NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Slow-release potassium bicarbonate and potassium citrate for treating distal renal tubular acidosis [ID3787]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Slow-release potassium bicarbonate and potassium citrate for treating distal renal tubular acidosis [ID3787]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

Pre-technical engagement documents

1. **Company submission from** Advicenne
2. **Clarification questions and company responses**
3. **Patient group, professional group, and NHS organisation submissions** from:
   a. NHS England
4. **Evidence Review Group report** prepared by ScHARR
5. **Evidence Review Group report – factual accuracy check**

Post-technical engagement documents

6. **Technical engagement response from company**
7. **Evidence Review Group technical engagement critique**
8. **Evidence Review Group Addendum changing the utility multiplier associated with end stage renal disease**
9. **Patient expert statement from Nicola MacArthur**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

ADV7103/ADV7103 for treatment of distal Renal Tubular Acidosis - ID9790

Document B

Company evidence submission

November 2021

File name	Version	Contains confidential information	Date
NICE SUBMISSION FINAL	**V2**	**Yes**	**14th January 2022**

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

In this template any information that should be provided in an appendix is listed in a box.

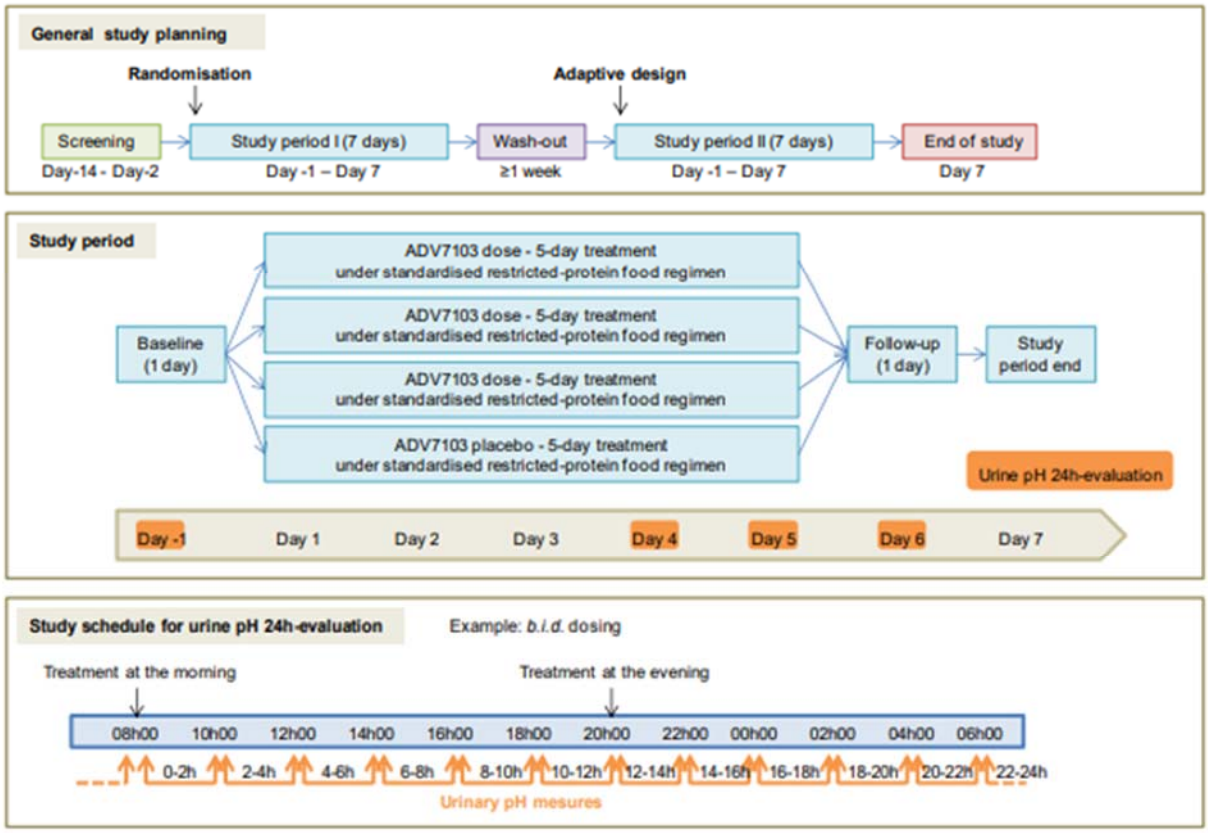
Abbreviation list

ACCP	Amorphous carbonated calcium phosphate
ACE	Angiotensin converting enzyme
AD	Autosomal dominant
AE	Adverse events
ANCOVA	Analysis of covariance
AR	Autosomal recessive
AUC	Area under curve
BID	Bidaily
BMD	bone mineral density
BMI	Body mass index
BMJ	British Medical Journal
CA	Carbonic anhydrase
CHMP	Committee for Human Medicinal Products
CI	Confidence interval
CKD	Chronic kidney disease
CPRD	Clinical Practice Research Datalink
CRD	Centre for Reviews and Dissemination
CRF	Chronic renal failure
CS	Clinically significant
CSR	Clinical Study Report
CT	computerised tomography
dRTA	Distal renal tubular acidosis
ECG	electrocardiogram
EMA	European Medicines Agency
EU	European Union
FHS	Facial hedonic scale
GFR	Glomerular filtration rate
GI	Gastrointestinal
GTS	Growing Teratoma Syndrome
HIV	Human immunodeficiency virus
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IFU	Information for use
IMP	Investigational medical products
ITT	intention-to-treat
LOQ	Limit of quantification
LS	Least square
LYG	Life years gained
MDRD	Modification of Diet in Renal Disease
NCS	Not clinically significant
NICE	National Institute for Health and Care Excellence
NORD	National Organisation for Rare Disorders
OLE	Open-label extension
PbR	Payment-by-results
PP	Per Protocol

PSS	Personal and Social Services
QALY	Quality-adjusted life year
QoL	Quality of life
ROMK	renal outer medullary potassium channel
SAE	Serious adverse events
SD	Standard deviation
SDS	standard deviation score
SE	Standard errors
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SoC	Standard of care
SP	Study periods
STA	Single technology appraisal
TEAE	Treatment-emergent adverse events
VAS	Visual analogue scale
WHO	World Health Organisation

Contents

Tables and figures



B.1 Decision problem, description of ADV7103 and clinical care pathway

The submission covers the technology's full marketing authorisation for this indication.

B.1.1 The decision problem

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with distal renal tubular acidosis aged 1 year and older	People with distal renal tubular acidosis aged 1 year and older	Not applicable.
Intervention	Prolonged-release potassium citrate and potassium bicarbonate (ADV7103)	Prolonged-release potassium citrate and potassium bicarbonate (ADV7103)	Not applicable.
Comparator(s)	Established clinical management without prolonged-release potassium citrate and potassium bicarbonate (ADV7103), which may include alkalinising treatments alone or in combination with one another	Established clinical management without prolonged-release potassium citrate and potassium bicarbonate (ADV7103), which may include alkalinising treatments alone or in combination with one another	Not applicable.
Outcomes	The outcome measures to be considered include: • Bicarbonate level in the blood • Potassium level in the blood • Calcium level in the urine • Citrate level in the urine • Renal function • Measures of impaired growth • Bone mineral density • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Bicarbonate level in the blood • Potassium level in the blood • Calcium level in the urine • Citrate level in the urine • Renal function • Measures of impaired growth • Bone mineral density • Adverse effects of treatment • Health-related quality of life	Not applicable.

Economic analysis	The outcome measures to be considered include: • Bicarbonate level in the blood • Potassium level in the blood • Calcium level in the urine • Citrate level in the urine • Renal function • Measures of impaired growth • Bone mineral density • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Bicarbonate level in the blood • Potassium level in the blood • Calcium level in the urine • Citrate level in the urine • Renal function • Measures of impaired growth • Bone mineral density • Adverse effects of treatment • Health-related quality of life	Not applicable.

B.1.2 Description of the technology being appraised

ADV7103/SIBNAYAL® is a fixed-dose combination of two alkalising agents: potassium citrate and potassium hydrogen bicarbonate. The aim of the therapy is to correct metabolic acidosis while maintaining normal blood bicarbonate concentration (generally between 21 and 29 mEq/L, with some adaptations according to the subset of age) to achieve blood pH normalisation (7.35<pH<7.45) and serum potassium (between 3.5 and 5.5 mmol/L) control, as well as to correct other parameters related to dRTA pathophysiology. Citrate provides an alkali load, corrects hypocitraturia and ensures chelation of calcium in excess in urine, which may otherwise lead to nephrocalcinosis and nephrolithiasis. Bicarbonate guarantees the prolonged alkali effect on blood pH. The potassium cation allows hypokalaemia correction (1).

The pharmacological and clinical profile of ADV7103 has the potential to provide consistent and efficacious effects, which translate into a clinical benefit for patients with dRTA (1).

ADV7103 is the first approved treatment for dRTA. It is innovative, patented and adapted for all ages. dRTA is a debilitating orphan disease, with severe long-term consequences especially on patient's kidney and bones, and therefore growth for children, causing a substantial quality of life and cost burden. dRTA can be life-threatening in some specific severe cases. Adequate metabolic control is necessary to prevent severe and long-term renal and bone outcomes of dRTA. So far, there is no efficacious treatment available to achieve the appropriate control necessary to optimally treat dRTA patients. ADV7103 has demonstrated superiority versus current treatment on metabolic control with a sustained efficacy, a good GI tolerance and a high level of compliance. [1-4]

Table 2: Technology being appraised

UK approved name and brand name	**ADV7103 (SIBNAYAL®)**
Mechanism of action	ADV7103 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 ADV7103 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. ADV7103 provides a source of potassium to correct hypokalaemia. In addition, citrate acts also as a calcium chelating agent. Oral prolonged-release citrate granules are absorbed at a pH between 4.8 and 6.4 along the upper portion of the small intestine (duodenum, early part of jejunum). Under these conditions, the intestinal absorption of citrate is rapid and almost complete. Oral prolonged-release bicarbonate granules are absorbed throughout the gastrointestinal tract. Bicarbonate neutralises gastric acid with the production of CO_2 eliminated by the respiratory route. Bicarbonate not involved in that reaction is rapidly absorbed by the intestinal mucosa. The potassium ions are fully absorbed, irrespective of the amount consumed. Most of the potassium absorption occurs in the small intestine, mainly through passive diffusion. The absorption of citrate and bicarbonate into different parts of the gastrointestinal (GI) tract allows the preparation of ADV7103 to achieve

<table>
<tr><td></td><td>sustainable control of metabolic acidosis [5]</td></tr>
<tr><td>Marketing authorisation/CE mark status</td><td>Advicenne submitted a Marketing Authorisation Application to the European Medicines Agency (EMA) in November 2019, with a positive Committee for Medicinal Products for Human Use (CHMP) opinion recommending approval of ADV7103 for treatment of dRTA received in mid-December 2020. EU market authorisation was obtained 30th April 2021. Great Britain MA was received 1st July 2021.

On 20 June 2017, orphan drug designation (ODD) (EU/3/17/1888) was granted by the European Commission to Advicenne Pharma SA, France, for tripotassium citrate monohydrate and potassium hydrogen carbonate (also known as ADV7103) for the treatment of distal renal tubular acidosis. On 19th March 2021, Advicenne decided to withdraw its application for the ODD as it was informed by EMA that additional data would be needed to grant/confirm ODD status.

On the 7th of June 2021 Advicenne decided to withdraw its application for the Great Britain ODD as it was informed that additional data would be required.

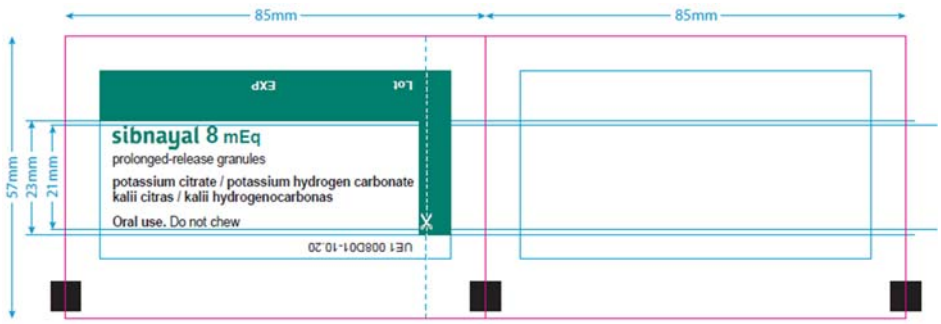
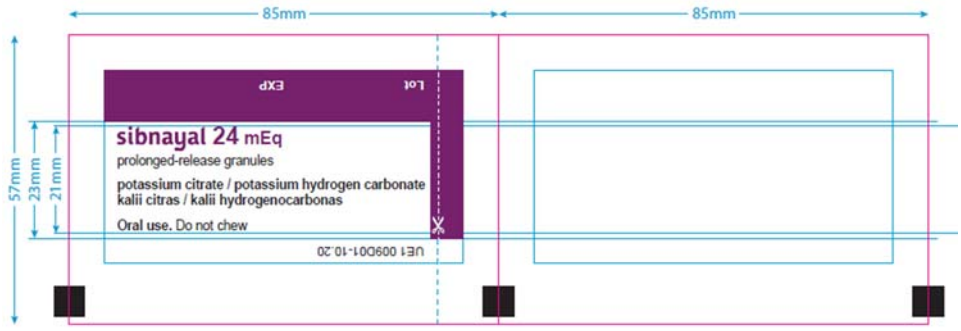
To date, 70 patients have been/are treated with ADV7103 in the frame of an early access program (EAP) approved by the local competent authorities, mainly in the indication of dRTA, and only single cases of proximal RTA and cystinuria, according to the available information. The distribution of the patients per country, per indication and the date of the first EAP date of authorisation is presented in Table 3.

Table 3: Availability of ADV7103 per country to date
<table>
<tr><th>Country</th><th>Date of first authorisation</th><th>Indication</th><th>Number of treated patients [a]</th></tr>
<tr><td>Spain</td><td>December 2019</td><td>dRTA</td><td>5</td></tr>
<tr><td>France</td><td>July 2018</td><td>dRTA/proximal RTA and cystinuria</td><td>55</td></tr>
<tr><td>Great Britain</td><td>Early 2020</td><td>dRTA</td><td>1</td></tr>
<tr><td>Serbia [b]</td><td>May 2020</td><td>dRTA</td><td>1</td></tr>
<tr><td>Slovakia</td><td>October 2018</td><td>dRTA</td><td>1</td></tr>
<tr><td>Sweden</td><td>March 2018</td><td>dRTA</td><td>6</td></tr>
<tr><td>Denmark*</td><td>unknown</td><td>dRTA</td><td>1</td></tr>
<tr><td>Total</td><td></td><td></td><td>70</td></tr>
</table>
a: Patient treated means the treatment has been ordered and provided

b: Patient enrolled not yet treated</td></tr>
<tr><td>Indications and any restriction(s) as described in the summary of product characteristics (SmPC)</td><td>ADV7103 is indicated for the treatment of distal renal tubular acidosis (dRTA) in adults, adolescents and children aged one year and older.

Contraindications include those patients with renal impairment with glomerular filtration rate (GFR) ≤ 44 mL/min/1.73m², and those with hyperkalaemia. Another contraindication is hypersensitivity to the active substances or any excipients, which include:

Granules: Hypromellose (E464), Microcrystalline cellulose (E460(i)), Glycerol</td></tr>
</table>

	dibehenate, Magnesium stearate (E470b), Silica colloidal anhydrous, Magnesium oxide, heavy (E530) Coating: Ethylcellulose (E462), Chlorophyllin (E140 (ii)) Technological agent: Talc.
Method of administration and dosage	**Pack size** ADV7103 8 mEq prolonged-release granules: One sachet contains 282 mg of potassium citrate and 527 mg of potassium hydrogen carbonate. 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). ADV7103 24 mEq prolonged-release granules: One sachet contains 847 mg of potassium citrate and 1,582 mg of potassium hydrogen carbonate. 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) [5]. A pack contains 60 sachets. *Figure 1: ADV7103 packaging: 8mEq*  *Figure 2:ADV7103 packaging: 24mEq*  For oral use. The total daily dose is administered twice daily, typically twelve hours apart. ADV7103 must be taken orally, swallowed with a large glass of water. The full dose of granules per intake can be swallowed in several smaller portions, if necessary, but the content of each sachet must be entirely taken. Doses should be taken preferably during meals.

For patients who are unable to swallow granules as described above, the granules may be mixed (without crushing) with small amounts of soft food (e.g., fruit puree, yoghurt). The ADV7103 soft food mixture must be used immediately and cannot be stored. The mixture should be swallowed without chewing. Care should be taken to ensure that ADV7103 is not retained in the mouth.

In no instance granules must be mixed with hot food, hot liquid or alcohol or chewed or crushed 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.

ADV7103 granules are not suitable for administration via feeding tubes due to high risk of obstructing the tubes.

Dosing of ADV7103 is based on age and weight.

When initiating alkalising therapy, the target starting daily dose indicated below for each age group should be used and incrementally titrated to obtain the optimal dose that provides adequate metabolic acidosis control based on plasma bicarbonate and potassium levels.

- Adults: initiation at 1 mEq/kg/day, with a maximal incremental increase/decrease of 0.5 mEq/kg/day to optimal dose
- Adolescents from 12 years: initiation at 1 mEq/kg/day, with a maximal incremental increase/decrease of 1.0 mEq/kg/day to optimal dose
- Children from 4 to 11 year inclusive: initiation at 2 mEq/kg/day, with a maximal incremental increase/decrease of 1.5 mEq/kg/day to optimal dose
- Children from 1 to 3 years inclusive: initiation at 4 mEq/kg/day, with a maximal incremental increase/decrease of 1.5 mEq/kg/day to optimal dose

When switching from another alkalising therapy to ADV7103, treatment should be initiated at the target dose used with the previous therapy (in mEq/kg/day) and titrated where necessary as described above.

The maximum dose, regardless of the age group, is either 10mEq/kg/day or a total daily dose of 336 mEq, whichever is lower.

The total daily dose should be administered in two intakes. For each individual patient, the nearest dose to the target dose should be fixed by combining sachets of the two available strengths.

In case of vomiting within two hours after intake, the patient should take another dose.

The use of this medicine requires medical supervision.

<u>Special populations</u>

Renal impairment

ADV7103 should only be used in individuals with GFR > 44mL/min/1.73m². For individuals with GFR between 45 and 59 mL/min/1.73m² ADV7103 should only be used if the potential benefits are considered to outweigh the potential risks.

GFR	**Treatment of dRTA**

<table>
<tr><td></td><td>
<table>
<tr><th>mL/min/1.73m²</th><th></th></tr>
<tr><td>45-59</td><td>Plasma potassium levels in the normal ranges:
A regular monitoring of renal function parameters and blood potassium levels is necessary.</td></tr>
<tr><td></td><td>Elevated plasma potassium:
Contraindicated</td></tr>
<tr><td>≤ 44</td><td>Contraindicated</td></tr>
</table>
No dose adjustment is required for the elderly or those with hepatic impairment. No data are available for the safety and efficacy of ADV7103 in children below one year of age [5]
</td></tr>
<tr><td>Additional tests or investigations</td><td>ADV7103 is also being investigated as a therapy for Cystinuria.</td></tr>
<tr><td>List price and average cost of a course of treatment</td><td>
Table 4: ADV7103 price per box
<table>
<tr><th>Price per box (approved by Department of Health)</th><th>0.25 per mEq</th></tr>
<tr><td>24 mEq</td><td>£ 360.00</td></tr>
<tr><td>8 mEq</td><td>£ 120.00</td></tr>
</table>
Table 5: Total mEq of ADV7103 per year
<table>
<tr><th></th><th>8 mEq</th><th>24 mEq</th></tr>
<tr><td>Boxes for average adult patient per year</td><td>7</td><td>29</td></tr>
<tr><td>Sachets per year</td><td>408</td><td>1,740</td></tr>
<tr><td>mEq per year</td><td>3,264</td><td>41,760</td></tr>
<tr><td>Total mEq per year</td><td colspan="2">45,024</td></tr>
</table>
Average cost for an average adult per year £11,256 (45,025*0.25).
</td></tr>
<tr><td>Patient access scheme (if applicable)</td><td>Yes, a simple PAS scheme has been applied for.</td></tr>
</table>

B.1.3 Health condition and position of the technology in the treatment pathway

dRTA

Distal renal tubular acidosis (dRTA), also known as Type 1 RTA, is a rare and severe disease, characterised by a renal defect in hydrogen ion secretion (distal renal tubule localisation) inducing an hyperchloremic metabolic acidosis (blood pH ≤ 7.35) with no urine acidification. Typically, non-RTA patients have a blood pH of approximately 7.4, which corresponds 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 22mmol [6].

dRTA can be of inherited origin, usually presenting in childhood, or of acquired form, usually presented in adults [7]. The inherited form of dRTA may present with various degrees of severity depending on the gene mutation and can be transmitted as autosomal dominant or autosomal recessive trait, the latter being more severe and frequently associated with sensorineural hearing loss [8]. The active acidification process that constantly occurs in the ear to maintain the endolymph pH closer to 6.6 in the endolymphatic sac is weakened in patients with dRTA [8].

Acquired forms of the disease are usually associated with autoimmune diseases, such as Sjögren's syndrome, systemic lupus erythematosus or autoimmune chronic liver disease [8]. The acquired forms are thought to be because of the suppression that the autoimmune disease causes to the expression of acid-base transporters (H^+-ATPase or AE1) in the α-intercalated cells of the distal tubule.

A list of both inherited and acquired causes of dRTA are presented in Table 6 [8].

Table 6: Inherited and acquired causes of dRTA [8]

Origin	Cause
Inherited	Autosomal dominant
	Autosomal recessive with deafness
	Autosomal recessive without deafness
Acquired, associated with systemic disease	Multiple myeloma
	Amyloidosis
	Systemic lupus erythematosus
	Sjögren's syndrome
	Primary biliary cirrhosis
	Chronic active hepatitis
	Cryoglobulinemia
	Thyroiditis
	Post transplantation rejection
	Balkan nephropathy
Acquired, associated with nephrocalcinosis	Hyperparathyroidism
	Primary nephrocalcinosis
	Idiopathic hypercalciuria
	Vitamin D intoxication
	Medullary sponge kidney
Acquired and associated with drugs	Amphotericin B
	Toluene
	Vanadate
	Lithium
	Analgesics

Origin	Cause
	Cyclamate

Source: Yaxley and Pirrone, 2016.

dRTA is characterised by [7], hyperchloremic (non-AG) metabolic acidosis, inability to acidify urine pH <5.5, hypokaelemia, positive UAG, nephrolithiasis and nephrocalcinosis, skeletal abnormalities, Sensorineural hearing loss and intact proximal tubule function (in most patients).

Epidemiology

There are little published data available for dRTA, therefore retrospective analysis is used to provide an estimate for prevalence in England. Clinical Practice Research Datalink (CPRD) is an ongoing primary care database of anonymised medical records from general practitioners. Using data extrapolated from the CPRD, the lower bound prevalence (those diagnosed and coded in the database with dRTA) was found to be 0.46 in 10,000 people. The upper bound prevalence, inclusive of both coded patients and those suspected to have dRTA, was estimated to be 1.60 in 10,000 people.

In confirmed diagnosed cases, 22.1% were defined as inherited dRTA. The mean age of diagnosis, defined as the first visit to a nephrologist or first record of dRTA by a GP, was 46 [3].

The global incidence of dRTA is not known with certainty, mainly due to its complex relationship with the range of coexisting diseases and conditions in conjunction with it being a hereditary or acquired condition [9].

Literature suggests that primary distal renal tubular acidosis affects females and males in equal numbers. The exact number of people with this disorder is unknown. Rare disorders like primary dRTA often go misdiagnosed or undiagnosed, making it difficult to determine their true frequency in the general population [10]. The hereditary forms of dRTA are more prevalent in areas of high consanguinity (Arabic peninsula and North Africa) whereas acquired dRTA has been reported more frequently in Western countries [11].

In June 2017, when ADV7103 was designated as an orphan medicinal product in the EU for the treatment of dRTA (since withdrawn), dRTA was said to affect approximately 2.1 in 10,000 people in the EU 33. For the purpose of the designation, the prevalence of primary (inherited) dRTA was calculated based on publications and consultations of national reference hereditary centre databases. Prevalence of acquired dRTA is mainly driven by Sjögren syndrome, a systematic autoimmune disease Secondary Sjogren[12], since 2.6% to 5.3% of Sjögren patients develop dRTA. This led to an estimated number of patients with dRTA of around 108,000 (i.e., 2.1 in 10,000 persons) at mid-2017 in the EU 25 countries including Iceland, Liechtenstein and Norway, which is below the threshold for orphan designation (5 in 10,000). Since then, a re-evaluation of dRTA prevalence was done to complete ADV7103/ADV7103 Orphan Drug maintenance report and concluded with an unchanged prevalence [13].

Symptoms

Inherited dRTA can present in infancy, with symptoms including vomiting, diarrhoea and/or constipation, and in extreme cases, profound episodes of dehydration, tachypnoea, loss of appetite, polydipsia and obtundation (altered level of consciousness), requiring hospitalisation [4,6,14]. From childhood, clinical complications can include growth failure, sensorineural hearing loss, vomiting, obtundation, nephrolithiasis, and rickets [15].

