did not seem to compromise treatment continuation. Overall, no new or unexpected safety signals were identified during the conduct of the study in the dRTA population, although the safety base is very limited.

In light of absence of data in children <1 year the submitted data was considered by the CHMP to support positive B/R only in patients >1 year old. Therefore, the applicant agreed to apply for treatment in patients > 1 year old.

3.7.2. Balance of benefits and risks

An overall treatment effect of plasma bicarbonate levels within the normal range was observed in adults, adolescents and children >12 months of age with dRTA during 24 months of treatment with Sibnayal, which is of clinical relevance, also in terms of responder rates. The safety and tolerability profile of Sibnayal is considered acceptable.

The benefit/risk of Sibnayal is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

None

3.8. Conclusions

The overall B/R of Sibnayal is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Sibnayal is favourable in the following indication:

"Sibnayal is indicated for the treatment of distal renal tubular acidosis (dRTA) in adults, adolescents and children aged one year and older"

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0355/2018 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.