Common clinical consequences of dRTA in adults include vomiting, diarrhoea and/or constipation, loss of appetite, paralysis, muscle weakness, polydipsia and polyuria, nephrocalcinosis, nephrolithiasis, osteomalacia, and rickets [15].

Table 7 shows manifestations associated with dRTA, from the study of 95 Chinese dRTA cases [16.]

Table 7: Common Clinical Manifestation Analysis of 95 dRTA cases (adult and paediatric cohort)

	Manifestation	Number	Percentage (%)
Common clinical manifestation	Muscle weakness	65	84.2%
	Over drinking due to thirst and diuresis	22	23.16
	paralysis	30	32.00
	anorexia	13	13.68
	arthralgia	10	10.53
	dyspnoea	11	11.58
	muscle ache	10	11.00
	acroanaesthesia	18	18.95
	palpitation	11	12.00
	tic of limbs	9	9.47
	growth retardation in children	9/14	64.29
Renal involvement manifestation	increased nocturia	39	41.05
	urinary infection	6	6.32
	urinary lithiasis	11	11.58
	kidney calcification	4	4.21
	eGFR<60ml/min/1.73m^2	28	29.47

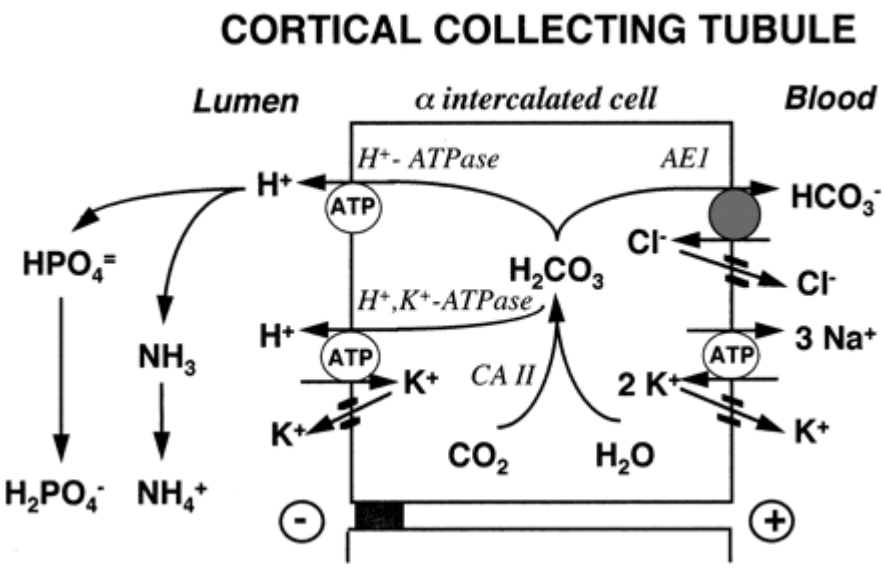
Source: Zhang, 2015. Abbreviations: eGFR = Estimated Glomerular Filtration Rate.

Pathophysiology

dRTA is a hyperchloremic metabolic acidosis disorder because of an insufficient renal excretion of protons (H^+) by the distal segment of the renal tubule, and insufficient reabsorption 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 [9,17].

Cellular mechanisms involved in the acid-base homeostasis by α-intercalated cells of the distal tubule are presented in Figure 3. The key 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 [9,18].

Figure 3: Cellular mechanisms involved in the acid-base homeostasis by α-intercalated cells of the distal tubule [17]



Source: Roy et al. 2015.

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^-/HCO3- exchange pump (i.e. Anion Exchange AE1) [18]. The activity of both transporters, H^+-ATPase and AE1, are functionally linked since their substrates (H^+ and $HCO3^-$, respectively) are produced by the same catalytic activity of the cytosolic carbonic anhydrase II (CA II) [18].

Likewise, 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 Cl^- into the blood. Most relevant are the Cl^-/K^+ co-transporter (KCC4) and the Cl^- transporter, ClC^-Kb [19].

Therefore, 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, leading to a reduction in secretion of $HCO3^-$ into the blood [1]. 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 [18].

The exact mechanism of hypokaelemia in dRTA still remains unknown [20]. Enhanced K+ secretion by ROMK and by maxi-K voltage-gated potassium channel in β-intercalated cells is probably responsible for K+ loss [20].

Failure to secrete H+ may also contribute to K+ secretion because of the change in transtubular gradient [20,21]. Another explanation for hypokaelemia could be that patient with dRTA exhibit some degree of sodium depletion with mild hypovolemia that results in high levels of aldosterone, which, in turn, promote K+ secretion. However, since hypokaelemia suppresses aldosterone secretion, other factors rather than secondary hyperaldosteronism may play a role in severe hypokalaemic state in dRTA.

Biochemical consequences of dRTA

dRTA is marked by decreased proton secretion from the α-intercalated tubular cell into the urine due to the impairment in the luminal H^+-ATPase pump and decreased $HCO3^-$ secretion into the blood by the AE1 ($HCO3^-/Cl^-$) exchange pump [17].

Ineffective acid-base transportation of the α-intercalated cells results in abnormal blood biochemistry manifested by abnormally low concentrations of HCO3- (hypobicarbonataemia) and of K^+ (hypokalaemia), as well as an increase in Cl^- concentration (hyperchloremia). Therefore, the

hyperchloremic metabolic acidosis is accompanied by a normal plasma anion gap. There is also abnormal urine biochemistry, which consists in decreased concentration of protons and increased urinary excretion of NH_3 (ammoniuria) and $HPO42^-$ (hyperphosphaturia) due to decreased formation of urinary $NH4^+$ and $H2PO4^-$ [17].

The reduced $HCO3^-$ blood concentration induces blood pH acidification. Two mechanisms are activated to compensate low $HCO3^-$ to buffer the acid blood pH. The first is endogenous citrate is reabsorbed from the renal tubules into the blood, which decreases the levels of citrate in the urine (hypocitraturia) [6,19,22]. The second is release of bicarbonate and often phosphate combined with calcium stored in bone. The excess calcium released from bone mineral reduction leads to hypercalciuria, intensified by an acidosis-related down-regulation of renal calcium transport proteins and an increased distal sodium release [19].

Clinical consequences of dRTA

Growth

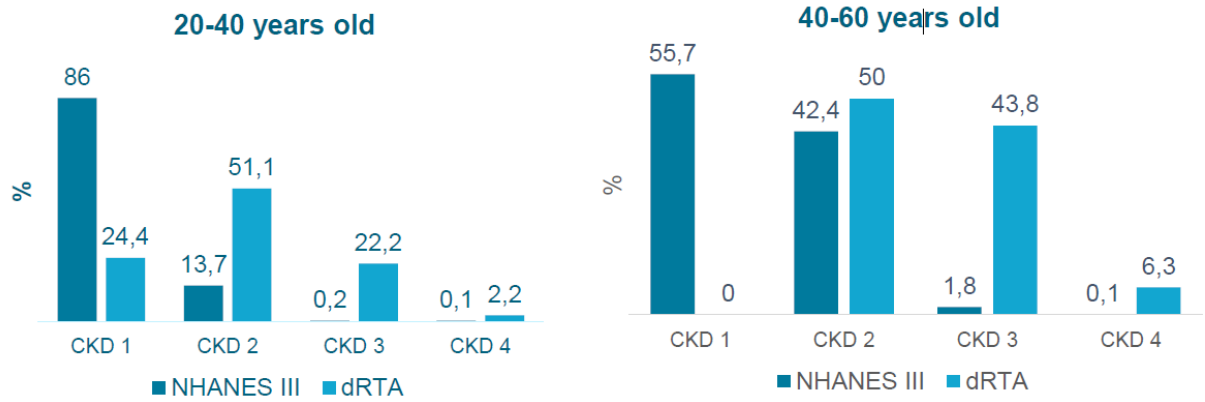
Blood pH homeostasis is required for the secretion of growth hormones, metabolic acidosis induces stunted growth which will usually lead to a physician diagnosis of dRTA in children. For this reason, an Italian cohort of 89 children showed failure to thrive in 58% of children with dRTA and in a UK cohort of 24 inherited dRTA patients, growth retardation was found in ten patients at presentation (41.6%) and persisted in 3 (12.5%) [23].

Kidney complications

Hypercalciuria, hyperphosphaturia, hypocitraturia and a high urine pH, encourage atypical renal calcium deposition such as nephrocalcinosis and/or nephrolithiasis (specifically, multiple and bilateral type IVa2 renal stones), both of which may result in chronic kidney disease (CKD). Renal insufficiency, in the form of CKD stage 2 or worse has been found in 37.5% of a cohort of 24 UK children with dRTA [23]. In the long-term of chronic metabolic acidosis, it can lead to end-stage renal disease [7,14,15,19,24].

In a recently published retrospective study, from a large cohort of patients with inherited dRTA, the authors showed that most of the adults (85%) had CKD stage 2-4, compared to a much lower 26% of patients aged 20-60 in the general population suffering from CKD stage 2-4 (National Health and Nutrition Survey [Nhanes] III data).

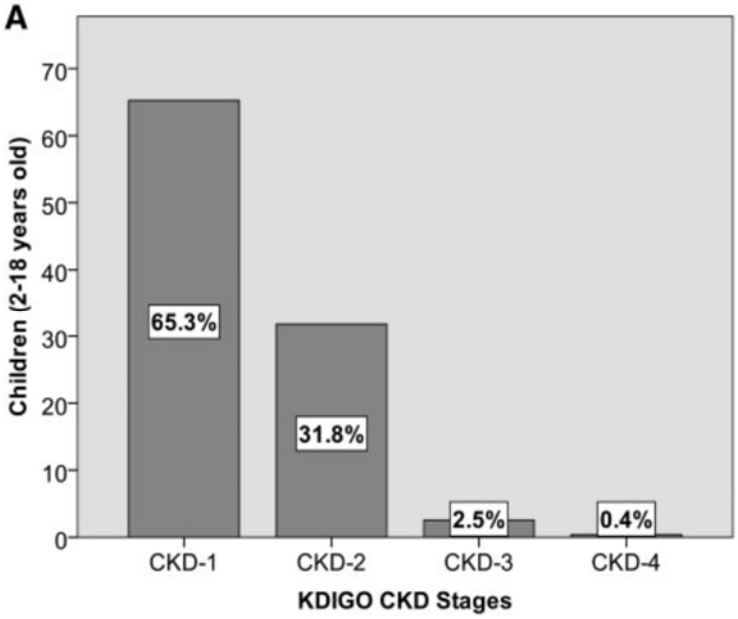
Table 8: Comparison of CKD stage ≥ 2 in dRTA adult patients and the general population



Source: Lopez-García (2019). Abbreviations: dRTA = distal Renal Tubular Acidosis, NHANES = National Health and Nutrition Survey.

A third (34.7%) of the dRTA children (aged 2–18 years) had an impaired eGFR (<90mL/min/1.73m^2), mostly CKD stage 2.

Figure 4: CKD in children from retrospective study



Source: Lopez-García, 2019. Abbreviations: CKD = chronic kidney disease.

The authors also observed that adequate metabolic control (i.e., normal plasma bicarbonate and normocalciuria) was achieved [7] in only half of the patients presenting an substantial unmet need in current management.

Long-term outcomes associated with dRTA

The following section will explore long-term outcomes associated with dRTA. It has been reported that CKD prevalence in dRTA is 41-71% at 20- and 40-years follow-up. In general population CKD prevalence reported is 5-17% at 20 and 40 years, respectively. Almost half of the patients (43%) at 40 years follow-up had moderate to severe CKD, with eGFR < 35 ml/min/1.73m^2. The rate of decline of kidney function was 2 ml/min per year from 10 to 20 years of follow-up and 1.65 ml/min per year from 20 to 40 years of follow-up [25].

Bone

Rickets are present in a large proportion of children with RTA. The proportion of dRTA children with rickets was 25% (7/28). Jha et al. 2011 reported that 59% (26/44) of dRTA children suffered from rickets.

Osteoporosis, another bone manifestation, was found in 43% of the children, and bone issues were observed in 92% of the patients with late alkalising therapy onset. Osteomalacia has been reported in 9.6% (5/52) to 23.3% (24/103) of adult patients with dRTA [26,27].

In the cohort of 95 genetic dRTA Chinese patients of mean age 38 years the prevalence of bone consequence was described: osteoporosis (90%), bone pain (7.4%), fractures (6.3%), bone deformation (7,1%) as well as retardation in bone age in children (21.4%) [16].

Table 9: Bone disease in Chinese cohort of 95 patients

Presentations	Number	Percentage (%)
Osteoporosis	9/10	90
Bone pain	7/95	7.37
Bone fracture	6/95	6.32
Bone deformity	7/95	7.14

Presentations	Number	Percentage (%)
Retardation of bone age in children	3/14	21.43%

Source: Zhang, 2015.

Clinical consequences of hypokalaemia

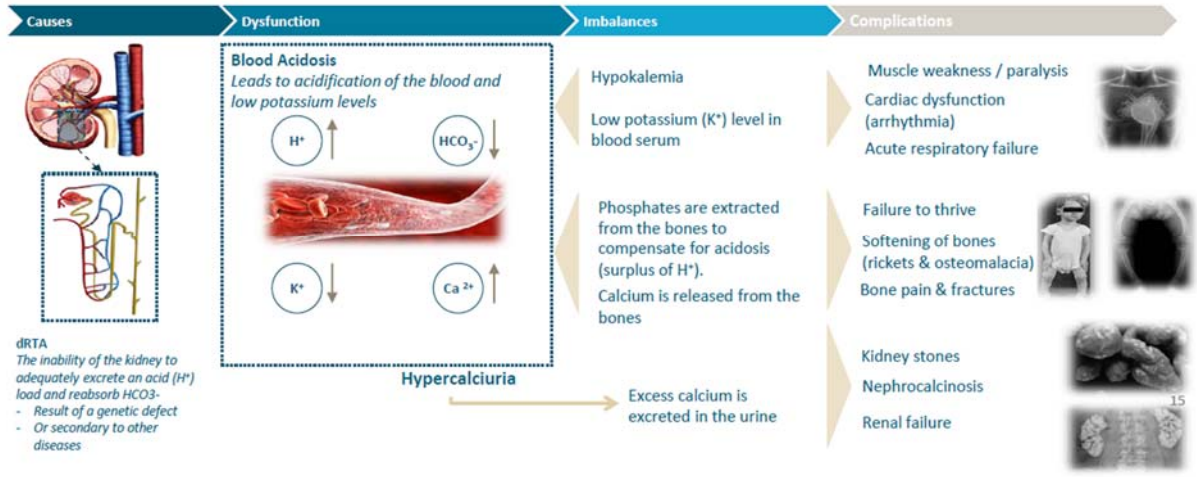
dRTA can cause low levels of potassium in the blood, a serious condition known as hypokaelemia [28]. It is estimated that hypokalaemia presents in 30-50% of patients with dRTA [29]. The main presentation of hypokalaemia is muscle weakness, but it can also present in mild signs of fatigue, constipation, myalgia, bone pain and in some cases muscular paralysis [30,31]. The main presentation of hypokalaemia is muscle weakness, but it can also present in mild signs of fatigue, constipation, myalgia, bone pain and in some cases muscular paralysis [30,31]. Hypokaelemia is present in a high proportion of dRTA patient: 47% in the Italian cohort [15] to 63% in the Chinese cohort [16].In a population in the north-east of Thailand where dRTA is high prevalent, hypokalaemia has been identified as the prime and possibly the most fundamental factor causing hypokalaemic periodic paralysis and five sudden unexplained nocturnal death [32].

Hearing loss

Sensorineural hearing loss is a classic-associated feature of dRTA. Lopez-García (2019) confirms the close association of deafness with mutations in ATP6V1B1 [19]. However, there is also clinically relevant deafness in almost a third of patients with ATP6V0A4 mutations, with hearing aids or cochlear implants present in 26 and 5%, respectively. There is also a 6% rate of hearing aids prescription in patients with SLC4A1, the youngest at 4 years of age. This reflects the prevalence of hearing loss in the general population [2,33].

Figure 5 presents a step-by-step diagram of dRTA, from causes through to complications.

Figure 5: dRTA causes, dysfunction, imbalances and complications



Source: Advicenne Data on File, 2020.

Necessity of restoration of adequate metabolic control

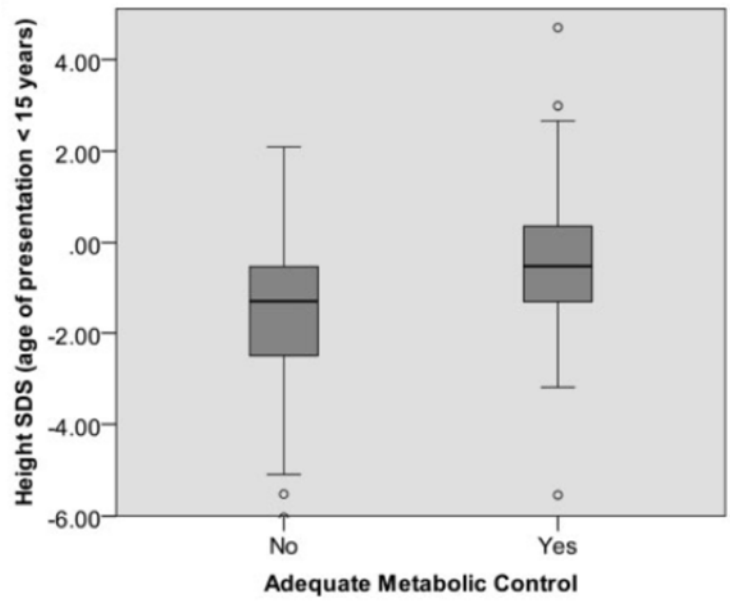
Restoration of adequate metabolic control is key to lowering the risk and the development of the long-term and life-threatening outcomes of dRTA. Adequate metabolic control is defined as plasma or serum bicarbonate 22.0 mmol/L and the absence of hypercalciuria. The correct metabolic control will have a significant impact on limiting the long-term consequences on kidneys and bones [7].

Growth

When untreated, dRTA can have a severe impact on growth. However, when treated with alkaline therapy, a patient's height and weight has been shown to improve [34]. Adequate metabolic control is required for optimal growth. In the Lopez-García (2019) study, adult height is only mildly impaired at -

0.57 standard deviation (SD) and, again, the majority (90%) of adult patients had achieved a final height in the normal range (SDS>-2.0). Height SDS was significantly (P<0.001) better in those patients with adequate metabolic control compared with those without, suggesting that growth can be optimised with adequate treatment.

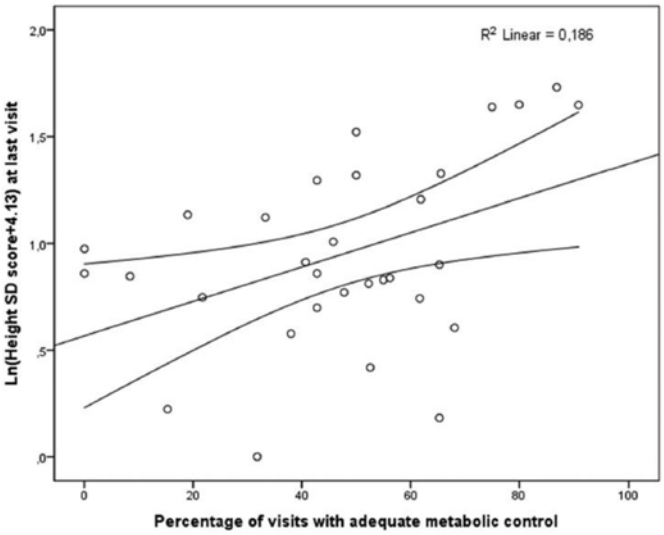
Figure 6: Metabolic control and height



Source: Lopez-García, 2019.

This is further reinforced by a study of 21 Turkish inherited dRTA children, the mean height SD score was significantly higher in patients who had adequate metabolic control at > 75% of all visits as compared with that in patients who had adequate metabolic control at 50-75% and < 50% of all visits (p = 0.003 and p = 0.003) [35].

Figure 7: Linear regression analysis of the height SD score at last visit and percentage of visits with adequate metabolic control



Source: Atmis et al. 2020.

Kidney function

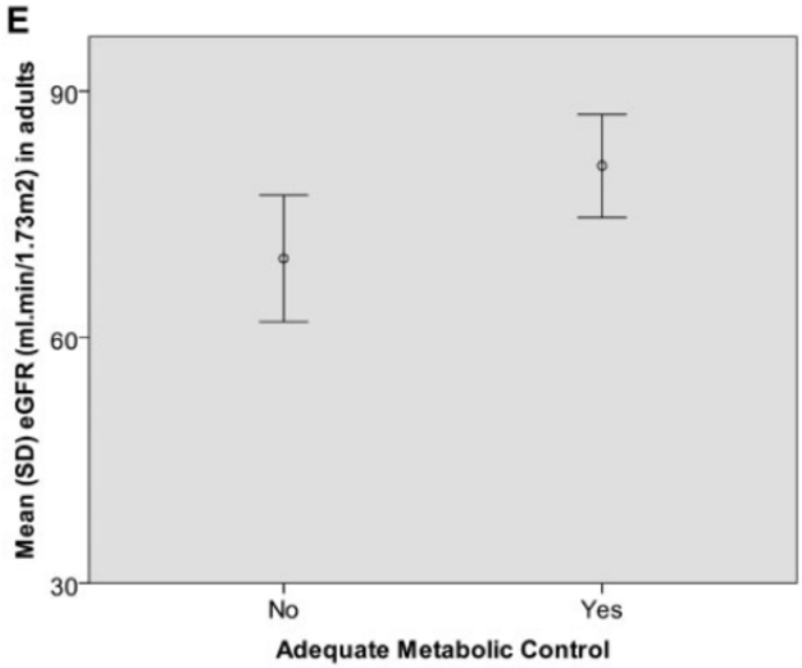
Lopez-García (2019) uses estimated GFR (eGFR) in adults (≥ 20 years old, using the Modification of

Diet in Renal Disease (MDRD) equation to evaluate kidney function. For children and young adults (2–20 years), the authors used the modified 'Schwartz' formula [36].

From a cohort of 340 patients in 29 countries, mean eGFR in adult patients was decreased at 75mL/min/1.73m^2, and the presence of CKD Stages 2–4 in >80% of adults suggests that dRTA has a long-term impact on eGFR. The observed overall decline in eGFR in adults was 0.8mL/min/1.73m^2/year, which is comparable to the normal population [37]. However, in healthy individuals, decline starts during the fourth decade from a starting eGFR of 130– 140mL/min/1.73m2. In contrast, mean eGFR in the dRTA cohort at the age of 18 years was already equivalent to CKD stage 2, which suggests that the kidney damage has already started during childhood.

Metabolic control has an impact on e-GFR. Mean eGFR was significantly higher (p=0.023) in dRTA patients with adequate metabolic control at 79 compared with those without at 67 mL/min/ 1.73m^2.

Figure 8: Adequate metabolic control and eGFR



Source: Lopez-García, 2019. Abbreviations: eGFR, Estimated glomerular filtration rate; SD, standard deviation.

In another study, 16 dRTA genetically tested patients were followed up to 40 years. At 20 years and 40 years follow-up, eGFR was abnormal in 41-71% of patients whereas in general population it was 5-17% respectively. In addition, at 40 years follow-up, almost half of the patients (43%) had moderate to severe CKD, with eGFR < 35 ml/min/1.73m^2. The rate of decline of kidney function was 2 ml/min per year from 10 to 20 years of follow-up and 1.65 ml/min per year from 20 to 40 years of follow-up [25].

Bones

The cohort of 95 dRTA patients, among whom 82 were receiving an alkalising treatment showed that dRTA patients with renal lithiasis and/or kidney calcification show a higher level of calciuria, and dRTA patients with bone disease have a more severe acidosis with a blood pH lower than those without bone disease [16].

Another study was conducted in 10 dRTA patients evaluating bone parameters before and after alkali treatment for one year. After 1-year treatment, significant elevations in serum bicarbonate were observed (16.5 ± 3.0 vs. 24.6 ± 2.8 mEq/L, $p < 0.05$). In the meantime, bone parameters were controlled [22]. The basal bone mineral density (BMD) values of dRTA patients were significantly lower than those of normal controls in all studied bone areas ($p < 0.05$) except in the lumbar spine. In controlling blood bicarbonate, alkaline therapy has been shown to correct abnormal osteocyte

function and subsequently raise BMD in dRTA patients [22].

Mortality and life expectancy

dRTA has a mortality rate of 11% in the paediatric population, as stated by outcomes from an Iran cohort publication [38]. Very recently, it has been reported that UK dRTA patient life expectancy is estimated in 72 years. Compared to the UK general population life expectancies of 79.0 years for males and 82.9- years for females, this estimation shows a quite significant reduction [3,39].

Diagnosis

Reaching the diagnosis of dRTA is complex and often delayed, resulting in suboptimal treatment [8], therefore thoughtful investigation is required given the complex nature of the condition.

The defining feature of most cases of RTA is impaired renal acid-base buffering and the development of non–anion gap metabolic acidosis. Many cases are detected inadvertently upon the discovery of unexplained acid-base disturbance during routine investigations for other purposes. The first step in diagnosing dRTA of any type is confirmation of a persisting hyperchloremic metabolic acidosis. Unreported chronic diarrhoea must be excluded in this context because it is the most common reason for hyperchloremic acidosis [8].

Definitive testing to confirm the diagnosis of dRTA is complex and primarily involves urinary measurement of indices of acid and HCO3− secretion [8].

Due to the complex presentation of the condition diagnosis may not be straightforward, British Medical Journal (BMJ) Best Practice summarises the diagnostic path of renal tubular acidosis [40], as presented in Table 10.

Table 10: BMJ Best Practice Diagnostic Path of dRTA[40]

Test	Evaluation
Laboratory evaluation	Determination of arterial pH, PCO_2 and bicarbonate. Plus, serum bicarbonate, chloride, sodium and potassium together with serum anion gap. In hyperkalaemia measurement of serum aldosterone is also taken to differentiate between aldosterone deficiency from aldosterone resistance
	Urine pH measured by pH electrode or blood gas analyses
	If diagnosis is uncertain or in which distal RTA is incomplete, physiological tests are used to confirm diagnosis of dRTA
Physiological tests of acidification	Response of Urine pH and potassium concentration to furosemide administration or alternatively the response to urine pH to furosemide and fludrocortisone (confirms hyperkalaemic dRTA)
	Measurement of urine pH after ammonium chloride loading to include acidosis (unpleasant for patients), which confirms incomplete dRTA or dRTA
	Measurement of urine minus blood PCO_2, presence or absence of an increase I urine PCO_2 after phosphate loading, and /or the response to urine PH to sulphate loading – which confirms site of lesion in dRTA or the mechanism
Radiology evaluation	Radiological investigation to confirm nephrocalcinosis, osteopenia and osteopetrosis, cerebral calcifications in inherited CA II deficiency
	Abdominal X-ray or CT scan
	Urinary tract obstruction by ultrasound, nuclear renal scan or spiral CT scan
	Radiological confirmation of rickets
Additional diagnostic tools	Discovery of abnormally low serum bicarbonate concentration and hyperchloremia
	Recognition of significant risk factors or consequences of RTA (e.g., nephrocalcinosis, diabetes, prostatism, growth retardation and renal calculi)
	Inherited testing
	Hearing tests

Source: Diagnostic Pathway of RTA, BMJ Best Practice, 2019.

Once diagnosed, there are recommended tests to keep surveillance of those with dRTA, as listed in Table 11.

Table 11: Recommended Surveillance for Individuals with Distal Renal Tubular Acidosis[41]

System/ Concern	Evaluation	Comment
Renal	Venous blood gas	In rapidly growing individuals (infants & young children): at least every 3-4 months once blood pH is normalised w/out evidence of respiratory compensation; in older children & adults: at least every 6 months. Sample to be drawn in fasting conditions & immediately before scheduled dose of alkali
	Serum creatinine, urea, sodium, potassium, chloride, calcium, phosphate, alkaline phosphatase, albumin	In rapidly growing individuals (infants & young children), at least every 3-4 months once adequate control is achieved In older children & adults, at least every 6 months
	Urinalysis, urine creatinine, sodium, potassium, calcium, citrate	Annually; more frequently when adjusting treatment
	Renal ultrasound	Annual evaluation for nephrocalcinosis, urolithiasis, & cysts in asymptomatic individuals
ENT	Audiometry	Annual evaluation for hearing loss
Skeletal	Bone densitometry	There is no consensus on the benefit of follow-up bone densitometry
Constitutional	Measurement of length/height, weight; calculation of body mass index	In infants, at least every 3 months in older children, at least every 6 months until achievement of final height

Source: Alexander, 2019.

ERKNet/ESPN Clinical Practice Points (2021) provide guidelines for the management and treatment of dRTA. Two groups were assembled: a core leadership group, and a voting panel. The core leadership group included paediatric and adult nephrologists and geneticists. Working groups focusing on specific topics were formed. A systematic literature search was performed.

Statements were elaborated and discussed by experts according to their level of agreement after literature review. Due to the rarity of the disease and the poor level of evidence, these statements were not graded. The voting group included seven members of the ESPN and ERKNet with expertise in paediatric and adult dRTA or genetic testing. Voting group members were asked by use of an electronic questionnaire to provide a level of agreement on a 3-point scale (agree, disagree, unsure) (Delphi method). A minimum 70% level of consensus was required for final adoption of recommendations.

Table 12: ERKNet/ESPN Recommendations for diagnosis of dRTA

Indication	Recommendation
For diagnosis	In a patient with symptoms suggestive of dRTA we recommend obtaining comprehensive clinical, biochemical and radiological information to ascertain the underlying diagnosis
	We recommend offering genetic testing to all patients with a clinical suspicion of primary dRTA
	We recommend that a negative genetic test should prompt a careful review of clinical features to confirm the correct clinical diagnosis, as well as analysis of the relevant genes for the differential diagnosis
	We do not recommend routine assessment of bone mineralisation by methods such as X-

Indication	Recommendation
	rays and dual energy X-ray absorptiometry (DEXA) in children with dRTA. In adults, assessment of BMD by DEXA every 2-3 years may be helpful in assessing fracture risk and treatment adequacy
	We recommend assessing urinary acidification in patients with nephrocalcinosis/lithiasis and borderline low plasma bicarbonate levels
	Any patient with primary Sjögren's syndrome (pSS) and urolithiasis or hypokalaemia should be assessed for dRTA

Source: ERKNet/ESPN Clinical Practice Points. Trepiccione et al. 2021.

The guidelines confirm that the diagnosis of distal renal tubular acidosis (dRTA) is based on an association of clinical, biochemical and radiographic findings and confirmed by genetic analysis.

Table 13: Clinical and biochemical parameters for diagnosis and follow-up

Clinical	Initial evaluation	Follow-up[a]
All patients: Absence of extrarenal bicarbonate loss (e.g. diarrhoea, stoma, laxative abuse)	X	
Children: presence of growth failure	X	X
Adults: history of autoimmune disease, especially Sjögren syndrome	X	X
Children: height and weight, evidence of rickets	X	X
Adults: frequency of stone episodes		X
Biochemistries		
Blood: Na^+, K^+, Cl^-, HCO_3^-[b], urea, creatinine, Calcium, Magnesium, Phosphate, pH	X	X
Spot urine: Na^+, K^+, Cl^-, pH, creatinine, Calcium	X	X
Calculations		
$U_{Ca/Crea}$ ratio[c], eGFR	X	X
Urine anion gap	X	
Imaging		
Renal ultrasound**:** nephrocalcinosis/lithiasis?	X	X
Wrist and/or knee/or ancle radiographs (rickets)[d]	X	
Molecular genetics		
Analysis of causative genes[e]	X	

Listed are recommended parameters for assessment at diagnosis and follow-up of patients with dRTA
[a]Frequency of follow-up depends on the stability of the patient: for stable patients with no change in dosage and no apparent stone disease, 6-monthly (paediatrics) or annual (adults) follow-up may be sufficient. In newly diagnosed patients and those with rapid growth (paediatrics) or unstable biochemistries, more frequent follow- up (every 1-3 months) is recommended.
[b] HCO^- can be measured directly (as total CO) or assessed indirectly via a venous blood gas analysis
[c] There are no data to suggest superiority of a spot urine calcium/creatinine ratio vs a 24-h urine calcium collection.
[d] in children in case of clinical signs of rickets or markedly elevated alkaline phosphatase (ALP)
[e] in case that the above clinical and biochemical parameters support the diagnosis of dRTA

Treatment pathway for dRTA

For dRTA, the primary objective of treatment is the correction of metabolic acidosis and avoidance of disease related complications, such as faltering growth, growth retardation, rickets, osteomalacia, nephrolithiasis, and nephrocalcinosis. It is especially important to prevent nephrocalcinosis because progressive nephrocalcinosis may lead to CKD and end-stage renal disease in patients with dRTA. [14]. Alkali replacement therapy is given to maintain a normal serum bicarbonate concentration of >20 mEq/L in infants and >22 mEq/L in children and adults [14]. Soares et al, 2019 [29] state the principal aim of the therapeutic approach of dRTA is to correct the metabolic acidosis and other biochemical abnormalities. Treatment with alkali restores normal acid-base balance, prevents the consumption of the skeleton and muscle mass by buffering processes, and restores growth in children [40].

There are currently no licensed treatments for dRTA. Current treatments are off label or pharmacy/hospital compounded products. Results from Lopez-García (2019) show that in a total of 340 patients, more than 30 different alkali formulations were used. A total of 84 patients (25%) were treated with oral bicarbonate, 141 (42%) with oral citrate and 113 (33%) with both. Two patients (both with SLC4A1 mutations) were not treated with alkali. A sodium-containing salt was used in 21%, potassium in 29% and a combination in 50%. Sodium salts were more commonly used in countries with low per capita income.

In primary dRTA, the treatment is based on alkali replacement with lifetime administration of alkaline formulas according to the patients' necessities [29]. Alkaline therapy with either citrate salts or sodium/potassium bicarbonate should be given to reach plasma level of $HCO3^-$ at reference range (22–24 mEq/L) [14].

In dRTA patients, treatment with potassium citrate 3 mEq/kg/day for 2 months can normalise metabolic acidosis [42]. It can also substantially reduce the risk of calcium oxalate stone formation but cannot normalise the risk of calcium phosphate stone formation. Alkali therapy restores growth in children and prevents the progression of nephrocalcinosis at all ages. However, if therapy is delayed to late childhood or adulthood progression to end-stage renal insufficiency may not be avoided.

Patients are not adequately controlled, and treatment compliance is often limited mainly by gastrointestinal side effects, especially in children. There are key issues with regards to palatability, dosing frequency (day and night-time dosing) and tolerance of existing treatments. As a lifelong condition compliance to daily treatment is important [43].

Potassium deficits may be significant. Administration of bicarbonate drives potassium into cells and can acutely worsen hypokalaemia. For this reason, severe potassium deficits should be at least partially corrected before beginning bicarbonate administration. Potassium supplements should be given as needed. In patients with distal RTA associated with Sjögren's syndrome, amiloride has been used to improve hypokalaemia with reported good effect [12].

Over time alkali treatment restores extracellular fluid volume, which decreases the stimulus for potassium excretion. Correction of acidosis provides benefits such as prevention of renal failure (especially if the patient has nephrocalcinosis) and decrease in the frequency of nephrocalcinosis [40].

The patient may be started with a dose of 1 to 3 mmol/kg (1-3 mEq/kg) of alkali given in divided doses. Shohl's solution, K-Shohl's solution, or potassium citrate/citric acid solution may be used. In patients with problematic hypokalaemia, potassium-containing solutions may be preferable.

In a study of patients with defined mutations leading to distal RTA, 55.9% had hypokalaemia. Interestingly, patients with ATP6V1B1 or ATP6V0A4 mutations were noted to have more severe hypokalaemia than patients with the SLC4A1 mutation [15].

The amount of alkali needed usually decreases with age from as much as 5–8 mEq/kg/day in infants to 3–4 mEq/kg/day in children after the age of 6 years to 1–2 mEq/kg/day in adults. The dose of alkali is titrated to raise bicarbonate and pH to normal if possible. In a study of 340 patients with inherited dRTA, alkali treatment achieved normal serum bicarbonate and normocalciuria in only 51% of

patients. Effective treatment was associated with greater adult height and higher estimated GFR [7]. Unfortunately, alkali treatment does not improve sensorineural hearing loss [14]. Children with distal RTA require higher doses (up to 5-8 mmol/kg/day [5-8 mEq/kg/day] in infants) of alkali [44].

Table 14: ERKNet/ESPN Recommendations for treatment and follow-up of dRTA

Treatment and follow-up recommendations
We recommend using alkali supplementation for the treatment of dRTA
We recommend maintaining plasma HCO3-, Cl- and K+, as well as urinary calcium excretion within the age-appropriate normal range
We recommend providing additional K^+-supplementation in patients with persistent hypokalaemia, yet well controlled acidosis
We recommend informing patients of the effects of diet on acid load and alkali supplementation
We do not recommend the use of thiazides in the routine treatment of patients with dRTA
We do not recommend the use of growth hormone in children with dRTA, unless there is persistent growth retardation despite adequate metabolic control
We recommend that patients with dRTA are regularly assessed, clinically and biochemically
We recommend that all patients have a renal tract ultrasound performed at diagnosis and in regular intervals at follow-up
We recommend that a tertiary care centre with experience in the diagnosis and treatment of dRTA should be involved in the care of patients with dRTA
For recessive dRTA linked to ATP6V1B1, ATP6V0A4 or FOXI1, we recommend early and developmentally appropriate hearing screening. In addition, all patients at risk should have at least one diagnostic audiology assessment by 24-30 months of age. Patients with sensorineural hearing loss should have appropriate audiological follow-up
There is currently insufficient evidence to recommend that children with inherited dRTA related to genetic defects other than WDR72 should undergo a specific dental assessment for AI

Source: ERKNet/ESPN (2021).

Positioning of ADV7103 in dRTA treatment

Medical need

Until now, there has been no specific medicine or ready-to-use licensed product with a well-defined benefit/risk ratio proposed for the treatment of dRTA. The dosing and pharmaceutical form of ADV7103 has been optimised to allow blood bicarbonate and potassium normalisation and demonstrates appropriate gastrointestinal tolerability and acceptability in children as well as in adults, to address this unmet medical need.

Current treatments do not have enough efficacy in terms of reaching adequate metabolic control, which is needed to reduce the chances of dRTA having multisystemic effects on the body. In a large cohort of 340 dRTA treated patients, half of the patients did not reach a correct metabolic control. dRTA, if untreated or not treated appropriately can have serious multisystemic, long-term effects on the renal, Cardiovascular and musculoskeletal systems. Less multisystemic effects reduce the cost consequences of dRTA.

A significant yet understated unmet need of the condition is the need to prevent nephrocalcinosis because progressive nephrocalcinosis may lead to CKD and end-stage renal disease in patients with dRTA [14]. Lasting restoration of adequate metabolic control is key to lowering the risk and the development of the long-term and life-threatening outcomes and consequences of dRTA.

Drawbacks of current treatment

Sodium is found to be widely used in the different alkalising formulations, furthermore some adult patients may exceed the daily recommended intake of more 2g of sodium, which presents a challenge to those attempting to reduce blood pressure and risk of cardiovascular disease. Likewise, for children

the recommended maximum level of sodium intake should be adjusted downwards based on their energy requirement, sodium is not the recommended cation.

The current, available immediate release formulations of citrate or bicarbonate salts necessitate multiple daily intakes (usually 3-6 daily intakes, including at night) to compensate for a short duration of action. Practitioners are used to prescribing tridaily intakes to improve treatment compliance although six would be preferable. Night intakes are also particularly necessary for children since growth hormone is secreted mainly at night but at physiological pH. With dRTA, when blood pH decreases, so does growth hormone secretion too thus growth impairment often observed in patients. In addition, quality of life of dRTA patients and their relatives is impacted by the need of intakes at night to ensure an appropriate control of metabolic acidosis.

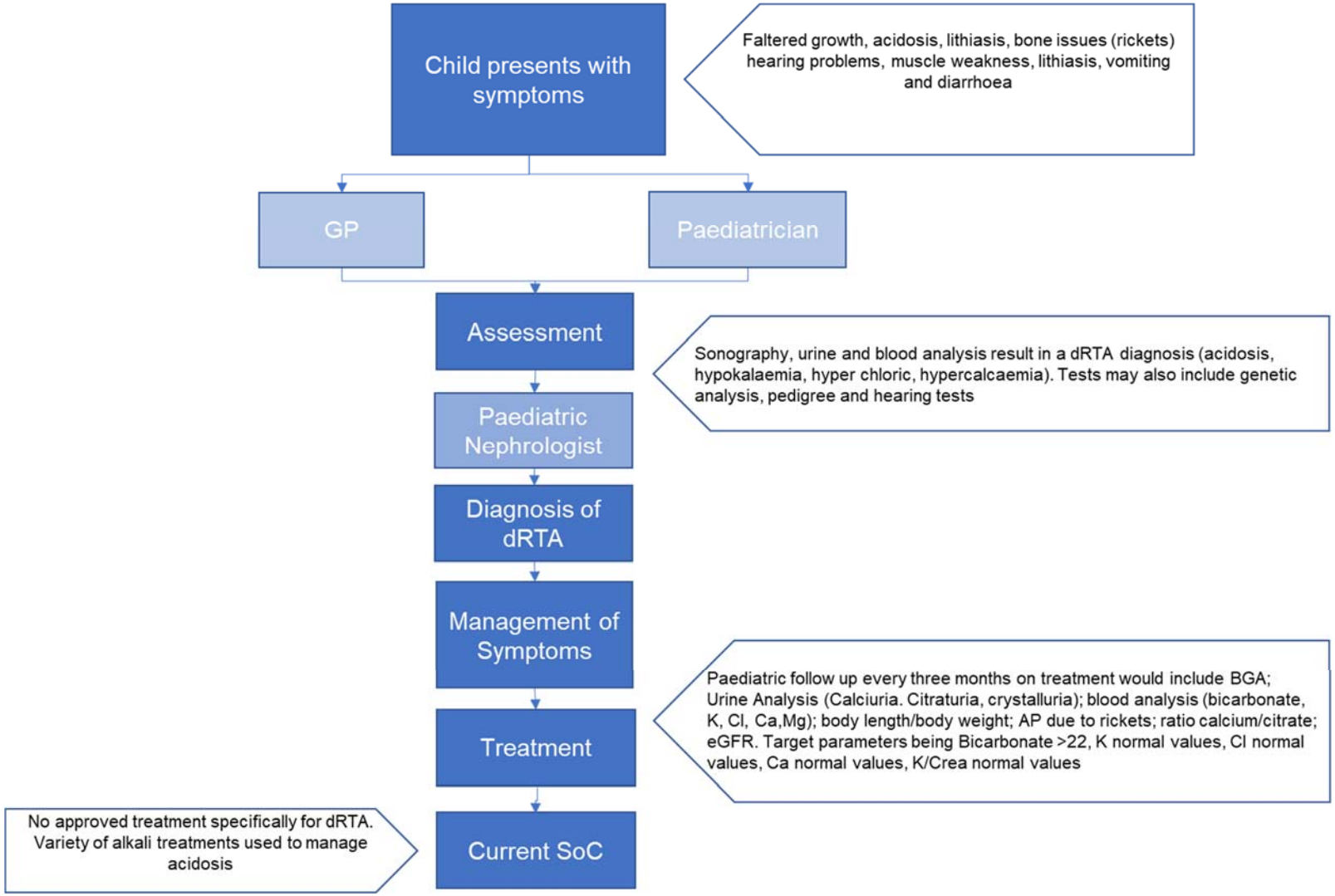
Compliance, and thus efficacy is negatively affected by the requirement for multiple intakes, which is further exacerbated by the products' unpleasant taste and gastrointestinal tolerability issues [18]. Again, efficacy is hindered when the dose must be decreased to control gastrointestinal side effects [45].

As the disease occurs during infancy/childhood for inherited forms, there is a need for a more palatable pharmaceutical form child that a can swallow easily. As the taste is also known as being an important factor for the adherence to the treatment, the masking of the taste of the active ingredients is another requirement.

Various existing alkali medicinal products are authorised for the prevention/partial prevention/treatment of dRTA but none of are specifically authorised for dRTA or were studied in appropriate clinical trials and are therefore not the preferred therapeutic options. Most often, pharmacy or magistral preparations are used. The current clinical pathways of dRTA child and adult patients are shown in Figure 9 and Figure 11. Proposed pathways are displayed in Figure 10 and Figure 12. There is now sufficient evidence of ADV7103's significant clinical benefit for those affected by the condition. ADV7103 compares very favourably to existing therapies, with clinically relevant advantages as shown with Studies B21CS and B22CS [46,47], including:

- Sustained control of metabolic acidosis and hypokalaemia, since plasma bicarbonate and potassium levels are well controlled
- Compared to standard of care (SoC) treatment (taken in Study B21CS), ADV7103 allows a reduction of the number of patients with hypocitraturia, with abnormally high UCa/UCi and with a risk of lithogenesis, which are important in avoiding future nephrocalcinosis and renal impairment
- Treatment compliance with this twice daily treatment is good in the long-term
- ADV7103 allows a continuous and significant clinical improvement of the Z-score of the BMD of the spine after 48 months of treatment
- ADV7103 allows to restore a normal growth of the child with a severe stunted growth at study entry.
- Patients' QoL is improved after 48 months of ADV7103 treatment.

Figure 9: Current clinical pathway of care for children with dRTA



Abbreviations: BGA, blood gas analysis.

Figure 10: Proposed clinical pathway for children with dRTA

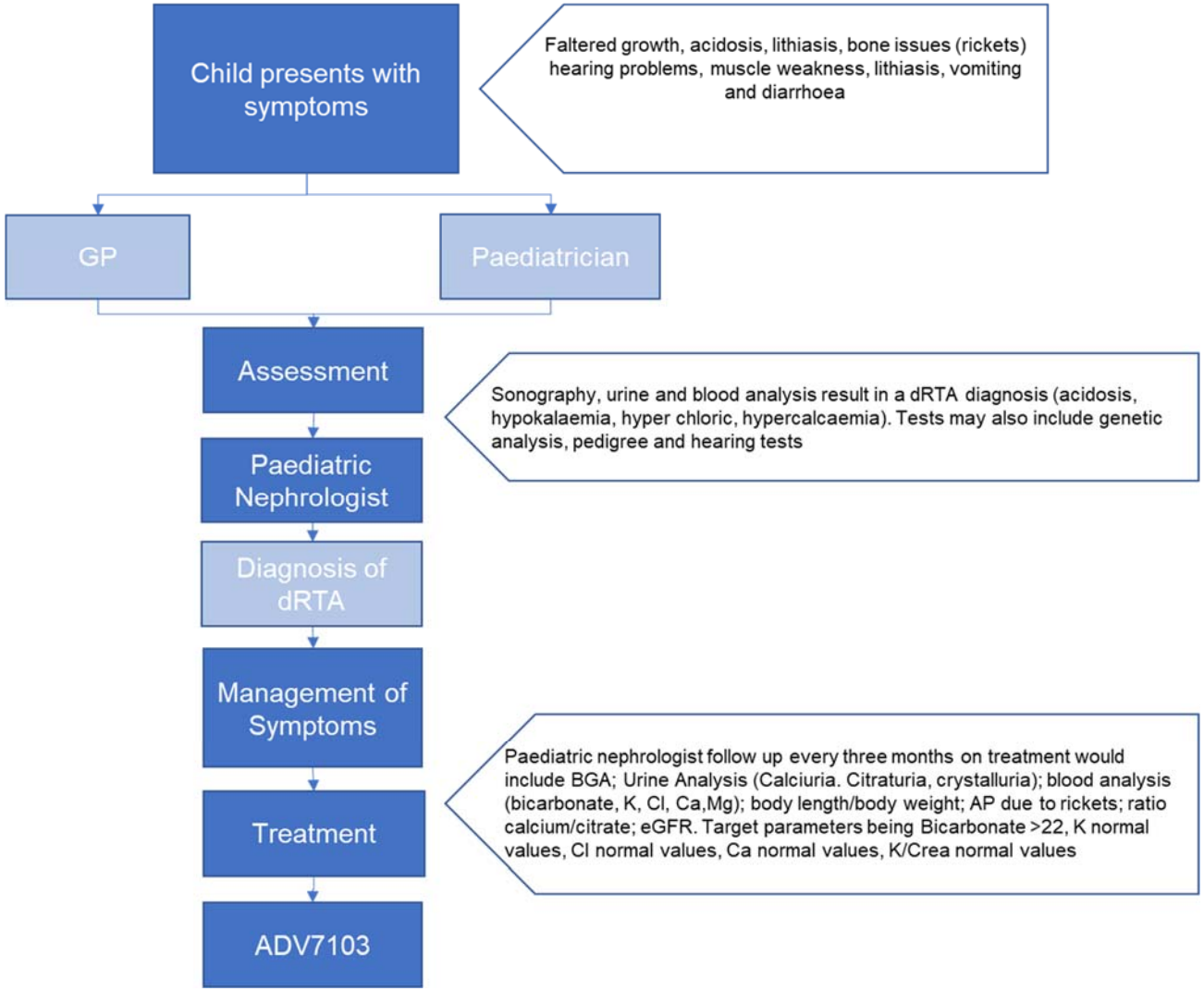


Figure 11: Current clinical pathway for adults with dRTA

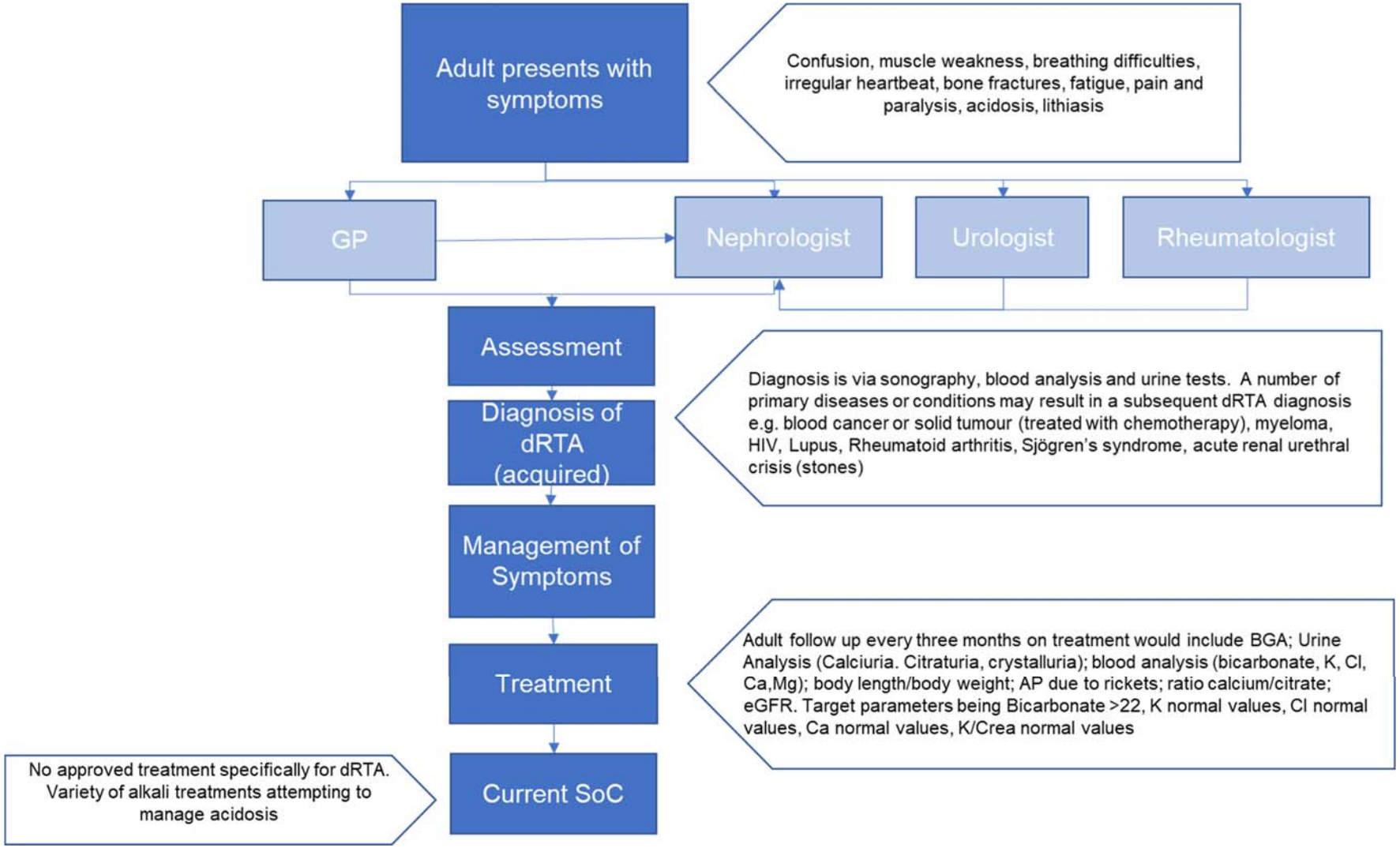
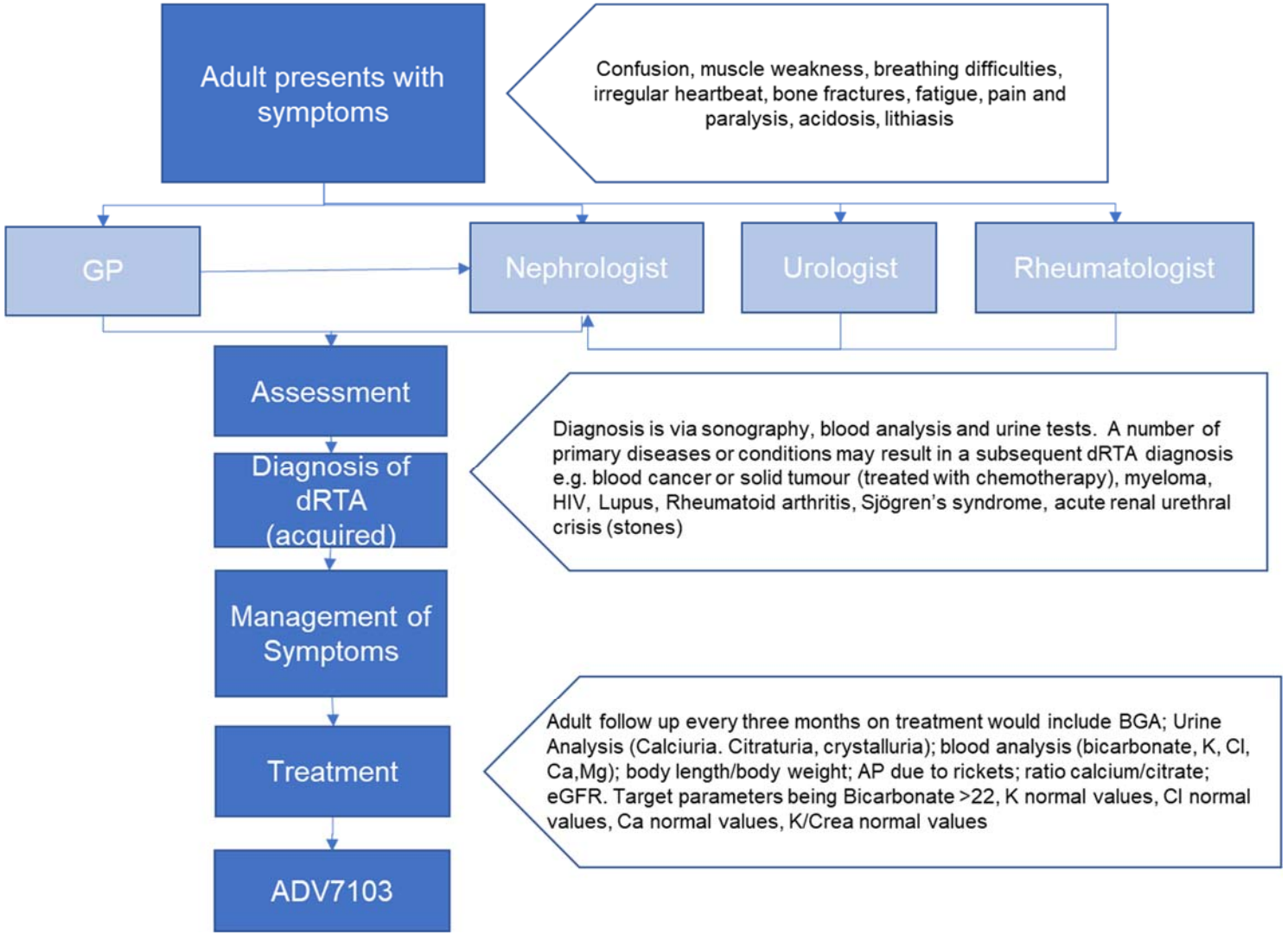


Figure 12: Proposed clinical pathway for adults with dRTA



B.1.4 Equality considerations

Advicenne aims to comply fully with all legal obligations to: promote race and disability equality and equality of opportunity between men and women, eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010). Advicenne cannot see any equality issues with the use of ADV7103.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

Please see appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

Table 15: Clinical effectiveness evidence for study B21CS

Study	**B21CS**				
Study design	A multicentre, open-label, non-inferiority sequential study, evaluating the efficacy, safety, tolerability and acceptability of ADV7103 compared to SoC in distal renal tubular acidosis patients.				
Population	Patients with an established diagnosis of distal Renal Tubular Acidosis (dRTA) with metabolic acidosis were enrolled in a staggered approach into four age subsets (≥18 years, 12 to 17 years, 4 to 11 years, and 6 months to 3 years), with a minimum of four patients in each subset.				
Intervention(s)	ADV7103: a combination of potassium citrate (ADV7103-CK) and potassium bicarbonate (ADV7103-BK) prolonged-release granules. During study period (SP) II, the initial ADV7103 dose was half of the daily dose of the patient's usual alkalising treatment (SoC); titration was subsequently performed to determine the optimal dose of ADV7103 for each patient. Patients were treated with the specific optimal dose during SP III. ADV7103 was taken orally twice daily: in the morning and in the evening.				
Comparator(s)	Unlicensed: alkali therapy, sodium bicarbonate or sodium citrate (recommended in BMJ)				
Indicate if trial supports application for marketing authorisation	Yes	**Yes**	Indicate if trial used in the economic model	Yes	**Yes**
	No			No	
Rationale for use/non-use in the model	**B21CS is the pivotal trial for ADV7103 and was utilised as it demonstrates the benefit of ADV7103 over SoC. The alkali products used in the trial and model reflect current clinical practice.**				
Reported outcomes specified in the decision problem	The outcome measures to be considered include: **Blood bicarbonate level** **Mean change in blood bicarbonate level** **Reduction of excess calcium in the urine** **Correction of low citrate levels in the urine** **Adverse effects of treatment**				

Study	B21CS
	Health-related quality of life (EQ-5D, KDQoL)
All other reported outcomes	Acceptability Compliance

Table 16: Clinical evidence for study B22CS

Study	B22CS				
Study design	This study was a multicentre, open-label extension (OLE) study of the Phase II/III Study B21CS in patients with dRTA. Study B21CS was a multicentre, open-label, non-inferiority, sequential study comparing the efficacy, safety, tolerability and acceptability of ADV7103 with SoC during two successive phases involving a switch from SoC to ADV7103 in patients with a confirmed diagnosis of dRTA.				
Population	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 >24 months (originally planned for 24 months but extended in France until market authorisation and availability of ADV7103 and extended for six additional months (30 months in total) in Slovakia and Serbia, until approval of the import licence for ADV7103). A total of 30 patients with inherited dRTA were thus enrolled into Study B22CS after satisfactory completion of Study B21CS.				
Intervention(s)	ADV7103: unit-dose (pillboxes then sachets) containing prolonged-release granules of potassium citrate (ADV7103-CK) and prolonged-release granules of potassium bicarbonate (ADV7103-BK), with two strengths 8 milliequivalent (mEq) and 24 mEq. ADV7103 dose used in the OLE was the one determined by the investigator during Study B21CS, over two years (i.e., the long-term treatment) and which the investigator could adapt during the study if needed. ADV7103 was administered orally twice daily (BID), in the morning and evening.				
Comparator(s)	Unlicensed: alkali therapy, sodium bicarbonate or sodium citrate (recommended in BMJ)				
Indicate if trial supports application for marketing authorisation	Yes		Indicate if trial used in the economic model	Yes	**Yes**
	No	No		No	
Rationale for use/non-use in the model	To inform transition probabilities and patient percentages in each health state.				
Reported outcomes specified in the decision problem	**Baseline study patient characteristics** **Blood bicarbonate level** **Mean change in blood bicarbonate level** **Reduction of excess calcium in the urine** **Correction of low citrate levels in the urine** **Adverse effects of treatment**				
All other reported outcomes	Acceptability Compliance				

Study B03CS was not used to populate the economic model but is included in sections 2.2 to 2.6. The results of this study support the positive efficacy and safety findings of ADV7103/ADV7103 in the pivotal Study B21CS.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B03CS

Study design

Study B03CS was a phase I, randomised, placebo-controlled, double-blind, two-period crossover study, to investigate the pharmacodynamics, safety and tolerability of repeated oral doses of ADV7103, in healthy subjects [48].

The main objective was to establish the pharmacodynamic effect on urine pH of oral doses of ADV7103 versus placebo after 5 days of treatment [48]. Secondary objectives were:

- to assess the relationship between oral doses of ADV7103 and urine pH after 5 days of treatment
- to assess the pharmacodynamics effects of oral doses of ADV7103 on other urine biomarkers after 5 days of treatment.
- To assess the residual effect of oral doses of ADV7103 on urine pH after treatment discontinuation over a 24-hour period.
- To assess safety and tolerability of oral doses of ADV7103 after 5 days of treatment.

Since body weight was expected to influence the PD effects of ADV7103 and on the urinary pH, ADV7103 dosing was normalised for body weight. Three doses (low, medium and high) were tested during period I, including respectively for potassium citrate (CK) and potassium bicarbonate (BK) 17/34mg/kg, 33/66mg/kg and 50/100mg/kg. Doses were administered bidaily in period I since ADV7103 was expected to be released during about 8 to 12 hours. These doses were expected to be safe, well tolerated and to cover the PD dosage range on the pH responses. The high dose was expected to tend to the saturation of the urine pH curve. The medium dose was intended to be an effective dose while the low dose should be a sub-effective dose.

At the end of period I, the initial dose-pH response relationship was characterised to select optimal doses for Period II. These doses were selected to demonstrate proof of pharmacology, to identify a minimum active and a saturating dose level.

In Period II, the maximal dose did not exceed 67/134 mg/kg CK/BK bidaily, used as high alkalinising dose and described as safe and the dose regimen could be divided up to three doses a day.

At least sixteen eligible subjects were to be included in a balanced manner to one of the four possible treatment sequences, as detailed in table and in accordance with the randomisation table.

The study was divided in two SPs. Each SP included a day lead in phase to assess baseline effects (day-1) followed by a 5-day treatment period (day 1 to day 5).

In period I, the allocation of placebo and ADV7103 doses was pre-specified in the randomisation table. ADV7103 low, medium and high doses of period I are described in the table above and in Appendix B of the protocol.

In Period II, ADV7103 doses X, Y and Z and regimens were determined after the end of SP I, further to an interim review of safety and PD data. The selected doses had to not exceed CK/BK 67/134 mg/kg bidaily of alkalising, this maximum practical dose being safe. On both SPs, the treatment was administered under standardised protein normalised food regimen. The admission of the subjects to the investigator centre was planned from day -2 evening to day 7 morning for both SPs.

Subjects were randomised and received Investigational medical products (IMPs) according to one of the four treatment sequences during five days in the two SPs, i.e., from day 1 morning to day 5

evening. In period I, the IMPs were administered two times a day, in the morning and in the evening, at defined doses. In SP II, the IMP doses, the daily regimen and the timing of administration were determined further to the interim analysis.

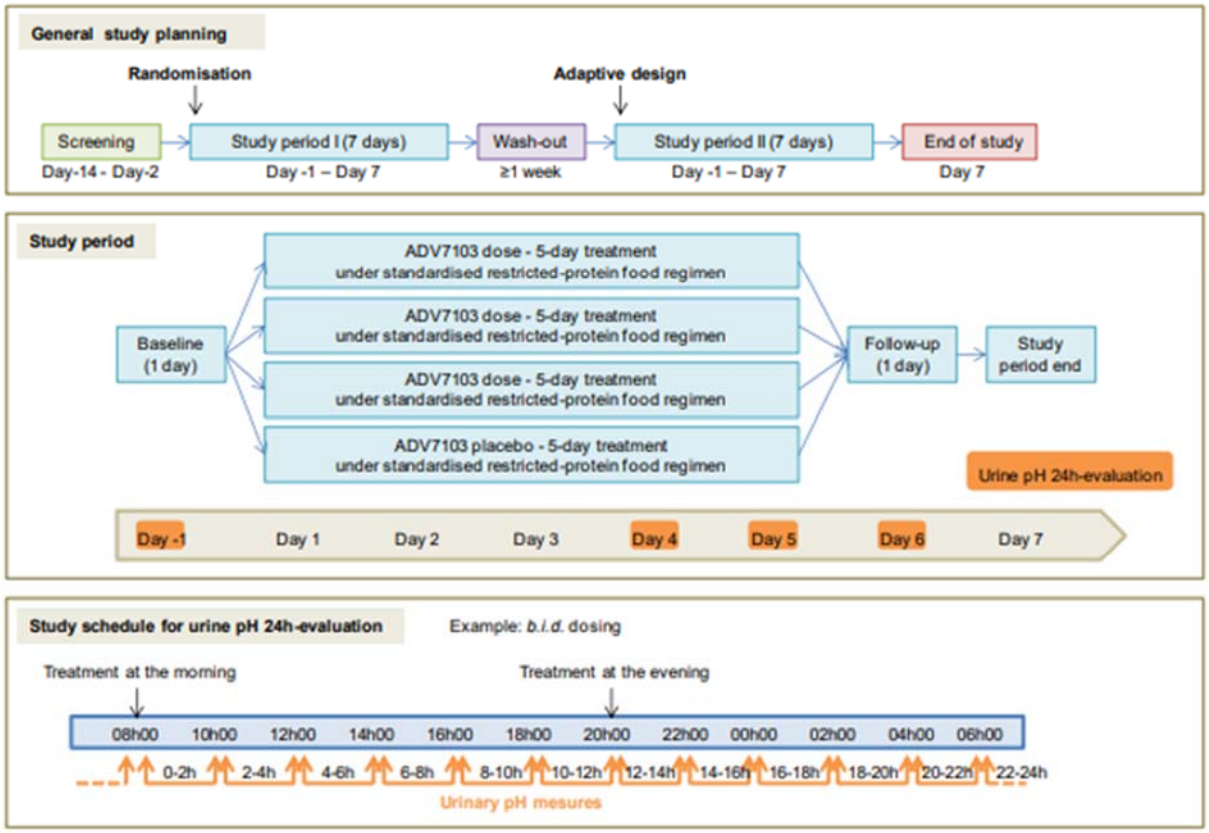
On both SPs, the treatment was administered under standardised protein normalised food regimen. The admission of the subjects to the investigator centre was planned from day -2 evening to day 7 morning for both SPs. A wash-out period of at least one week was planned between the two SPs, see Figure 13. A wash-out period of at least one week was planned between the two SPs. Reversibility was assessed in a day during 24-hour after the end of treatment period assessment (day 6). The screening was planned within the 2 weeks before inclusion and at least 24h before the first SP baseline (day-14 to day-2). Safety assessments were conducted and criteria for eligibility were controlled. The end of study visit was planned on the day following the end of Period II, i.e., on day 7.

Table 17: Subjects by Analysis sets

Number of subjects	SP I (CK/BK dose)	SP II (CK/BK dose)
4	Placebo *bidaily*	ADV7103 41.5/83.0 [+2h]* *bidaily*
4	ADV7103 17/34 *bidaily*	ADV7103 41.5/83.0 *bidaily*
4	ADV7103 33/36 *bidaily*	Placebo *bidaily*
4	ADV7103 50/100 *bidaily*	ADV7103 33/36 and 50/100

* [+2h] = was used to indicate that ADV7103 was taken 2h after the meal and not before a meal as done for the other arms.. In the period 1 of the study, 3 different doses were evaluated with the same way of intake. In the period 2 of the study, the same dose was tested with three different ways of intake, including one arm with intake 2 hours after a meal.

Figure 13: B03CS Study Schedule



In B03CS both subjects and care providers in charge of the assessments were blinded. Blinding was ensured, when required, by the addition of a dose of placebo to the assigned doses. The sponsor

medical responsible and the study statistician were unblinded to enable the interim data review at the end of SP I. The pharmacist of the investigator site was unblinded to prepare the doses, while the other sponsor personnel in direct contact with the investigator site remained blinded to avoid any accidental unblinding at the site level. The sponsor monitor was blinded.

Criteria for evaluation in study B03CS are summarised in Table 18 [48].

Table 18: Study B03CS Endpoints (46)

	Endpoint
Primary endpoints	Pharmacodynamic • Urine pH (measured with pH-metre): over 2 consecutive nychthemeral recordings days after 5 days of treatment (day 4 and day 5) with ADV7103 or placebo: • The mean urine pH values over 24-hour pooled across the 2 days • The urine pH values in the first morning and pre-dose urines during the 2 days, in order to assess the ADV7103 residual effect, with changes from baseline defined as followed: urine spot on Day 4 t0h* versus urine spot on Day -1 t-24h and the 2h-urine collection on Day 5 (i.e. Day 4]22h – 24h]) versus the 2h-urine collection Day 1 (i.e. Day-1]-2h – 0h]) • The percentage of urine pH values ≥ 7.0 over 24-hour pooled across the 2 days • The urine pH fluctuation (difference between maximal and minimal values) over 24-hour pooled across the 2 days
Secondary endpoints	Pharmacodynamic • Citraturia: mean change from baseline of the values pooled across the 2 days. • Return to baseline urine pH (measured with pH-metre): mean change from baseline of the values obtained in • Day 6 of each SP, throughout the nychthemeral period and in the first morning urines. Safety • Adverse events during the study • The incidence of urine pH values > 8.0 over the course of the study • Vital signs and ECG parameters: mean values and changes from baseline during the study, incidence of abnormal values after treatment • Standard laboratory parameters and special laboratory parameters (such as kalaemia, blood pH, arterial alkaline reserve, urine electrolytes): mean values and changes from baseline during the course of the study, incidence of abnormal values after treatment.

Source: B03CS Clinical Study Report.

Recruitment, screening and enrolment

Enough subjects were screened so that sixteen completed period I. Subjects of both genders were enrolled, including at least 40% male subjects and 40% female subjects. Randomisation was stratified by gender so that at least one female subject and one male subject were assigned to each treatment sequence. A subject who completed the two SPs as defined by the protocol including any post-treatment assessments were considered as ‘completer’. A subject was prematurely withdrawn from the study whether she/he could not fully complete the two SPs.

Withdrawal was mandatory in the following situations:

- Pregnancy
- Occurrence of a disease that could preclude the participation to the study
- Serious/non-serious adverse event as described
- Use of prohibited medications
    - acidic drugs, such as salicylates, tetracyclines and barbiturates,
    - basic drugs, such as quinidine

- drugs administered per os that can have reduced or increased rate and/or extent of absorption in case of concomitant oral administration of alkalising agents
- aluminium containing compounds
- methenamine,
- potassium-sparing diuretics/aldosterone antagonists, such as amiloride, triamterene or spironolactone
- digitalis glycosides
- drugs increasing serum potassium concentrations, such as angiotensin converting enzyme (ACE) inhibitors, heparin, nonsteroidal anti-inflammatory agents, potassium-sparing diuretics
- any potassium supplement, such as any dietetic or food supplement or mineral water with potassium load.

Withdrawal could be requested in the following situations:

- Hypersensitivity reactions
- Protocol violations, including non-compliance
- Administrative reasons
- Investigators or subject's decision
- Sponsor's decision

Within 24 to 48 hours post-last dose, subjects underwent the same assessments as those planned during the end of study visit. In addition, PD assessments (based on a urine sample) were performed as possible whether the withdrawal occurred within the 36 hours after administration of one of the IMPs.

The replacement policy was the following: any subject who did not complete period I had to be replaced, any subject who discontinued after period I but prior to study completion could be replaced at the discretion of the investigator and performed Period II only. If possible, subjects were replaced with gender-matching and had a similar body weight.

Table 16 provides the criteria for inclusion and exclusion of subjects in the study.

Table 16: B03CS Inclusion and exclusion criteria [48]

Inclusion criteria
1. Subject who was healthy, male or female, between the ages of 18 to 55 years inclusive, at inclusion, with a body mass index (BMI) between 18 and 30 2. Subject who presented no medical major history or chronic treatment 3. Subject who was a female without childbearing potential, i.e., surgically sterilised or post-menopausal or using adequate contraception (i.e., a double-barrier method including a local barrier at least during the all duration of her participation to the study) 4. Subject who was willing and able to participate in the study and to understand and to comply with study procedures for the entire length of the study 5. Subject who provided a signed written informed consent 6. Subject who was affiliated to a social health insurance system and/or in compliance with the recommendations of the French Law in force relating to biomedical research
Exclusion criteria
1. Subject who presented any previous or concurrent medical condition or laboratory findings that precludes participation, within the Month before the inclusion in the study 2. Subject who presented a urinary infection 3. Subjects with a recent (within the 2 weeks before the inclusion in study) febrile illness that precluded or delayed participation 4. Female subject who was pregnant or who breastfed 5. Subject who received medications within the 4 weeks before the inclusion in the study including

salicylates, tetracyclines, barbiturates, aluminium containing compounds, quinidine, methenamine, potassium-sparing diuretics/aldosterone antagonists (such as amiloride, triamterene or spironolactone), digitalis glycosides, ACE inhibitors, heparin, nonsteroidal anti-inflammatory agents, potassium supplements

6. Subject who presented renal impairment (creatinine clearance <90 mL/min), hepatic impairment (values of total bilirubin, alkaline phosphatases, transaminases and gamma-glutamyl transferases ≥2.5 times the upper limit of the reference ranges), or clinical laboratory results with clinically significant abnormalities (such as Calcemia or kalemia outside normal limits)
7. Subject who presented contradictions to the administration of the IMPs
8. Subject who had known allergic reactions or hypersensitivity to the active pharmaceutical ingredients or other excipients of the formulations of the IMP
9. Subject who received a treatment with another investigational medicinal product within the 3 months prior to the start of the study or who was scheduled to receive another IMP during the study
10. Subject who presented a history of or current drug and/or alcohol abuse (i.e., alcohol intake greater than fourteen units per week, [1 unit = 8 g ethanol, e.g. ½ pint beer, one glass wine, one measure spirits])
11. Subject who smoked (>10 cigarettes/day) and who could not stop smoking during the study
12. Subject who had an infection with human immunodeficiency virus (HIV), active hepatitis B, or active hepatitis C
13. Subject who had a history of difficult access to the oral administration route and/or conditions that could hamper compliance and/or absorption of the IMPs (e.g., any difficulty of swallowing, malabsorption or other chronic gastrointestinal diseases)
14. Subject who did blood donation in the 2 months prior to study start
15. Subject who was at risk of non-compliance in the judgement of the Investigator
16. Subject who presented any other condition, which in the opinion of the Investigator, precluded participation in the study
17. Subject who would receive more than 4500 euros as indemnities for his/her participation in biomedical research within the last 12 months, including the indemnities for the present study
18. Subject who could not be contacted in case of emergency
19. Subject under any administrative or legal supervision

Source: B03CS Clinical Study Report.

Patient characteristics

42 subjects were screened of which sixteen subjects were included in the study. All the subjects completed the study [48].

In study B03CS, 100% of the subjects were Caucasian male (N=9) or female (N=7) healthy volunteers. Age ranged from 19 to 53 years (mean 32.4 ± 10.76), The median age was 27.0 years, with an interquartile range of 19-53 years. Height ranged from 158 to 181 cm (mean 171.9 ± 7.20), weight ranged from 54.9 to 80.9 kg (mean 66.62 ± 6.15) and BMI ranged from 18.5 to 26.4 kg/m² (mean 22.64 ± 2.55).

All subjects were non-smokers (75%) or smokers of not more than ten cigarettes a day (25%), half of the subjects were alcohol consumers (no more than seven units/week) and most of the subjects (81.25 %) were caffeine consumers (≤ 3 cups/day).

Nearly half of the subjects (43.75 %) had a medical or surgical history (rhinitis allergic, breast enlargement, polyp, female sterilisation), which was not considered to have an impact on the assessment of safety and pharmacokinetics. All subjects were thus considered to be healthy, as full examination (including blood pressure and heart rate), ECG and laboratory tests were normal or slightly out of normal ranges, without clinical relevance [48].

A summary of demographic information for study B03CS is provided in Table 30.

B21CS

Study design

Study B21CS was a multicentre, open-label, non-inferiority sequential study to evaluate the efficacy, safety, tolerability and acceptability of ADV7103 compared to SoC in distal renal tubular acidosis patients [47].

The primary objective of the study was to evaluate the relative efficacy of ADV7103 and SoC on correcting metabolic acidosis as measured by pre-morning dose blood bicarbonate levels during 3 days of treatment at steady state (day 2 to day 4) [47]. Secondary objectives were:

- To compare the efficacy on other blood bicarbonate derived parameters of ADV7103 to SoC given after 5 days of treatment at steady state
- To evaluate the efficacy on the reduction of hypercalciuria of ADV7103 as compared to SoC after 4 to 5 days of treatment at steady state
- To evaluate the efficacy on the correction of hypocitraturia of ADV7103 as compared to SoC 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 SoC during 5 days of treatment at steady state
- To evaluate the acceptability (palatability, swallowing, ease of administration) of ADV7103 as compared to SoC for 5 days of treatment at steady state
- To evaluate the compliance to ADV7103 as compared to SoC during 5 days of treatment at steady state [47].

Since no alkali products are licensed for the treatment of dRTA, the initial study design presented for the scientific advice was a randomised, dose ranging, placebo-controlled, double-blinded crossover study. However, the Committee for Medicinal Products for Human Use (CHMP) was concerned about the inclusion of a placebo group due to ethical and safety reasons. Indeed, since patients with dRTA require alkalinising therapy and are titrated to their individual optimal dose, withdrawing such a therapy could cause undue risks and was not recommended. The CHMP recommended the pivotal clinical study design to be based on a switch from SoC (i.e. patients' own alkalinising therapy) to ADV7103.

Following discussion, the CHMP endorsed a switch study (from SoC at the usual therapeutic dose to ADV7103 at the therapeutic dose) with a treatment period longer than the one originally proposed for the placebo-controlled study. The CHMP remarked that the goal such study was not to formally demonstrate superiority or inferiority in terms of efficacy, but rather to obtain adequate data for the CHMP to evaluate the effectiveness (and safety) of the ADV7103 treatment. This design was also endorsed by the Paediatric Committee.

A 5-day period was selected as the chosen study length period as it enabled sufficient time to achieve steady state and allow adequate and valid comparison of both treatment arms.

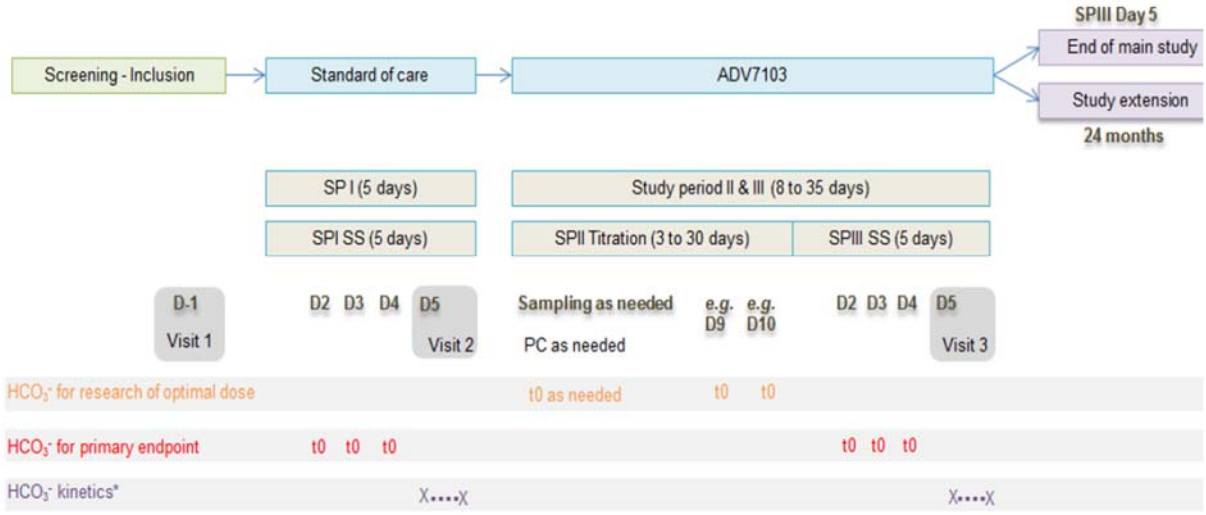
The study included three consecutive SPs; SP I, SP II and SP III) during which enrolled patients were to receive an alkalising treatment (their SoC without modification, and subsequently ADV7103) via oral administration. A total of three visits were planned: Visit 1 (day 1; screening/inclusion visit), visit 2 (last day [day 5] of SP I) and visit 3 (last day [day 5] of SP III). The length of the study was up to 40 days, depending upon the titration period in SP II, which could be from 3 to 30 days. Treatment at each SP was as follows:

- SP I (5-day period). Patients were to receive their usual SoC alkalising treatment at the usual therapeutic dose without modification. For 5 days. On day 5 (visit 2), the patients' bicarbonataemia and other defined parameters were assessed.
- SP II (variable duration period, up to 30 days). 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 (5-day period). Patients were to receive ADV7103 twice a day for 5 days at the fixed optimal dose identified during SP II. On day 5 (visit 3), the patients' bicarbonataemia and other defined parameters were assessed [47].
- To assess 24-hour bicarbonataemia fluctuation patients of age subsets 1 and 2 and some patients of subsets 3 and 4 were hospitalised at visits 2 and 3 for 24 hours. At visit 3 all patients were allowed at their will to continue their treatment with ADV7103 in a follow-up extension study (Study B22CS) for at least 48 months [47].

Figure 14: B21CS study design



Source: Study B21CS. Abbreviations: D = day, SP = study period, t = time.

The chosen study design enabled evaluation of the non-inferior efficacy on metabolic acidosis of ADV7103 in comparison to the patients' SoC after 5 days of treatment at an appropriate and stable dose. The sequential study design allowed robust data to be obtained, using intra-individual comparisons, while limiting the number of study patients and in particular children. The small number of patients included ensured feasibility of the study because dRTA is a rare disease with less than 10,000 children being expected to require ADV7103 therapy in Europe.

The study B21CS was an open-label study with treatment switch. The primary endpoint is a laboratory assessment (plasma bicarbonate), an introduction of bias by the assessor is not considered likely. In addition, the laboratories did not know the SPs, timepoints and therefore treatment. During both evaluation SPs, the doses of SoC and ADV7103 doses cannot be adapted according to the plasma bicarbonate values, so there is no risk a bias from the investigator. There is no interim analysis planned in the study. There are no secondary endpoints depending on a subjective evaluation or outcome to assess by the investigator, except the adverse events, and the treatment experience (palatability, ease of administration, ease of swallowing) assessed by the patients themselves.

Criteria for evaluation in Study B21CS are summarised in Table 19 [47].

Table 19: B21CS Endpoints

	Endpoints
Primary endpoints	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 endpoints	Categorical • Number/proportion of patients with abnormal bicarbonataemia value (i.e., patients with at least one value of bicarbonataemia below 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 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 endpoints • Area under the curve from t0 to t12h (AUC0-12h) on day 5 • area-under-curve (AUC) from t0 to t24h (AUC0-24h) on day 5 • Fluctuation: Maximum minus minimum concentrations over 24 h on day 5. Other • Number of patients with a hypokalaemia after 4 to 5 days of treatment at steady state • Number of patients with a hypercalciuria after 4 to 5 days of treatment at steady state • Number of patients with a 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)
Safety endpoints	• Number/proportion of patients with treatment-emergent adverse events (TEAEs), incidence and severity of these TEAEs during the study. • Gastrointestinal tolerability evaluated with age-appropriate scales: a facial hedonic\ scale (FHS) for the 4-11-year-old children and a 100mmVisual Analogue Scale (VAS) ranging from zero “no complaint” to 100 “extremely severe complaint” for the other patients) at inclusion, on SP I day 5 (visit 2) and SP III day 5 (visit 3) Incidence of abnormal values of: • Venous blood chemistry, at the screening visit (visit 1, day 1) and day 5 of SP I and SP III (Urea/Blood Urea Nitrogen, urate, creatinine, creatinine clearance, total protein, albumin, serum electrolytes (potassium, sodium, chloride, calcium, magnesium, bicarbonate, phosphorus). Bone alkaline phosphatases, 25-hydroxy-vitamin D, 1α,25-dihydroxy-vitamin D, parathormone, new bone marker). • Urine chemistry, at the screening visit (visit 1, day 1) and day 5 of SP I and SP III: pH, specific gravity, bicarbonate, creatinine, urea, citrate, potassium, sodium, chloride, calcium, magnesium and phosphate and crystalluria. • Urine analysis (pH, leucocytes, glucose, ketones, protein, blood) at the screening visit (visit 1, day 1) and day 5 of SP III (end of study). • A complete physical examination was performed at screening (visit 1, day 1) and day 5 of SP III (end of study).
Acceptability assessed based on compliance, palatability, ease of swallowing and ease of administration	• Palatability – A 100mm VAS (ranging from 0 “I dislike it very much” to 100 “I like it very much”) was used for patients in the age subsets 1 and 2 (self-assessment) and for patients in the age subset 4 (assessment performed by one parent). A 5-point FHS (ranging from “dislike very” much to “like very much”) was used for patients in the age subset 3. • Ease of administration and ease of swallowing. A 100mm VAS (ranging from zero “very difficult” to 100 “very easy”) was used for all age subsets (self-assessment for patients in the age subsets 1 and 2; assessment performed by one parent for the patients in the age subsets 3 and 4)

Source: B21CS Clinical Study Report. Abbreviations: AUC, area under curve; SP, study period; VAS, Visual Analogue Scale.

In study B21CS, 49% of patients received more than one SoC, 62% received sodium salt, 86% had 3 to 6 intakes per day, and 27% required intake during the night.

Table 19: Average doses of SoC compared to ADV7103

	Average dose of SoC	Average dose of ADV7103
Adult	2 ±1.5 mEq/kg a day	1.7 ±1 mEq/kg a day
Adolescents	2.2±1.4 mEq/kg a day	2.8±1.7 mEq/kg a day
Children	2.7±1.2 mEq/kg a day	3.8±1.1 mEq/kg a day
Infants	5.3±2.5 mEq/kg a day	6.1±2.3 mEq/kg a day

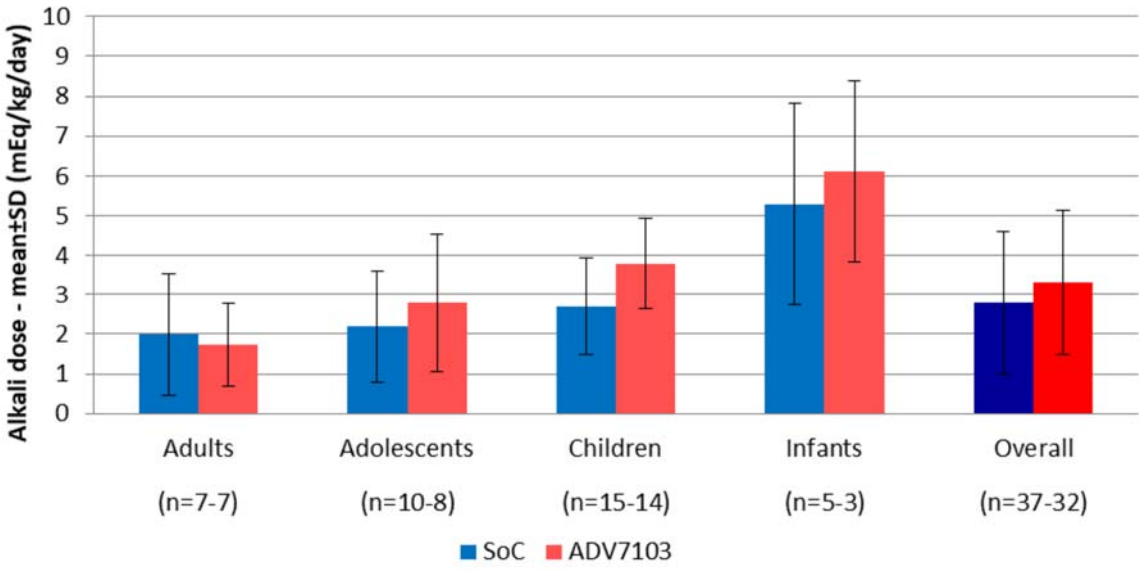
Source: B21CS CSR. Abbreviations: N = number, SoC = standard of care.

Table 20: Pivotal trial, SoC dosing vs ADV7103

	SoC* (N=37)	ADV7103 (N=32)
Taking >1 medication	18 (48.6%)	0
Taking alkali + K^+ supplement	3 (8.1%)	0
Sodium load (mean ± SD)	1.08 ± 0.47 g/day	0
≤ 2 intakes per 24 hours	5 (13.5%)	32 (100%)
≥ 3 intakes per 24 hours	32 (86.5%)	0
At least one intake at night	10 (27%)	0

Source: B21CS CSR. Abbreviations: N = number, SoC = standard of care.

Table 21: Pivotal trial treatment dosage



Source: B21CS CSR. Abbreviations: n = number; SD = standard deviation; SoC = standard of care.

Visits to the investigator site to perform all the examinations (visit 1, visit 2 and visit 3), phone calls with the investigator and local laboratory visits were organised throughout the study for patients enrolled in France and Slovakia. For organisational reasons, patients enrolled in Serbia were hospitalised throughout the 3 SPs, so all visits were conducted at the hospital [47].

Historical data about the usual SoC of the patients took before study entry were collected. Nevertheless, data were not always available in the medical records of the patient due to changes of physician and patients moving location. For data available (for 25 patients), it appears that most patients received their usual SoC alkalising treatment for 4 years (8 months to 4.7 years), and the last

treatment without product or dose modification before study entry lasted in average 18 months, but was variable according to the patient (from 0.5 to 51 months), as detailed in

Table 22. Alkalinising treatment was changed between 1 and 6 times before study entry (i.e., from 0 to 5 times before the line of SoC) with modification of the alkalising agents and/or the daily doses.

There was no inclusion criterion about the time on stable dose of SoC prior to study.

Table 22: Treatment before study enrolment

B21CS – B22CS Subject age	SoC treatment duration	Lines of SoC before study entry	SoC treatment duration at the last therapeutic dose
Adults			
19 years old	4 years	2 different doses	8.5 months
18 years old	4 years	1	48 months
46 years old			
19 years old			
21 years old	3 years	6 products and/or doses	4.5 months
19 years old	4.7 years	3 different doses	14.5 months
18 years old	>2 years	2 different doses	25.5 months
Adolescents			
15 years old	4 years	3 products and/or doses	23.5 months
14 years old	4 years	4 products and/or doses	10.5 months
12 years old			
17 years old	4 years	6 different doses	7 months
13 years old	4 years	6 different doses	1 month
15 years old	3.8 years	4 products and/or doses	0.5 month
13 years old	4 years	3 different doses	4 months
14 years old			
Children			
4 years old	4 years	3 different doses	13.5 months
4 years old	4 years	4 products and/or doses	22 months
5 years old	3.7 years	5 different doses	1 month
6 years old	4 years	5 products and/or doses	14.8 months
8 years old	8 months	1	8 months
7 years old	4 years	2 products and/or doses	37 months
11 years old	1.2 years	2 products and/or doses	2 months
8 years old			
4 years old	1.2 years	3 different doses	7 months
4 years old	4 years	6 products and/or doses	7.8 months
8 years old	4.3 years	1	51 months
8 years old	3.7 years	1	44 months
8 years old	4 years	1	48 months
5 years old			
Infants/Toddlers			
3 years old			

2 years old	2 years	4 products and/or doses	17 months
3 years old		1?	37 months?

Source: B21CS CSR. Abbreviations: n = number; SD = standard deviation; SoC = standard of care.

Mean titration period

Extent of exposure (start and end dose, and total number of days of treatment) during SP II is summarised in Table 31 for the overall study population (all age subsets). During SP II, most patients (33 [89.2%] patients) received a titration of ADV7103. The administration of ADV7103 was interrupted for three paediatric patients: 1 adolescent due to one treatment intake missing, one adolescent due to acute gastroenteritis for about 36 hours and one child due to infection with vomiting for about 3 weeks. The duration of the titration period ranged from 4 to 25 days; the minimal starting dose was 27.40 mEq/day, and the maximal ending dose was 292.00 mEq/day. The median titration period was 10 days for eleven patients. Duration of the titration period was similar across age subsets, except for the infants who had a longer titration (17 days).

The mean titration period was 12.76 days.

Table 23: Extent exposure to ADV7103 in SPII (Overall study population) B21CS

SP II ADV7103 titration			
Number of patients	**Start dose in mEq/day**	**End dose in mEq/day**	**Total number of days of treatment**
1	92.00	92.00	4 days
4	30.50	204.00	9 days
11	28.50	158.00	10 days
2	46.50	124.00	11 days
2	30.00	90.46	13 days
3	27.40	110.00	14 days
2	39.00	272.00	15 days
4	49.00	135.00	16 days
1	46.00	61.20	17 days
2	45.80	109.80	18 days
1	146.00	292.00	22 days
1	87.00	87.00	25 days

Table 24: Calculation of titration mean B21CS

SPII - ADV7103 titration		
Number of patients	**Total number of days treatment**	
1	4	4
4	9	36
11	10	110
2	11	22
2	13	26
3	14	42
2	15	30
4	16	64
1	17	17
2	18	36

1	22	22
1	25	25
Total = 34	Total= 174	Mean =12.76

Recruitment screening and enrolment

Patients with an established diagnosis of dRTA with metabolic acidosis were enrolled in a staggered approach into four age subsets (≥18 years, 12 to 17 years, 4 to 11 years, and 6 months to 3 years), with a minimum of four patients in each subset. A Data Safety Monitoring Board was formed and met when at least four patients of a defined age subset had completed the study to confirm or modify the initial dose of ADV7103 for the subsequent age subset and to review the bicarbonataemia fluctuation, and safety and tolerability data [47].

According to the clinical study protocol (CSP), 32 patients were to be enrolled. However, due to a higher-than-expected eligibility rate and problems with CSP compliance for the included patients, a total of 37 patients were screened and included in the study: 7 adults (≥18 years), 10 adolescents (from 12 to 17 years old inclusive), 15 children (from 4 to 11 years old inclusive) and five infants (from 6 months to 3 years old inclusive).

Table 18: B21CS Inclusion and Exclusion Criteria

Inclusion criteria
1. Patient who had a diagnosis of dRTA (acquired or inherited form) with metabolic acidosis 2. Patient male or female, including child aged between 6 months and 17 years old and adult aged ≥18 years old and ≤55 years old 3. For female patients (maiden after puberty or woman), non-childbearing potential had to be confirmed, for example using a contraceptive method judged effective by the investigator (or surgically sterilised) if sexually active and having a negative pregnancy test at inclusion 4. Patient and/or parents or legal representative(s) who was (were) willing and able to participate in the study, to understand and to comply with study procedures for the entire length of the study 5. Patient or parents or legal representative(s) who had provided a signed written informed consent 6. For patients of ≤17 years of age, collection or attempt to collect assent had to be confirmed 7. Patient who was affiliate to a social health insurance system and/or in compliance with the recommendations of the national law in force relating to biomedical research
Exclusion criteria

1. Patient who presented associated proximal tubular signs (i.e., presenting for example hypophosphoraemia, urinary betamicroglobulin, hyponatraemia)
2. Patient who presented a kalaemia (i.e., plasma potassium concentration) >5.0 mmol/L
3. Patient who presented a severe or moderate renal impairment (creatinine clearance <45 mL/min/1.73m^2 according to Schwartz formula for the children and both Cockcroft & Gault and MDRD formulas for adults)
4. Patient who presented – barring the study disease – 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
5. Patient who took or could not stop (last dose on day 1) potassium-sparing diuretics (e.g., SP ironolactone, aldactone, amiloride, triamterene), angiotensin converting enzymes inhibitors, angiotensin II receptor antagonists, tacrolimus, potassium desodic salts
6. Female patient who was pregnant or breast-feeding
7. Patient who received any medication within the 4 weeks before the inclusion in the study that could interfere with the study treatment
8. Patient who presented contraindications to the administration of the study treatment such as known allergic reactions or hypersensitivity to the active pharmaceutical ingredients or other excipients of the formulations of the study treatment, 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, malabsorption, delayed gastric emptying, oesophageal compression, intestinal obstruction or other chronic gastrointestinal disease)
9. Patient who was admitted to hospital in emergency settings
10. Patient who had participated in a clinical trial within the last 3 months before enrolment
11. Patient who was at risk of non-compliance of the study procedure in the judgement of the investigator
12. Patient who presented any other condition, which in the opinion of the investigator, would preclude participation in the study
13. Patient who could not be contacted in case of emergency
14. Patient under any administrative or legal supervision

Source: B21CS Clinical Study Report. *t0 refers to the period before the first dose on a particular day. The time point t0 was selected as it represents the residual effect of the product after its last administration (i.e. 12 hours for ADV7103 according to the BIDAILY intakes, and a flexible time- period for SoC but no more than 12 hours, due to the multiple daily intakes of SoC).

Non-completion/discontinuation of treatment

Most patients completed the study (32 [86.5%] patients) including all 7 (100%) adults, 8 (80%) adolescents, 14 (93.3%) children and 3 (60%) infants.

During SP I, a total 2 (5.4%) patients discontinued prior to period completion: 1 (6.7%) child due to consent withdrawal by subject (too many blood tests undertaken), and 1 (20%).1-year-old infant due to other reasons (difficulty in swallowing ADV7103). In agreement with the sponsor, an attempt was made to give first intake of ADV7103 a patient at the hospital during SP I but the patient was unable to swallow the tablets certainly due to his young age.

During SP II, a total of 3 (8.6%) patients discontinued prior to period completion: 1 (10%) adolescent due to a lack of efficacy, 1 (10%) 3-year-old infant due to consent withdrawal by subject (failure to take the treatment from the first intake) and 1 (25%) adolescent due to consent withdrawal by subject (difficulty of treatment intake). Overall, of 35 patients entered in SP II, 34 patients received at least one dose of ADV7103. During SP III, there was no premature discontinuation, see Table 25.

Table 25: B21CS Patient disposition

	Adults (≥ 18 years)	Adolescents (from 12-17 years inclusive)	Children (from 4-11 years inclusive)	Infants (from 6 months – 3 years inclusive)	Total
Screening					
Entered phase, N	7	10	15	5	37
Completed phase, n (%)	7 (100)	10 (100)	15 (100)	5 (100)	37 (100)
SPI					
Entered phase, N	7	10	15	5	37
Completed phase, n(%)	7 (100)	10 (100)	14 (93.3)	4 (80)	35 (94.6)
Discontinued prior to phase completion, n (%)	-	-	1 (6.7)	1 (20)	2 (5.4)
Primary reason for non completion of study phase (n[%])	-	-	Withdrawal by subject (1 [6.7])	Other (1[20])	Other (1[2.7]) Withdrawal by subject (1[2.7])
SPII/SPIII					
Entered phase, N	7	10	14	4	35
Completed phase, n(%)	7 (100)	8 (80)	14 (100)	3 (75)	32(91.4)
Discontinued prior to phase completion, n (%)	-	2 (20)	1	1(25)	3 (8.6)
Primary reason for non completion of study phase (n[%])	-	Lack of efficacy (1[10]) Withdrawal by subject (1[10])	-	Withdrawal by subject (1[25])	Lack of efficacy (1[2.9]) Subject withdrawal (2[5.7])
Overall total					
Screened, N	7	10	15	5	37
Completed study, n(%)	7 (100)	8(80)	14 (93.3)	3 (60)	32 (86.5)

Source: B21CS CSR. *Discontinuation during SPII only

Patient characteristics

A total of 37 patients were screened and underwent three SPs: SoC at steady state, ADV7103 titration, and ADV7103 at steady state. Most patients (86.5%) completed the study. The ITT set and the acceptability analysis (AA) set included all 37 patients, while the PP set included 30 patients (2 patients were excluded due to major protocol deviations and five patients due to early study discontinuation). Overall, many patients (62%) were female, except for the infant category where most patients (80%) were male. The mean age of adults, adolescents, children and infants was 23.3 years, 14.0 years, 7.3 years and 2.6 years, respectively [47].

The vast majority (35 [94.6%]) of patients had the inherited form of dRTA and one patient had an acquired form of dRTA concomitant to Sjögren syndrome. For one patient the type of dRTA was unknown, although an inherited dRTA was suspected as 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 32 [86.5%] patients), hearing impairment (in 23 [62.2%] patients), nephrolithiasis (in 5 [13.5%] patients), growth impairment (in 4 [10.8%] patients) [47].

B22CS

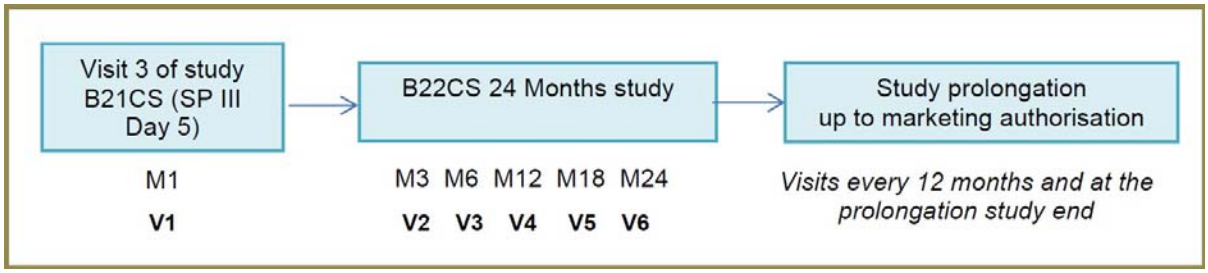
Study design

This study was a multicentre, OLE study of the Phase II/III Study B21CS in patients with dRTA. Study B21CS was a multicentre, open-label, non-inferiority, sequential study comparing the efficacy, safety, tolerability and acceptability of ADV7103 with SoC during two successive phases involving a switch from SoC to ADV7103 in patients with a confirmed diagnosis of dRTA. 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 24 months (originally planned for 24 months but extended in France until market authorisation and availability of ADV7103 and extended for six additional months (30 months in total) in Slovakia and Serbia, until approval of the import licence for ADV7103). A total of 30 patients with inherited dRTA were thus enrolled into Study B22CS after satisfactory completion of Study B21CS.

Six visits were scheduled during the first 24 months of the OLE study. The first visit of Study B22CS at M1 corresponded to visit V3 of Study B21CS (SP III, day 5) and a further five visits took place at M3, M6, M12, M18 and M24, respectively. One visit every year was scheduled thereafter for patients continuing beyond 24 months in France. For patients in Slovakia and Serbia, there was a further visit 6 months after M24 (M30).

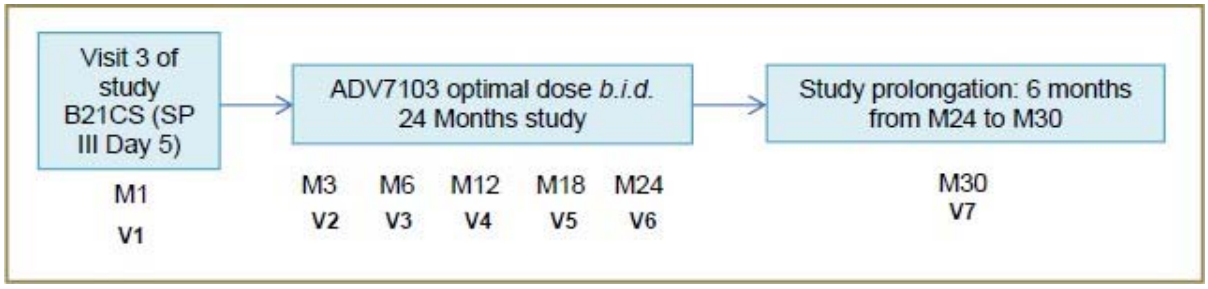
The daily dose of ADV7103/ADV7103 was provided in two doses per day (one dose in the morning and one dose in the evening) taken orally before a meal, directly in the mouth then swallowed with water or mixed with some semi-liquid foods for the youngest children. The morning dose was taken between approximately 7 and 8 am and the evening dose approximately between 7 and 9 pm. The prolonged-release granules of ADV7103/ADV7103 were not to be chewed or crushed. At the initiation of the B22CS OLE study, the dose of ADV7103/ADV7103 for each patient was the optimal dose defined by the investigator during SP III of Study B21CS. The dose of ADV7103/ADV7103 could be further adapted according to the needs of the patient, based on the investigator judgement [46].

Figure 15: B22CS study design for patients in France



Source: clinical study protocols. Abbreviations: M = month; SP = study period; V = visit.

Figure 16: B22CS study design for patients in Slovakia and Serbia



Source: clinical study protocols. Abbreviations: M = month; SP = study period; V = visit.

The primary objective of the study was to evaluate the long-term safety and tolerability of ADV7103 as measured by adverse events. Safety and tolerability were assessed by recording AEs and serious

adverse events (SAEs), physical examination (including body weight, height, body mass index [BMI], and Tanner stage [if appropriate]), vital signs and electrocardiograms (ECGs), and urine and blood laboratory tests.

The secondary objectives of this study were to evaluate:

- The long-term efficacy of ADV7103 on correcting metabolic acidosis as measured by bicarbonataemia.
- The long-term effects of ADV7103 on hypocitraturia.
- The long-term effects of ADV7103 on hypercalciuria.
- The long-term effects of ADV7103 on crystalluria.
- The long-term paraclinical and biological safety of ADV7103.
- The long-term compliance to ADV7103.
- The long-term effects of ADV7103 on kalaemia.
- The long-term effects of ADV7103 on hyperphosphaturia.
- The long-term effects of ADV7103 on hypermagnesuria [46].

Exploratory objectives were:

- The long-term effects of ADV7103 on nephrocalcinosis.
- The long-term effects of ADV7103 on nephrolithiasis.
- The long-term effects of ADV7103 on bone remodelling.
- The long-term effects of ADV7103 on rickets and osteomalacia, respectively in the paediatric and adult population.
- The long-term effects of ADV7103 on growth in the paediatric study population.
- The long-term effects of ADV7103 on pubertal maturity in the relevant paediatric study population.
- The long-term treatment acceptability of ADV7103.
- The long-term effects of ADV7103 on QoL [46]

Table 21: B22CS Endpoints

	Endpoint
Primary safety endpoint	The number/proportion of patients presenting adverse events (AE) throughout the course of the study, including the incidence and severity of these events.
Secondary safety endpoint	The number/percentage of patients presenting abnormal values after treatment at each study visit, including the incidence and clinical significance when appropriate of these abnormal values, for: • Physical examination (general appearance, bone system, muscular system, articular system), • Vital signs (systolic and diastolic blood pressures [SBP and DBP], heart rate [HR] and respiratory rate [RR]), • ECG parameters (HR, PR interval, QRS interval [QRS], QT interval [QT], QT interval with Bazett's correction [QTcB] and QT interval with Fridericia's correction [QTcF]), • Laboratory parameters (serum chloride, albumin, proteins, sodium, magnesium, urea, creatinine) and urine bicarbonate, potassium, chloride, proteins, sodium,

	magnesium, • Liver function tests (aspartate aminotransferase (AST) and alanine aminotransferase [ALT]), • Urinalysis (pH, leucocytes, glucose, ketones, proteins, blood and specific gravity) with microscopic examination if required, • Estimated GFR (eGFR) using the Schwartz formula for children and Cockcroft & Gault formula for adults.
Efficacy endpoints	The number/percentage of patients presenting normal ranges at each study visit in the following parameters: • Bicarbonataemia, • Kalaemia, • Citraturia (expressed as urinary ratio of citrate/creatinine [UCi/UCr]), • Calciuria (expressed as urinary ratio of calcium/citrate [UCa/UCi] and urinary ratio of calcium/creatinine [UCa/UCr]), • Phosphaturia (expressed as urinary ratio of phosphate/creatinine [UPh/UCr], tubular reabsorption of phosphorous [TRP] and ratio of renal tubular maximum reabsorption of phosphorous [TmP] to GFR [TmP/GFR]), • Magnesuria (expressed as urinary ratio of magnesium/creatinine [UMg/UCr]), • The number/percentage of patients at each study visit presenting crystalluria positive, including urine environment • Compliance to the treatment including the incidence of events of non-compliance at M3, M6, M12, M18, M24, M30 (for patients in Slovakia and Serbia) and for patients in France, at annual visits in the prolongation
Exploratory efficacy endpoints	• Nephrocalcinosis, • Calculi, • Bone remodelling (including biochemistry blood parameters and BMD), • Rickets and osteomalacia, • Evaluation of growth in children (including stature and body weight measurement, EAS balanced by the genetic target structure (GTS), and growth velocity), • Physical development of the sexual organs at puberty, • Treatment acceptability of ADV7103 • Patients' and parents' QoL (evaluated with a VAS to be filled in by the patient or the caregiver, depending on age), • Impact of dRTA and its treatment on daily life of patients and/or parents through individual exploratory interviews after M24, during prolongation period, • Medical history (disease history of the patient for the 4 years before Study B21CS in relation to their medical profile for the 4 years during Study B22CS: results of bicarbonataemia, kalaemia, blood creatinine, urine calcium, urine creatinine, urine citrate, eGFR, number of hospitalisations and any visits to hospital emergency service, number of renal calculi, anthropometric data, doses of alkalising treatment used and dRTA genetic mutation), • Most exploratory efficacy endpoints were assessed at M1 and M24, and at annual visits during the prolongation period and at end of study, except biochemistry blood parameters, stature, body weight, growth velocity and physical development of the

	sexual organs at puberty (assessed at each study visit), treatment acceptability (assessed at M24 only), and patients' and parents' QoL (assessed at M6 and M24).

Source: B22CS Clinical Study Report (CSR). Abbreviations: AE = adverse events, GTS = Genetic target structure, QoL = quality of life, VAS = visual analogue scale.

Recruitment, screening and enrolment

The study population consisted of children and adult patients with dRTA who had participated in Study B21CS and agreed to continue with ADV7103 treatment instead of their usual alkalising treatment for the duration of Study B22CS.

As many patients as possible (up to 32 patients) were to be enrolled from Study B21CS.

Four age groups were planned: infants from 6 months to 3 years old, children from 4 to 12 years old, adolescents from 12 to 17 years old and adults from 18 years old.

Table 20: B22CS Inclusion and Exclusion Criteria [46]

Inclusion criteria
1. Patient who had participated in and completed Study B21CS 2. Patient who had a diagnosis of dRTA (acquired or inherited form) with metabolic acidosis 3. Patient male or female, including child aged between 6 months and 17 years old and adult aged ≥18 years and ≤55 years old 4. Patient for whom the efficacy, safety and tolerability of ADV7103 was satisfactory during Study B21CS 5. Patient and/or parents or legal representative(s) who were willing and able to participate in the study, to understand and to comply with study procedures for the entire length of the study 6. Patient or parents or legal representative(s) who had provided signed written informed consent 7. Patient of ≤17 years of age for whom assent had been collected or had been tried to be collected
Exclusion criteria
1. Patient who had not participated in Study B21CS 2. Patient for whom any safety issue could have contraindicated her/his participation in the extension study 3. All exclusion criteria stated for B21CS

Source: B22CS CSR.

Non-completion/discontinuation of treatment

One adult withdrew from the study after M12 for personal reasons, and one adolescent and one child completed the study at M30 as per the country specific protocol. All patients were included in the safety, efficacy and QoL analyses.

Patient characteristics

The study population consisted of children and adult patients with dRTA who had participated in Study B21CS and agreed to continue with ADV7103/ADV7103 treatment instead of their usual alkalising treatment for the duration of Study B22CS [46].

Up to 32 patients were planned to be included, and 30 participated in this OLE study. Four subgroups of age were planned: infants from 6 months to 3 years old, children from 4 to 11 years old, adolescents from 12 to 17 years old and adults from 18 years old [46].

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. Only one patient who participated to B21CS study was not willing to continue in B22CS study. The only patient was an adult with acquired dRTA (all other patients had inherited dRTA, the most severe form of dRTA), The patient preferred to pursue her previous usual treatment as it was not so constraining for her, and she was not motivated to follow the B22CS study procedures. The previous treatment was an official preparation of potassium citrate

further dissolved in water by the patient.

The baseline dRTA status of patients in the study (from Study B21CS), including mode of diagnosis, form of dRTA and presence of associated symptoms, is summarised by age group and overall, in Table 26.

Most patients (23 patients, 76.7%), had a genetic diagnosis. One child was not genetically tested since his older brother presented a genetically diagnosed dRTA. Eighteen patients (60.0%) had a clinical and/or biochemical diagnosis (in the absence of or before genetic diagnosis). All the patients assessed had inherited dRTA (one child had missing genetic data to confirm the aetiology of dRTA).

All patients had past presence of metabolic acidosis (100%) and the majority had nephrocalcinosis (86.7%) and hearing impairment (66.7%), regardless of the subgroup of age. With regards to the nephrocalcinosis and hearing loss the population of the study is strictly comparable to dRTA patients published in the literature with very similar frequency for these two major symptoms [7]. Some patients (13.3%) presented nephrolithiasis, again in the same range as reported in the literature. Muscle weakness, cramp, periodic paralysis, nephrolithiasis, renal impairment, fractures/pseudo fractures, growth impairment (in children), short stature (in adults) and other clinical symptoms were only seen in small numbers at baseline (≤four patients). One infant had hypokalaemia, two patients (one adult and one child) had osteopenia and one child had polyuria. There were no cases of rickets, osteomalacia or bone pain at baseline. Thus, the population included in the study is comparable to the published cohort.

Table 26: Study B22CS Baseline Distal Renal Tubular Acidosis Status

Parameter	Yes/No	Adult [≥18Y] (N=6)	Adolescent [12-18Y] (N=8)	Child [4-12Y] (N=13)	Infant [0.5-4Y] (N=3)	Overall (N=30)
Mode of diagnosis						
Genetic	No	1 (16.7)	2 (25.0)	4 (30.8)	0	7 (23.3)
	Yes	5 (83.3)	6 (75.0)	9 (69.2)	3 (100.0)	23 (76.7)
Clinical diagnosis	Yes	6 (100.0)	2 (25.0)	5 (100.0)	1 (33.3)	14 (100.0)
Biochemical and clinical	Yes	0	1 (12.5)	0	0	1 (12.5)
Genetic diagnosis for brother	Yes	0	0	1 (12.5)	0	1 (12.5)
Biochemistry	Yes	0	0	0	1 (12.5)	1 (12.5)
Biochemical	Yes	0	1 (12.5)	0	0	1 (12.5)
Form of dRTA						
Inherited	Yes	6 (100.0)	8 (100.0)	12 (100.0)	3 (100.0)	29 (100.0)
Acquired	No	6 (100.0)	8 (100.0)	12 (100.0)	3 (100.0)	29 (100.0)
Associated Symptoms						
Metabolic acidosis	Yes	6 (100.0)	8 (100.0)	13 (100.0)	3 (100.0)	30 (100.0)
Hearing impairment	No	0	3 (37.5)	6 (46.2)	1 (33.3)	10 (33.3)
	Yes	6 (100.0)	5 (62.5)	7 (53.8)	2 (66.7)	20 (66.7)
Muscle weakness	No	6 (100.0)	7 (87.5)	13 (100.0)	3 (100.0)	29 (96.7)
	Yes	0	1 (12.5)	0	0	1 (3.3)
Cramp	No	5 (83.3)	6 (75.0)	13 (100.0)	3 (100.0)	27 (90.0)
	Yes	1 (16.7)	2 (25.0)	0	0	3 (10.0)
Periodic paralysis	No	5 (83.3)	8 (100.0)	13 (100.0)	3 (100.0)	29 (96.7)
	Yes	1 (16.7)	0	0	0	1 (3.3)
Nephrocalcinosis	No	0	2 (25.0)	1 (7.7)	1 (33.3)	4 (13.3)

Parameter	Yes/No	Adult [≥18Y] (N=6)	Adolescent [12-18Y] (N=8)	Child [4-12Y] (N=13)	Infant [0.5-4Y] (N=3)	Overall (N=30)
	Yes	6 (100.0)	6 (75.0)	12 (92.3)	2 (66.7)	26 (86.7)
Nephrolithiasis	No	6 (100.0)	6 (75.0)	12 (92.3)	2 (66.7)	26 (86.7)
	Yes	0	2 (25.0)	1 (7.7)	1 (33.3)	4 (13.3)
Renal impairment	No	6 (100.0)	7 (87.5)	13 (100.0)	3 (100.0)	29 (96.7)
	Yes	0	1 (12.5)	0	0	1 (3.3)
Rickets	No	6 (100.0)	8 (100.0)	13 (100.0)	3 (100.0)	30 (100.0)
Osteomalacia	No	6 (100.0)	8 (100.0)	13 (100.0)	3 (100.0)	30 (100.0)
Bone pain	No	6 (100.0)	8 (100.0)	13 (100.0)	3 (100.0)	30 (100.0)
Fractures/pseudo fractures	No	6 (100.0)	8 (100.0)	13 (100.0)	2 (66.7)	29 (96.7)
	Yes	0	0	0	1 (33.3)	1 (3.3)
Growth impairment	No	0	8 (100.0)	12 (92.3)	1 (33.3)	21 (70.0)
	Yes	0	0	1 (7.7)	2 (66.7)	3 (10.0)
	NA	6 (100.0)	0	0	0	6 (20.0)
Short stature	No	5 (83.3)	0	0	0	5 (16.7)

Source: B22CS CSR. Abbreviations: N= number; Y = years.

Previous and concomitant medications

Previous (all) and concomitant medications (taken by ≥2 patients overall) at baseline are summarised by age group and overall, in Table 27 and Table 28, respectively.

Eleven patients (36.7%) were taking previous medication, defined as medication started before the first study medication intake and maintained throughout the study duration at the same dose (Table 12). The most taken medication was cholecalciferol, which was taken by six patients (20.0%); one adult, one adolescent, three children, and one infant. Four patients (13.3%, three adults and one child) were taking mineral supplements, and two adults were taking sex hormones or modulators of the genital system. Two patients (6.7%, one adult and one child) were taking the diuretic hydrochlorothiazide. All other medications were taken by one patient only.

Table 27: Study B22CS previous medications

Medication Class	Medication drug name *	Adults [≥18Y] (N=6)	Adolescents [12-18Y] (N=8)	Children [4-12Y] (N=13)	Infants [0.5-4Y] (N=3)	Overall (N=30)
All	All	5 (83.3)	1 (12.5)	4 (30.8)	1 (33.3)	11 (36.7)
Analgesics	All	1 (16.7)	0	0	0	1 (3.3)
	Paracetamol	1 (16.7)	0	0	0	1 (3.3)
Anti-histamines for systemic use	All	1 (16.7)	0	0	0	1 (3.3)
	Desloratadine	1 (16.7)	0	0	0	1 (3.3)
Diuretics	All	1 (16.7)	0	1 (7.7)	0	2 (6.7)
	Hydrochlorothiazide	1 (16.7)	0	1 (7.7)	0	2 (6.7)
Drugs for obstructive airway diseases	All	1 (16.7)	0	0	0	1 (3.3)
	Salbutamol	1 (16.7)	0	0	0	1 (3.3)
	Seretide	1 (16.7)	0	0	0	1 (3.3)
Mineral supplements	All	3 (50.0)	0	1 (7.7)	0	4 (13.3)

Medication Class	Medication drug name *	Adults [≥18Y] (N=6)	Adolescents [12-18Y] (N=8)	Children [4-12Y] (N=13)	Infants [0.5-4Y] (N=3)	Overall (N=30)
	Copper	1 (16.7)	0	0	0	1 (3.3)
	Lekovitca	1 (16.7)	0	0	0	1 (3.3)
	Potassium chloride	1 (16.7)	0	0	0	1 (3.3)
	Sodium chloride	0	0	1 (7.7)	0	1 (3.3)
Otologicals	All	0	0	0	1 (33.3)	1 (3.3)
	Ofloxacin	0	0	0	1 (33.3)	1 (3.3)
Sex hormones and modulators of the genital system	All	2 (33.3)	0	0	0	2 (6.7)
	Chlormadione acetate	1 (16.7)	0	0	0	1 (3.3)
	Marvelon	1 (16.7)	0	0	0	1 (3.3)
Vitamins	All	1 (16.7)	1 (12.5)	3 (23.1)	1 (33.3)	6 (20.0)
	Cholecalciferol	1 (16.7)	1 (12.5)	3 (23.1)	1 (33.3)	6 (20.0)

Source: B22CS CSR. Abbreviations: N= number; Y = years.

Table 28: Study B22CS Concomitant Medications Reported in ≥2 Patients Overall

Medication Class	Medication drug name *	Adults [≥18Y] (N=6)	Adolescents [12-18Y] (N=8)	Children [4-12Y] (N=13)	Infants [0.5-4Y] (N=3)	Overall (N=30)
All	All	5 (83.3)	8 (100.0)	13 (100.0)	3 (100.0)	29 (96.7)
Analgesics	All	3 (50.0)	6 (75.0)	5 (83.3)	1 (33.3)	15 (50.0)
	Paracetamol	2 (33.3)	4 (50.0)	5 (38.5)	1 (33.3)	12 (40.0)
Anti-anaemic preparations	All	0	0	3 (23.1)	1 (33.3)	4 (13.3)
	Ferrous fumarate	0	0	2 (15.4)	0	2 (6.7)
	Sodium feredetate	0	0	1 (7.7)	1 (33.3)	2 (6.7)
Anti-bacterials for systemic use	All	1 (16.7)	2 (25.0)	3 (23.1)	1 (33.3)	7 (23.3)
	Amoxicillin	0	0	2 (15.4)	1 (33.3)	3 (10.0)
	Augmentin	1 (16.7)	1 (12.5)	0	0	2 (6.7)
	Bactrim	0	0	2 (15.4)	0	2 (6.7)
	Cefixime	1 (16.7)	0	1 (7.7)	0	2 (6.7)
Anti-diarrheals, intestinal, anti-inflammatory/ anti-infective agents	All	1 (16.7)	1 (12.5)	1 (7.7)	2 (66.7)	5 (16.7)
	Racecadotril	0	0	1 (7.7)	1 (33.3)	2 (6.7)
Anti-emetics and anti-nauseants	All	0	2 (25.0)	0	1 (33.3)	3 (10.0)
	Ondansetron	0	1 (12.5)	0	1 (33.3)	2 (6.7)
Anti-fungals for dermatological use	All	0	0	3 (23.1)	0	3 (10.0)
	Ketoconazole	0	0	3 (23.1)	0	3 (10.0)
Anti-inflammatory and anti-rheumatic	All	2 (33.3)	2 (25.0)	0	0	4 (13.3)
	Ibuprofen	0	2 (25.0)	0	0	2 (6.7)

products	Ketoprofen	2 (33.3)	0	0	0	2 (6.7)
Blood substitutes and perfusion solutions	All	0	3 (37.5)	0	2 (66.7)	5 (16.7)
	Osmotan	0	2 (25.0)	0	1 (33.3)	3 (10.0)
Corticosteroids for systemic use	All	1 (16.7)	0	3 (23.1)	0	4 (13.3)
	Glucocorticoids	0	0	2 (15.4)	0	2 (6.7)
	Prednisolone	0	0	2 (15.4)	0	2 (6.7)
Drugs for acid-related disorders	All	1 (16.7)	1 (12.5)	1 (7.7)	1 (33.3)	4 (13.3)
	Gaviscon	0	1 (12.5)	1 (7.7)	0	2 (6.7)
	Omeprazole	1 (16.7)	0	0	1 (33.3)	2 (6.7)
Drugs for functional GI disorders	All	2 (33.3)	2 (25.0)	2 (15.4)	1 (33.3)	7 (23.3)
	Domperidone	0	0	1 (7.7)	1 (33.3)	2 (6.7)
	Spasfon	2 (33.3)	1 (12.5)	0	0	3 (10.0)
Drugs for obstructive airway disease	All	1 (16.7)	0	0	1 (33.3)	2 (6.7)
	Montelukast	1 (16.7)	0	0	1 (33.3)	2 (6.7)
Mineral supplements	All	1 (16.7)	0	1 (7.7)	0	2 (6.7)
	Potassium chloride	1 (16.7)	0	1 (7.7)	0	2 (6.7)
Vitamins	All	2 (33.3)	7 (87.5)	10 (76.9)	2 (66.7)	21 (70.0)
	Cholecalciferol	2 (33.3)	7 (87.5)	9 (69.2)	2 (66.7)	20 (66.7)

Source: B22CS CSR. Abbreviations: N= number; Y = years.

2.3.1. Comparative summary of trial methodology

The key clinical trials used to inform the clinical efficacy, safety, and tolerability of ADV7103 are two phase 3 trials (B21CS and B22CS). All data from these studies are presented in this section. Study B22CS was an OLE of B21CS therefore the trial design and eligibility criteria are very similar.

Table 29: Comparative summary of trial methodology

Trial number	B03CS	B21CS	B22CS
Location	Performed in France	Performed in France, Serbia and Slovakia	Performed in France, Serbia, and Slovakia
Trial design	Double-blind, placebo-controlled, cross-over study	Multicentre open label, sequential non inferiority study	Multicentre open label extension study
Eligibility criteria for participants	1. Subject who was healthy, male or female, between the ages of 18 to 55 years inclusive, at inclusion, with a 2. body mass index (BMI) between 18 and 30. 3. Subject who presented no medical major history or chronic treatment. 4. Subject who was a female without childbearing potential, *i.e.,* surgically sterilised or post-menopausal or 5. using adequate contraception (*i.e.,* a double-barrier method including a local barrier at least during the all 6. duration of her participation to the study). 4. Subject who was willing and able to participate in the study and to understand and to comply with study procedures for the entire length of the study. 7. Subject who provided a signed written informed consent. 8. Subject who was affiliated to a social health insurance system and/or in compliance with the recommendations of the French Law in force relating to biomedical research.	1. Female without childbearing potential, i.e., using a contraceptive method judged effective by the investigator (or surgically sterilised) if sexually active and having a negative pregnancy test at inclusion 2. Patient and/or parents or legal representative(s) willing and able to participate in the study, to understand and comply with study procedures 3. Signed written informed consent 4. Children less than 18 years of age with assent 5. Patients affiliated to a social health insurance system and/or in compliance with the recommendations of the national law in force relating to biomedical research 6. Age 7. ≥ 6 months to ≤ 55 years	1. Participation in Study B21CS 2. Satisfactory efficacy, safety and tolerability with ADV7103 during Study B21CS 3. Patient and/or parents or legal representative(s) willing and able to participate, to understand and to comply with study procedures for the entire length of the study 4. Signed written informed consent by the patient or parents or legal representative(s) 5. Signed assent for children less than 18 years of age (or tried to be collected)
Settings and locations where data	Eurofins OPTIMED – 1 rue des Essarts – 38610 Gières - France.	A total of 13 centres in 3 countries participated in the study: 11 centres in France, 1 in Slovakia and 1 in Serbia.	

were collected			
Trial drugs	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 Washout: 7 days Period II: ADV7103 or placebo granules BID for 5 days.	ADV7103 BID or patients' usual SoC	ADV7103 BID
Dose titration	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		Onset dose identified in B21CS, which could be modified by the investigator where needed)
Efficacy assessments performed	Main objective: To assess the pharmacodynamics effect on urine pH of oral doses of ADV7103 versus placebo after 5 days of treatment. Secondary objectives: • To assess the relationship between oral doses of ADV7103 and urine pH after 5 days of treatment. • To assess the pharmacodynamics effects of oral doses of ADV7103 on other urine biomarkers after 5 days of • treatment. • To assess the residual effect of oral doses of ADV7103 on urine pH after treatment discontinuation over a 24-hour period.	• To evaluate the relative efficacy of ADV7103 and Standard of Care (SoC) on correcting metabolic acidosis as measured by pre-morning dose blood bicarbonate levels during 3 days of treatment at steady state (Day 2 to • Day 4). • 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 of ADV7103 as compared to standard of care after 4 • to 5 days of treatment at steady state • To evaluate the efficacy on the correction of hypocitraturia of ADV7103 as compared to standard of care after • 4 to 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	• The long-term efficacy of ADV7103 on correcting metabolic acidosis as measured by bicarbonataemia; • The long-term effects of ADV7103 on hypocitraturia; • The long-term effects of ADV7103 on hypercalciuria; • The long-term effects of ADV7103 on crystalluria; • The long-term paraclinical and biological safety of ADV7103; • The long-term compliance to ADV7103. • Note: additional secondary objectives specified in the 24-month SAP were to evaluate: • The long-term effects of ADV7103 on kalaemia; • The long-term effects of ADV7103 on hyperphosphaturia; • The long-term effects of ADV7103 on hypermagnesuria. • The long-term effects of ADV7103 on nephrocalcinosis; • The long-term effects of ADV7103 on nephrolithiasis;

		• state.	• The long-term effects of ADV7103 on bone remodelling; • The long-term effects of ADV7103 on rickets and osteomalacia, respectively in the paediatric and adult • population; • The long-term effects of ADV7103 on growth in the paediatric study population; • The long-term effects of ADV7103 on pubertal maturity in the relevant paediatric study population; • The long-term treatment acceptability of ADV7103; • The long-term effects of ADV7103 on quality of life (QoL).
Safety assessments performed	To assess safety and tolerability of oral doses of ADV7103 after 5 days of treatment.	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	The primary objective of the study was to evaluate the long-term safety and tolerability of ADV7103 as measured by adverse events (AEs).
Primary outcomes	• Urine pH (measured with pH-metre): over 2 consecutive nychthemeral recordings days after 5 days of treatment (Day 4 and Day 5) with ADV7103 or placebo • The mean urine pH values over 24-hour pooled across the 2 days, • The urine pH values in the first morning and pre-dose urines during the 2 days, in order to assess the • ADV7103 residual effect, with changes from baseline defined as followed: urine spot on Day 4 t0h • versus urine spot on Day -1 t-24h and the 2h-urine collection on Day 5 (i.e. Day 4]22h – 24h]) versus the 2h-urine collection Day 1 (i.e. Day-1]-2h – 0h]) • The percentage of urine pH values ≥ 7.0 over 24-hour pooled across the 2 days,	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).	• The number/proportion of patients presenting AEs throughout the course of the study, including the incidence • and severity of these events. • Secondary endpoints • The number/proportion of patients presenting abnormal values after treatment at each study visit, including the • incidence of these abnormal values and the change from baseline in: • Physical examination (general appearance, bone system, muscular system, articular system, body • weight, height, BMI); • Vital signs (systolic and diastolic blood pressures, heart rate and respiratory rate); • ECG parameters (PR, QRS, QT interval,

	• The urine pH fluctuation (difference between maximal and minimal values) over 24-hour pooled acrossthe 2 days.		QT interval with Bazett's correction and QT interval with • Fridericia's correction); • Blood chemistry (serum ionogram: chloride, albumin, proteins, sodium, magnesium, urea, creatinine); • Liver function tests (transaminases aspartate aminotransferase and alanine aminotransferase) • Urine chemistry (urine ionogram: bicarbonate, potassium, chloride, proteins, sodium, magnesium); • Urinalysis (pH, leucocytes, glucose, ketones, proteins, blood and specific gravity) with microscopic examination if required.
Secondary outcomes	• Citraturia: mean change from baseline of the values pooled across the 2 days. • Return to baseline urine pH (measured with pH-metre): mean change from baseline of the values obtained in • Day 6 of each study period, throughout the nychthemeral period and in the first morning urines. • Adverse events during the study. • The incidence of urine pH values > 8.0 over the course of the study. • Vital signs and ECG parameters: mean values and changes from baseline during the study, incidence of abnormal values after treatment. • Standard laboratory parameters and special laboratory parameters (such as kalaemia, blood pH, arterial alkaline reserve, urine electrolytes): mean values and changes from baseline during the study, incidence of abnormal values after treatment.	• 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. • Number/proportion of patients with abnormal bicarbonataemia value (i.e., patients with at least one value of bicarbonataemia below 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 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). • Area under the curve from t0 to t12h (AUC0-12h) on Day 5 • AUC from t0 to t24h (AUC0-24h) on Day 5	The number/proportion of patients presenting normal ranges at each study visit, mean and change from baseline in the following parameters: • Bicarbonataemia; • Kalaemia; • Hypocitraturia (expressed as UCi/UCr; including incidence and severity); • Hypercalciuria (expressed as UCa/UCr and UCa/UCi; including incidence and severity); • Hyperphosphaturia (expressed as UPh/UCr; including incidence and severity); • Hypermagnesuria (expressed as UMg/UCr; including incidence and severity); • Crystalluria at each study visit; • Compliance to the treatment, assessed at each study visit, including the incidence of events of non-compliance at M24 presented as number/proportion of patients compliant at least 50%, at least

		• Minimum concentration (Cmin) over 24 h on Day 5. • Fluctuation: Maximum minus minimum concentrations over 24 h on Day 5.	75% or at least 90% of the time. • The kalaemia endpoint was originally a safety endpoint but was added to the secondary efficacy endpoints during the study. • Hyperphosphaturia and hypermagnesuria were also added to the secondary efficacy endpoints during the study.
Exploratory outcomes	N/A	• Number of patients with a hypokalaemia after 4 to 5 days of treatment at steady state. • Number of patients with a hypercalciuria after 4 to 5 days of treatment at steady state. • Number of patients with a 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). • To assess bicarbonataemia fluctuation, blood samples for bicarbonataemia were collected during the 24-h hospitalisation on Day 5 of SP I and SP II. • To assess calciuria and citraturia of 24 hours, urine calcium/creatinine and citrate/creatinine excretion ratio • Number/proportion of patients with treatment-emergent adverse events (TEAEs), incidence and severity of these • Gastrointestinal tolerability Incidence of abnormal values of: • Venous blood chemistry, at the screening visit (Visit 1, Day -1) and Day 5 of SP I and SP III (Urea/Blood Urea Nitrogen, urate, creatinine, creatinine clearance, total protein, albumin, serum electrolytes (potassium, sodium, chloride, calcium, magnesium, bicarbonate,	• Nephrocalcinosis; • Nephrolithiasis; • Bone remodelling (including biochemistry blood parameters and bone mineral density); • Rickets and osteomalacia; • Growth in children (including stature and body weight measurement, patient's stature balanced by the • GTS and growth velocity) • Physical development of the sexual organs at puberty; • Long-term treatment acceptability of ADV7103; • Long-term effects of ADV7103 on patients' quality of life, evaluated with a VAS to be filled in by the patient or the caregiver (depending on the age).

		phosphorus). Bone alkaline phosphatases, 25-hydroxy-vitamin D, 1α,25-dihydroxy-vitamin D, parathormone, new bone marker). • Urine chemistry, at the screening visit (Visit 1, Day -1) and Day 5 of SP I and SP III: pH, specific gravity, bicarbonate, creatinine, urea, citrate, potassium, sodium, chloride, calcium, magnesium and phosphate and crystalluria. • Urine analysis (pH, leucocytes, glucose, ketones, protein, blood) at the screening visit (Visit 1, Day 1) and Day 5 of SP III (end of study). • A complete physical examination was performed at Screening (Visit 1, Day 1) and Day 5 of SP III (end of study). • Acceptability of the ADV7013 formulation and SoC was assessed based on compliance and on the following three parameters: palatability, ease of swallowing and ease of administration.	

2.3.3. Patient Demographics in the three studies

Table 30: Patient Demographics in the three studies

Trial number **Baseline characteristic**	**B03CS**	**B21CS**	**B22CS**
n (overall)	(n=16)	(n=37)	(n=30)
Age			
Mean	32.4 (10.76)	11.5 (8.15)	11.2 (5.9)
Median	27.0	11.5	10.3
Range	19-53	1-46	1-22
Sex			
Female	7 (43.8%)	23 (62%)	17 (56.7%)
Male	9 (56.3%)	14 (38%)	13 (34.3%)
Weight (kg)			
Mean (SD)	66.62 (6.149)	37.4 (22.30)	37.30 (19.17)
Median	66.55	39.0	41.05
Range	54.9 - 80.9	9-114	12.0-87.0
Height (cm)			
Mean	171.9 (7.20)	133.5 (27.79)	135.1 (26.5)
Median	173.0	139.0	141.0
Range	158-181	75-170	86-170
Type of dRTA			
Acquired – n (%)	Not specified	1 (2.7%)	0 (0)
Inherited - n (%)	Not specified	35 (94.6%)	29.0 (100%)
Not specified – n (%)	Not specified	1 (2.7%)	1.0 (0%)

Abbreviations: cm, centimetres; dRTA, distal renal tubular acidosis; kg, kilograms; n, number; SD, standard deviation.

The following table summarises the publications from B21CS and B22CS trials:

Table 31: Publications related to selected trials

Trial	Publications	Contents/Title	List of authors	Date
Phase II (adults and children) B21CS	Abstract ESPN 2017 Glasgow 6-9 Sept (published in Paediatric Nephrology 32(9): 1643–1834)	Efficacy and acceptability of ADV7103, an innovative prolonged-release oral alkalising formulation in distal renal tubular acidosis (dRTA) patients *https://link.springer.com/article/10.1007/s00467-017-3753-x*	A. Bertholet-Thomas, C. Guittet, M.A. Manso, F. Vandenhende, M. Cailliez, V. Baudoin, M. Di Maio, O. Gillion Boyer, E. Golubovic, J. Harambat, A. Klein, B. Knebelmann, F. Nobili, R. Novo, L. Podracka, G. Roussey-Kesler, LA Granier, P. Cochat (presenting author A Bertholet)	Submitted 12/04/2017 Accepted 08/06/2017 Pres. 9 Sep 2017 O-65 Published Sept 2017
	Abstract ESPN 2017 Glasgow 6-9 Sept (published in Paediatric Nephrology 32(9): 1643–1834)	Alkalising treatments used to treat distal renal tubular acidosis (dRTA) in clinical practice – observations during a clinical study *https://link.springer.com/article/10.1007/s00467-017-3753-x*	A. Bertholet-Thomas, C. Guittet, M.A. Manso, M. Cailliez, V. Baudoin, M. Di Maio, O. Gillion Boyer, E. Golubovic, J. Harambat, A. Klein, B. Knebelmann, F. Nobili, R. Novo, L. Podracka, G. Roussey-Kesler, LA Granier, P. Cochat (presenting author A Bertholet)	Submitted 12/04/2017 Accepted 08/06/2017 Poster 8 Sep 2017 P-409 Published Sept 2017
	Abstract ASNKW 2017 New Orleans 31 Oct-5 Nov (published in Journal of the American Society of Nephrology Oct 2017)	Treatment of dRTA with an innovative combination product as compared to current standards of care *https://www.asn-online.org/education/kidneyweek/archives/*	A. Bertholet-Thomas, C. Guittet, M.A. Manso, LA Granier (and investigators of B21CS study) (presenting author L Robin for A Bertholet)	Submitted 12/04/2017 Accepted 11/08/2017 Poster 2 Nov 2017 TH-PO1115 Published Oct 2017
	Abstract ERA-EDTA 2018 Copenhagen 24-27 May (published in Nephrology Dialysis Transplantation Volume 33, suppl.1)	Reduction of the number of daily intakes and improved blood bicarbonate level in distal renal tubular acidosis (dRTA) patients: interest of ADV7103, a new prolonged-release formulation *https://academic.oup.com/ndt/article/33/suppl_1/i50/4997109*	A. Bertholet-Thomas, C. Guittet, M.A. Manso, LA Granier (and investigators of B21CS study) (presenting author B Knebelmann for A Bertholet)	Submitted 12/01/2018 Accepted 22/03/2018 Poster 25 May 2018 FP001 Published May 2018
	Abstract ESPN 2018 Antalya 3-6 Oct (published in Paediatric Nephrology 33(10): 1807–2008)	Assessment of urine parameters after administration of ADV7103 in healthy adults and dRTA patients *https://rd.springer.com/article/10.1007/s00467-018-4028-x*	LA Granier, C. Guittet, M.A. Manso, A. Bertholet-Thomas (presenting author LA Granier)	Submitted 09/04/2018 Accepted 14/06/2018 Poster 5 October 2018 P-424 (page 1970) Published Oct 2018

	Abstract IPNA 2019 Venice 17-21 Oct (published in Pediatric Nephrology 34(10): 1821-2260)	Improved management of urine parameters in distal renal tubular acidosis with ADV7103 versus current treatments *https://rd.springer.com/article/10.1007/s00467-019-04325-4*	Bertholet-Thomas A, Guittet C, Manso M, Granier LA (presenting author, A Bertholet)	Submitted 24/05/2019 Accepted 23/07/2019 IPN10591-87 (A160) Poster 19 Oct 2019 Published Sept 2019
	Abstract IPNA 2019 Venice 17-21 Oct (published in Pediatric Nephrology 34(10): 1821-2260)	Improved management of blood parameters in distal renal tubular acidosis with ADV7103 versus current treatments https://rd.springer.com/article/10.1007/s00467-019-04325-4	Granier LA, Guittet C, Manso M, Bertholet A (presenting author, P. Cochat for LA Granier)	Submitted 24/05/2019 Accepted 23/07/2019 IPN10590-86 Oral pres.18 Oct 2019 Published Sept 2019
	Abstract UKKW 2020 Birmingham 5-8 June (cancelled)	Management of blood and urine parameters in distal renal tubular acidosis (dRTA) with a novel prolonged-release treatment	Böckenhauer D, Betholet-Thomas A, Manso M, Guittet C, Navas-Serrano V, Granier LA, Cochat P	Submitted 13/01/2020
T0	Published in Paediatric Nephrology 36 (1):83-91 (2021) Impact Factor: 2.676	Efficacy and safety of an innovative prolonged-release combination drug in patients with distal renal tubular acidosis: an open-label comparative trial versus standard of care treatments https://link.springer.com/article/10.1007/s00467-020-04693-2 https://rdcu.be/b6npw	A. Bertholet-Thomas, C. Guittet, M.A. Manso, A. Castang, investigators of B21CS, C. Stylianou, LA Granier	First draft 28/06/2019 Final draft 16/01/2020 First submission 28/01/2020. Resubmitted PNEP 12/03/2020. Revised version 16/06/2020, accepted 25/06/2020, published 26/07/2020
Extension study (adults and children) B22CS	Abstract SPNP 2019 Lisboa 11 Oct (book of abstracts)	Efficacy and safety of ADV7103, an innovative prolonged-release oral combination product, in distal renal tubular acidosis patients after 6 months of treatment	Bertholet-Thomas A, Guittet C, Manso-Silván M, Granier LA, Navas-Serrano VM, Cochat P (presenting author V Navas on behalf of A. Bertholet)	Submitted 12/09/2019 Pres. 11 Oct 2019 CO 4
	Abstract UKKW 2020 Birmingham 5-8 June (postponed 5-18 Oct, virtual meeting)	Long-term management of metabolic parameters in distal renal tubular acidosis (dRTA) with a novel prolonged-release treatment	Böckenhauer D, Betholet-Thomas A, Manso M, Guittet C, Navas-Serrano V, Granier LA, Cochat P (presenting author D. Böckenhauer)	Submitted 13/01/2020 Accepted (e-Poster) 28/07/2020. e-Poster and recorded presentation submitted 24/09/2020
	Abstract ERA-EDTA 2020 Milan 6-9 June (virtual) (published in	Adherence benefits of ADV7103, an innovative prolonged-release oral combination product, in patients with distal renal tubular acidosis	A. Bertholet-Thomas, C. Guittet, M.A. Manso, Navas-Serrano V, Granier LA, Cochat P	Submitted 16/01/2020 Accepted 21/04/2020

	Nephrology Dialysis Transplantation Volume 35, suppl.3)	https://doi.org/10.1093/ndt/gfaa142.P0003	(presenting author V Navas on behalf of A. Bertholet)	e-poster submitted 02/06/2020 Published June 2020 (Poster 003, page iii300)
	Abstract ESPN 2020 Lubjana 16-19 Sep (postponed to 2022, in 2020 virtual meeting with only some key lectures)	Long-term efficacy of ADV7103 in patients with distal renal tubular acidosis	A. Bertholet-Thomas, C. Guittet, M.A. Manso, Navas-Serrano V, Granier LA	Submitted 27/03/2020
	Abstract ESPN 2020 Lubjana 16-19 Sep (postponed to 2022, in 2020 virtual meeting with only some key lectures)	Long-term safety, tolerability and acceptability of ADV7103 in patients with distal renal tubular acidosis	A. Bertholet-Thomas, C. Guittet, M.A. Manso, Navas-Serrano V, Granier LA	Submitted 27/03/2020
	Abstract SPNP 2020 Virtual meeting 20 Nov	Long-term efficacy of ADV7103 in patients with distal renal tubular acidosis	A. Bertholet-Thomas, C. Guittet, M.A. Manso, Navas-Serrano V, Granier LA (presenting author V. Navas-Serrano)	Submitted 03/10/2020 Oral presentation
	Abstract ISPOR 2021 Montreal 15-19 May Virtual meeting (published in Value in Health Volume 24, S1, June 2021)	ADV7103 treatment adherence in patients with distal renal tubular acidosis (dRTA)	P. Goodyer, M.A. Manso, C. Guittet, A. Bertholet-Thomas (presenting author M. Manso on behalf of P. Goodyer)	Submitted 30/11/2020 Accepted 10/03/2021 iPoster 19 May 2021 Published June 2021 PRO9 (page S199)
	Abstract ESPN 2021 Amsterdam 16-19 Sep (published in Paediatric Nephrology 36(10): 3285-3491)	Assessment of quality of life through a patient-centred approach in children and adults with dRTA treated with a new prolonged-release alkalising drug (ADV7103) for 5 years https://link.springer.com/article/10.1007/s00467-021-05210-9	A. Bertholet-Thomas, M. Acquadro, C. Guittet, S. Joukoff, M.A. Manso, V. Navas-Serrano, A. Marrel (presenting author A. Bertholet-Thomas)	Draft 15/03/2021 Submitted15/04/2021 Accepted oral pitch presentation PI-7 and e-poster 17/09/2021. Published Oct 2021
	Abstract UKKW 2021 4-7 Oct (virtual)	Improved growth of a child with distal renal tubular acidosis after switching from a conventional alkalising treatment to a new prolonged-release formulation containing potassium citrate and potassium bicarbonate: a case report	O. Boyer, M.A. Manso-Silván, S. Joukoff, V. Navas-Serrano, C. Guittet, (presenting author O. Boyer)	Submitted 17/05/2021 Accepted as e-Poster Poster and recorded presentation submitted

				13/09/2021. Moderated poster session 07/10/2021
	Abstract SEN 2021 Granada 15-18 Oct (virtual)	Plasma bicarbonate as a corelate marker of BMD in adult patients with distal renal tubular acidosis (dRTA)	V. Navas-Serrano, A. Bertholet-Thomas, M.A. Manso-Silván, S. Joukoff, C. Guittet (presenting author V. Navas-Serrano)	Submitted 28/04/2021 Accepted as oral presentation O081 - 18/10/2021
	Published in Paediatric Nephrology 36 (7): 1765-1774 (2021) Impact Factor: 2.676	Safety, efficacy and acceptability of ADV7103 during 24 months of treatment: an open-label study in paediatric and adult patients with distal renal tubular acidosis https://link.springer.com/article/10.1007/s00467-020-04873-0 https://rdcu.be/cf35p	A. Bertholet-Thomas, C. Guittet, M.A. Manso-Silván, S. Joukoff, V. Navas-Serrano, investigators of B22CS study, LA Granier	Draft 5 March 2020 Submitted PNEP 06/07/2020. Minor and major modifications 21/07/2020. Revised 15/09/2020.Minor revision 28/09/2020 accepted 23/11/2020 published 26/02/2021
	Target journals: CJASN Impact Factor: 6.628 JASN Impact Factor: 9.274 Paediatric Nephrology Impact Factor: 2.676 Nefrología Impact Factor: 2.066	BMD and growth changes in patients with distal renal tubular acidosis after two years treatment with a new alkalising drug (ADV7103)	A. Bertholet-Thomas, M.A. Manso-Silván, V. Navas-Serrano, C. Guittet, S. Joukoff, J. Bacchetta, O. Boyer, M. Rodriguez-Portillo, LA Granier	Submitted 07/04/2021 CJASN. Refused 11/04/2021 Resubmitted JASN 13/04/21. Refused 26/04/2021. Resubmitted PEDN 18/06/21. Refused 15/07/2021 Resub. Nefrología 09/09/2021 (under review)

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Table 32: Summary of statistical analysis used in studies

Trial name	**B03CS**
Hypothesis objective	The primary endpoint was the mean urine pH over 24-hour after 5 days of treatment. The primary comparison was between each ADV7103 dose group and placebo. Additional co-primary endpoints included the pH in the first morning urine samples, the proportion of urine pH values above seven during 24-h periods, the 24-h mean pH fluctuation (maximum – minimum values) and the mean change from baseline in morning urine pH. Treatments were similarly compared for these endpoints.
Statistical analysis	Significance of the difference was assessed at the 2-sided, 5% significance level without adjustment for multiplicity. Additional co-primary endpoints included the pH in the first morning urine samples, the proportion of urine pH values above seven during 24-h periods, the 24-h mean pH fluctuation (maximum – minimum values) and the mean change from baseline in morning urine pH. Treatments were similarly compared for these endpoints.
Sample size, power calculation	This sample size of sixteen subjects (N=4/arm) provided approximately 83% power to detect at the end of SP I, a mean urine pH difference of one between any ADV7103 dose group and placebo at the two-sided 5% significance level. Powering assumed a residual SD equal to 0.4 and no correction for multiple comparisons.
Data management, patient withdrawals	Unless otherwise specified, baseline referred to the appropriate last observations prior to the first dosing occasion in a SP and endpoint was after 5 days of treatment. Missing data were not imputed in the calculation of derived parameters or in the summaries.
Trial name	**B21CS**
Hypothesis objective	A non-inferiority intra-individual comparison of ADV7103 vs. SoC was performed, considering the non-inferiority margin equal to – 2.5 mmol/L (for justification of the non-inferiority margin) Non-inferiority of ADV7103 vs. SoC was declared when the lower, one-sided 97.5% confidence limit on the mean difference lay entirely on the positive side of the non-inferiority margin equal to – 2.5 mmol/L.
Statistical analysis	Blood samples were planned at the following timepoints: At the end of the SoC steady state period SP I on day 2 t0, day 3 t0 and day 4 t0 (before first daily dose) and at the end of the ADV7103 steady state period SP III on day 2 t0, day 3 t0 and day 4 t0 (before first daily dose). Any bicarbonate concentration value below the lower limit of quantification (LOQ) was set to the LOQ value for the calculation of the primary endpoint. 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 in the PP set with a one-sided one-sample t-test. The study was designed as a non-inferiority study, the switch to superiority was made after non-inferiority was declared, in accordance with the EMA's Points to Consider on Switching Between Superiority and Non-inferiority (CPMP/EWP/482/99). The changing of the objective from non-

	inferiority to superiority was considered feasible as the required criteria were met. Since the non-inferiority analysis was performed on the PP set as per standard practice, it was considered important to repeat the superiority analysis on this population as well, using paired data only, as a sensitivity analysis. A non-inferiority intra-individual comparison of ADV7103 vs. SoC was performed, considering the non-inferiority margin equal to – 2.5 mmol/L (for justification of the non-inferiority margin). Non-inferiority of ADV7103 vs. SoC was declared when the lower, one-sided 97.5% confidence limit on the mean difference lay entirely on the positive side of the non-inferiority margin equal to – 2.5 mmol/L. $H0$: $(ADV7103-SoC) \leq -2.5$ mmol/L $H1$:$(ADV7103-SoC) > -2.5$ mmol/L The mean difference and its two-sided 95% confidence interval (CI) were reported. After non-inferiority was declared, in line with line with the EMA's Points to Consider on Switching Between Superiority and Non-inferiority (CPMP/EWP/482/99), the changing of the objective from non-inferiority to superiority was considered feasible as the required criteria were met. This meant that the mixed-effects analysis of variance model (ANOVA), in the ITT set, planned originally as sensitivity analysis, which included the treatment as fixed effect and the patient as a random effect was used to assess superiority. LS means, standard errors (SEs) and two-sided 95% CIs were reported for the treatment difference (ADV7103 – SoC).
Sample size, power calculation	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 derived by applying statistical reasoning following the EMA guidance.
Data management, patient withdrawals	The number of missing values for the primary endpoint was monitored, as well as the difference in the number of patients between the ITT and the PP sets. As this was a non-inferiority trial, the primary analysis was carried out on the PP set. A sensitivity analysis (a mixed-effect ANOVA) was provided on the ITT. This type of analysis handles missing values if data can be considered as missing at random. In case of a very large number of missing data or in case of the departure of the randomness of the missing data, a conservative imputation method, replacing any missing individual difference between ADV7103 and SoC by the non-inferiority margin (-2.5 mmol/L) was to be considered as an additional sensitivity analysis. If one or several of the three bicarbonate blood levels at Day2 t0, day 3 t0 and day 4 t0 were missing, the following replacement procedure was used: This set included any additional bicarbonate blood levels on day 1 t0, day 5 t0, or day 5 t24h, in the same SP, that was not missing if it was quantified strictly in the same conditions as for the primary timepoints. This means, using the same analysis laboratory, the same analysis method, the same equipment, and the same normal ranges as for day 2 t0, day 3 t0 and day 4 t0. Replace any missing value(s) from the primary set in their order of appearance (i.e., first day 2 t0, then day 3 t0 and finally day 4 t0) by the first available values in the replacement set. The order of priority for the replacement set is (day 1 t0, day 5 t0, day 5 t24h). After the replacement procedure, any remaining missing samples were skipped when calculating the mean. If all the three samples were still

	missing, the average was reported as missing.
Trial name	**B22CS**
Hypothesis objective	According to the study design, descriptive statistics were performed, no statistical comparison were planned.
Statistical analysis	Safety, efficacy, compliance and QoL data and their change from baseline (when appropriate) were summarised by age group, overall and over time using descriptive statistics.
Sample size, power calculation	The assumption was that almost all the patients who completed B21CS would be included in Study B22CS. Of the 32 patients enrolled in Study B21CS, as many patients as possible were expected to be included in Study B22CS.
Data management, patient withdrawals	All data from the case report form (CRF) and all derived variables (e.g., abnormality: low high, normality, velocity, etc.) were listed by age group, patient and visit. Listings were presented by theme (e.g., Baseline, ECG, etc.) and displayed the indication of “missing data” or “not done” for each missing value. Abnormalities clinically significant (CS)/not clinically significant (NCS) were flagged when normal ranges were available. Missing data were not imputed in the calculation of derived parameters or in the summaries. Age at inclusion was calculated based on age value (in months) at B22CS baseline: Calculated age (in months) at inclusion = (visit date of month 1 – birth date)/30.4375.

Abbreviations: ANOVA = analysis of variance; ECG = electrocardiogram; LOQ = lower limit of quantification; SE = standard error; SoC = standard of care; SP = study period.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

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. Though the sample size is relatively small this is common to most trials for rare disease therapies.

The clinical pathway for dRTA could be viewed as uncertain due to the lack of a licensed comparator and therefore little comparative data. This may also pose uncertainty in the cost-effectiveness modelling with relation to comparator costing, since there are over 30 treatments used. Research from the Lopez-García (2019) study, and to further reduce uncertainty, Delphi panels were carried out with clinicians to confirm these findings.

Scientific advice suggested a placebo-controlled trial, however the CHMP recommended that the study was to be based on a switch from SoC. This was due to concerns surrounding the ethics and safety of withdrawing alkalinising therapy from patients.

Though non-responder analysis may be viewed as weak from a statistical efficiency point of view, it is imperative to include responder analyses for a clinically meaningful result.

The trial contains limited quality of life evidence; however, this is included in Study B22CS, which contains long-term outcomes. Bicarbonataemia is recognised as the marker of dRTA and is considered as predictive of long-term consequences of the disease.

Though non-responder analysis may be viewed as weak from a statistical efficiency point of view, it is imperative to include responder analyses for a clinically meaningful result.

The trial contains limited quality of life evidence; however, this is included in Study B22CS, which contains longer-term outcomes. Bicarbonataemia is recognised as the main marker of dRTA and is considered as predictive of long-term consequences of the disease.

Further statistical analysis to account for missing data in study B21CS

For plasma bicarbonate as primary endpoint

For the primary endpoint, the study protocol required to evaluate the plasma bicarbonate of blood samples drawn at t0, i.e., in pre-morning dose, on day 2, day 3 and day 4. Data were missing when these samples were not done (blood test not possible for the youngest for example) and/or when the time of sampling was after the morning dose or unknown.

A mixed-effects analysis of variance model, in the ITT set, which included the treatment as fixed effect and the patient as a random effect was used to assess superiority. From this model, evidence of superiority was shown (p=0.0008) in the ITT set. As the lower bound of the 95% CI is 0.67 mmol/L, the results suggested also a potentially clinically relevant difference between ADV7103 and SoC.

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 33: 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)	

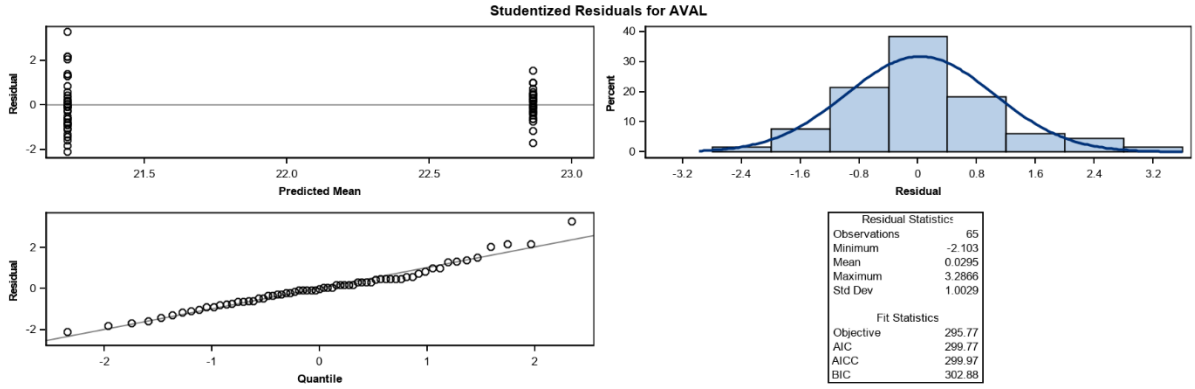
Non-inferiority p-value	<0.0001	
Superiority p-value	0.0037	0.0008

Source: B21CS CSR. Abbreviations: CI=confidence interval, ITT=intent-to-treat, LS=least square, n=number of patients with recorded values, PP=per protocol, SD=standard deviation

The sensitivity analysis was specified a priori in the statistical analysis plan. It was performed using a mixed model with treatment as a fixed effect and subject as a random effect.

Goodness-of-fit was assessed visually by inspection of the residual's plots from the statistician and no evidence of non-normality of the residuals was observed.

Figure 17: Diagnostic plots: non-inferiority analysis on blood bicarbonate levels - Sensitivity analysis - Intent-to-treat analysis set - The mixed procedure



In addition to the mixed-effects analysis of variance model (ANOVA) with data missing at random (MAR), other sensitivity analyses were conducted to assess the robustness of the superiority analysis. The ANOVA of the primary endpoint has been repeated on the ITT set with two different imputation methods for missing data. In addition, a Tipping Point analysis has been performed as described below:

- **Last observation carried forward (LOCF) imputation:** When this method was applied all missing data from the ADV7103 period were imputed by their respective data from their SoC period, if available. A total of three values were imputed. There was one missing record in the SoC period with data in the ADV7103 period and no imputation was performed, as MAR was a valid assumption for this single case.
- **Worst Observed Case (WOC) imputation:** This method assumed that the worst observed case was used for imputation, this meant that any missing data in the ADV7103 period were imputed from the SoC period (like LOCF), but also that missing SoC period data were imputed from the ADV7103 period. A total of four values were imputed. This method was expected to produce slightly more conservative results than LOCF.
- **Tipping point analyses:** The aim of the analyses was to assess how worse the missing data from the ADV7103 had to be from the values we would have in case the MAR assumption held. This analysis drew several imputed samples for the missing ADV7103 using the stochastic distribution assuming data were MAR (under the same model as the original analysis) and then penalised them by shifting them by said shift (in the direction of no-benefit). Then the same mixed model was run using each imputed sample and then the estimated difference was obtained (at each shift separately) using the combined results as in a Multiple Imputation framework.

The results of these additional analyses are described below and summarised in Table 34.

Table 34: Additional statistical analyses from B21CS

Analysis methods	Plasma bicarbonate (mmol/L)		Difference of ADV7103 versus SoC		
	SoC	ADV7103			
	Mean (SE)		Estimate	95% CI	p-value
Initial ANOVA using MAR	N = 34	N = 31	1.64	[0.668, 2.603]	0.0008
	21.23 (0.43)	22.86 (0.45)			
ANOVA using LOCF	N = 34	N = 35	1.28	[0.419, 2.144]	0.0024
	21.23 (0.46)	22.52 (0.45)			
ANOVA using WOC	N = 35	N = 35	1.24	[0.397, 2.088]	0.0026
	21.27 (0.45)	22.52 (0.45)			
Tipping point analyses	Delta (mmol/L)		0.97	[-0.003; 1.941]	0.0253
	5.8				

Source: B21CS CSR. Abbreviations: ANOVA=mixed-effects analysis of variance model; CI=confidence interval; LOCF=last observation carried forward imputation; MAR=missing at random; N=number of subjects; SE=standard error of the mean; SoC = standard of care; WOC=worst observed case imputation

a. Results from LOCF imputation

When LOCF was applied, the superiority of ADV7103 over LOCF was maintained as statistically significant with a minor increase to the p-value to 0.0024 from 0.0008 observed in the original analysis. This increase in the p-value was accompanied by a reduction of the estimated difference of the two products from 1.64 mmol/L in the original analysis to 1.28 mmol/L in the LOCF analysis, with the 95% CI changing from [0.668, 2.603] to [0.419, 2.144].

b. Results from WOC imputation

When WOC was applied the superiority of ADV7103 over LOCF was maintained as statistically significant with a very minor increase to the p-value to 0.0026 from 0.0024 observed in LOCF. This increase in the p-value was accompanied by a further minor reduction of the estimated difference of the two products from 1.28 mmol/L in the LOCF analysis to 1.24 mmol/L in the WOC analysis, with the 95% CI changing from [0.419, 2.144] to [0.397, 2.088].

c. Results from tipping point analyses

The tipping point analyses suggested a tipping point where treatment superiority is lost (i.e. p-value became higher than 0.025) of 5.8 mmol/L. This means that to lose the superiority claim, it would have needed the results of the four subjects with missing values during ADV7103 to be 5.8 mmol/L worse than what the original model under the MAR assumption projected them to be.

To quantify the magnitude of the tipping point, it must be noted that the original treatment effect under the MAR assumption was 1.64, thus 5.8 mmol/L is 3.5 times higher than the original observed treatment effect.

The magnitude of the decrease needed to reach the tipping point, and lose the superiority claim, is therefore considered as unlikely. Especially considering the only patient who decreased over 2.7 mmol/L (had a decrease of 5.3 mmol/L) had an abnormally high SoC at 29.4 mmol/L and remained within normal range with ADV7103. It is noted that all other patients in both arms never exceeded 26.7 mmol/L, furthermore the four patients with missing data had a plasma bicarbonate level with SoC of 16.0, 17.3, 19.3 and 22.0 mmol/L, with all but one patient in that range of SoC having experienced a benefit from ADV7103, and the one patient experiencing only a slight decrease of one mmol/L.

B.2.6 Clinical effectiveness results of the relevant trials

B03CS

Pharmacodynamic endpoints

Urine pH in the first morning and pre-dose urines on day 4

To assess the pharmacodynamics effect on urine pH of oral doses of ADV7103 versus placebo after 5 days of treatment, the mean urine pH values over 24-hour pooled across the 2 days were evaluated as well as three other co-primary endpoints, as detailed hereafter [48].

Urine pH increased as expected from the mechanism of action of ADV7103. This increase is directly linked to the dose administered [48].

All doses administered demonstrated a statistically significant increase of pH as compared to placebo ($p<0.05$ and in multiple occasions even $p<0.0001$, Table 35) [48].

The lowest dose (17/36 mg/kg CK/BK) was statistically significantly different from the highest dose (50/100 mg/kg CK/BK) administered ($p<0.0098$, Table 24). The medium dose (33/66 mg/kg CK/BK) tended to be significantly different from the highest dose (50/100 mg/kg CK/BK) administered (p 0.0527, Table 35)) [48].

No saturating effect occurred within the dose-range tested.

Table 35: pH in the first morning and pre-dose urines on Day 4 [48]

Endpoint: pH in the first morning and pre-dose 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;	<.0001

Endpoint: pH in the first morning and pre-dose urines on Day 4						
			Comparison to placebo			
Treatment	**Lsmeans**	**(95% CI)**	**Comparator**	**Difference**	**(95% CI)**	**p-value**
					2.072)	
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)				

Source: B03CS CSR. Abbreviations: CI = confidence interval; LSmeans = least squared means.

Citraturia

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, Table 36) [48].

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 36) [48].

Table 36: B03CS levels of citraturia compared to placebo

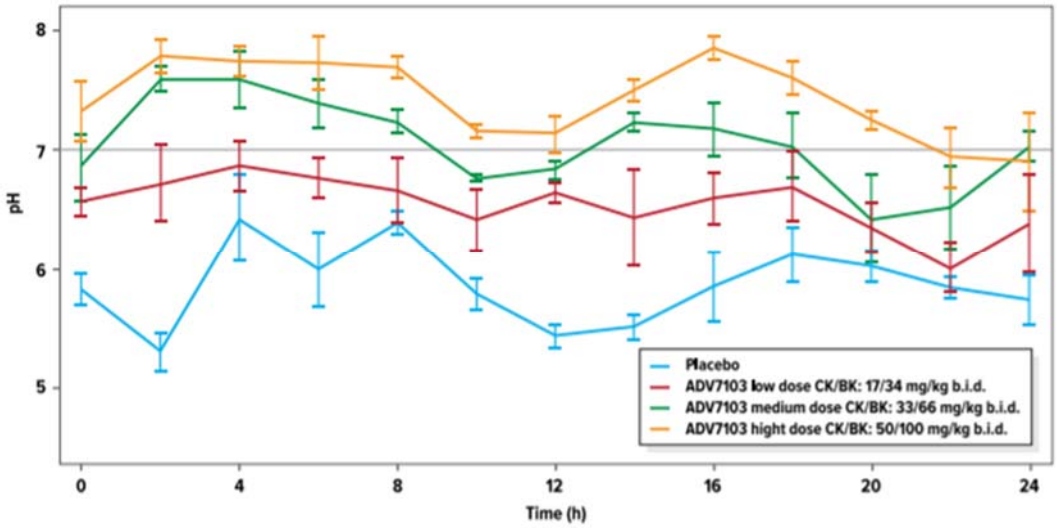
Comparison to placebo						
Treatment	**Lsmeans**	**(95% CI)**	**Comparator**	**Difference**	**(95% CI)**	**p-value**
ADV7103 41.5/83.0 T:[+2h]	1.704	(0.413; 2.994)	Placebo	2.001	(0.730; 3.271)	0.0037
ADV7103 33/66 and 50/100	1.332	(0.228; 2.436)	ADV7103 33/66	-1.211	(-3.247; 0.825)	0.2234
			Placebo	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)				

Source: B03CS CSR. Abbreviations: CI = confidence interval; h = hours; LSmeans = least squared means.

Return to baseline pH

As shown in Figure 18 the return to urine pH baseline values is reached within 24 hours after the last administration of ADV7103 regardless of the dose [48].

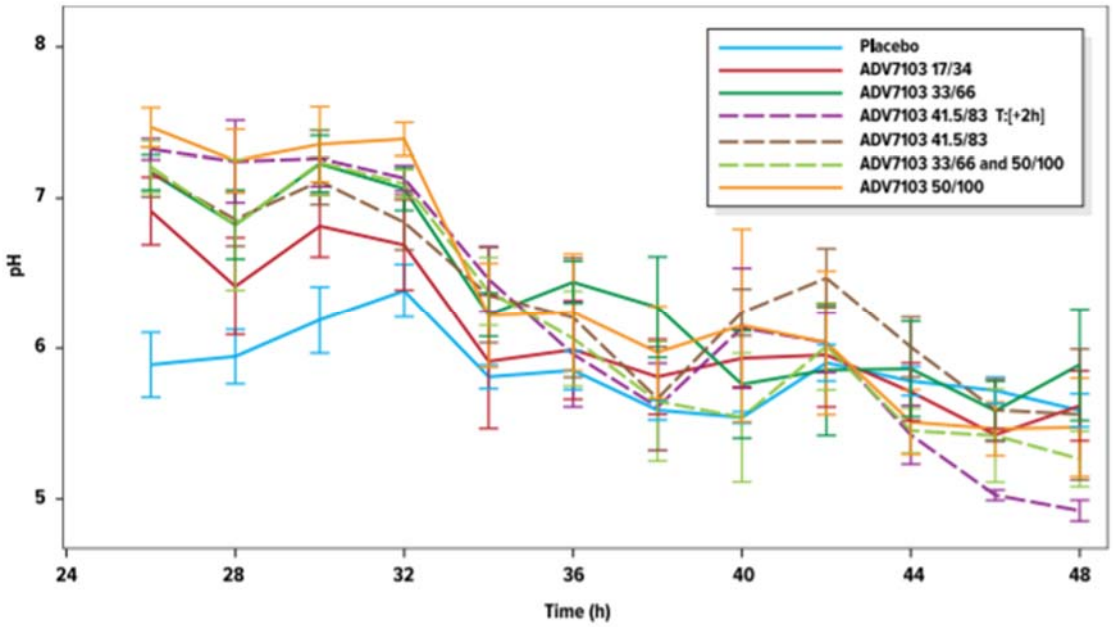
Figure 18: Mean (±SE) urine pH values measured at 2 h-intervals during 24 h on Day 4 of Period I (treatment



Source: Guittet et al. 2020. Abbreviations: b.i.d = bidaily.

Figure 19 shows the return baseline pH on day 6 of the trial.

Figure 19: B03CS Return to baseline pH on day 6



Source: Guittet et al. 2020. Abbreviations: h = hours.

Figure 19 is taken from Guittet et al 2020 (summarising the B03CS results) - it shows the return to baseline pH on day 6. The reason that the x axis starts at 24 hours, but values do not begin until 26 hours is that 24hrs represents end of day 5, with 26 hours (2 hours later) being the first point measurements were taken on day 6. Follow-up day [day 6] - 12 urine samples for urine pH measurements (PD assessment) by 2-hour period until 24h later (i.e.]24-26],]26-28],]28-30],]30-32],

]32-34],]34-36],]36-38],]38-40],]40-42],]42-44],]44-46],]46-48] hours). The seven lines of data represent the different dosing across SP I and SP II.

B21CS

Data from the pivotal B21CS study have demonstrated that ADV7103 was an appropriate and efficient alkalising treatment, providing additional clinical benefit over SoCs in patients with dRTA [47]:

- There is consistency in primary endpoint and other supportive secondary endpoint results to support the use of ADV7103 as an effective dRTA treatment option, which has shown its significant superiority to SoCs by acting on:
- Metabolic acidosis
    - Bicarbonataemia was normalised in all age subsets receiving ADV7103 which superiority versus SoC was convincingly demonstrated, as recommended in the EMA's Point to Consider on Switching Between Superiority and Non-inferiority
    - With the bicarbonataemia non-responder analysis, the superiority of ADV7103 relative to SoC was demonstrated as per the EMA guideline on Multiplicity Issues in Clinical Trials (EMA/CHMP/44762/2017) showing a clinically meaningful benefit for patients receiving ADV7103.
- Kalaemia was normalised in all age subsets
- Risk of lithogenesis: This is defined as the urine calcium to citrate ration (uCa/uCi), which are urine parameters used in the clinical practice to evaluate the risk for nephrocalcinosis and for calcium nephrolithiasis. This was significantly improved in terms of mean (SD) values and non-responders [47]

Primary efficacy endpoint: Bicarbonataemia

Non-inferiority 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.

After non-inferiority was declared, in line with line with the EMA's Points to Consider on Switching Between Superiority and Non-inferiority (CPMP/EWP/482/99), the changing of the objective from non-inferiority to superiority was considered feasible as the required criteria were met. This meant that the mixed-effects analysis of variance model in the ITT set (which included the treatment as fixed effect and the patient as a random effect), planned originally as sensitivity analysis, was used to assess superiority.

In the PP set, the overall mean (SD) blood bicarbonate levels were 23.1 (1.62) mmol/L with ADV7103 (N=30) and 21.7 (3.06) mmol/L with SoC (N=29), as shown in Table 37. Similar results were obtained for the ITT set. The overall mean (SD) blood bicarbonate levels were 23.0 (1.62) mmol/L with ADV7103 (N=31) and 21.2 (3.11) mmol/L with SoC (N=34) [47].

Non-inferiority of ADV7103 relative to SoC was demonstrated in the PP set using the 29 patients with available assessments at both SP I and SP III. 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 (SD) difference between treatments was 1.4195 (2.647) mmol/L (95% CI: 0.4128, 2.4263), with a non-inferiority p-value <0.0001 [47].

Table 37: B21CS Blood bicarbonate levels compared with SoC

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

Source: B21CS CSR. Abbreviations: ITT=intent-to-treat, Max=maximum, Min=minimum, N=total number of patients, n=number of patients with recorded values, PP=per protocol, SD=standard deviation, SoC=standard of care, SP=study period

Table 38: B21CS Bicarbonataemia non-inferiority of ADV7103 relative to SoC

	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	

Source: B21CS CSR. Abbreviations: CI = confidence interval, ITT=intent-to-treat, PP=per protocol, SD = standard deviation, SoC=standard of care

Number/proportion of patients with abnormal bicarbonataemia value (i.e., patients with at least one value of bicarbonataemia below lower normal range, on Day 2 t0, Day 3 t0 or Day 4 t0).

The number/proportion of non-responder patients with at least one value of blood bicarbonate below the lower normal value on day 2 t0, day 3 t0 or day 4 t0 in SP I (SoC) and SP III (ADV7103), and the

statistical comparison between the two treatments are summarised in Table 39 [47].

In the PP set, 12 (41%) patients were non-responders with SoC but responders with ADV7103, while only 1 (3.4%) patient was a non-responder with ADV7103 but a responder with SoC. Similarly, in the ITT set, 13 (43%) patients were non-responders with SoC but responders with ADV7103, while only 1 (3.3%) patient was a non-responder with ADV7013 but a responder with SoC. In both analysis sets, the McNemar's test determined that there was a statistically significant difference between the probabilities of patients presenting at least one blood bicarbonate value below the normal ranges on day 2 t0, day 3 t0 and day 4 t0 during the two treatments (p=0.003 for the PP set and p=0.002 for the ITT set), which indicated a greater probability of a responder occurring with ADV7103 [47]. 82.4% (14/17) of the non-responders became responders when switching from SoC to ADV7103.

Table 39: Number/proportion of patients with abnormal bicarbonataemia value

PP Set			**ITT Set**		
SoC	**ADV7103**	**n/N (%)**	**SoC**	**ADV7103**	**n/N (%)**
No	No	10/29 (34%)	No	No	10/30 (33%)
Yes	No	12/29 (41%)	Yes	No	13/30 (43%)
No	Yes	1/29 (3.4%)	No	Yes	1/30 (3.3%)
Yes	Yes	6/29 (21%)	Yes	Yes	6/30 (20%)
p-value[a]		0.003	p-value[a]		0.002

Abbreviations: ITT=intent-to-treat, PP=per protocol, SoC=standard of care
Note: Post-dose samples are excluded from the analysis. n=number of patients per combination of treatment responses (No/No, No/Yes, Yes/No or Yes/Yes)
[a]exact p-value obtained from a McNemar's test

Continuous endpoints

Mean differences between ADV7103 and SoC for AUC0-12h, AUC_{0-24h}, Cmin, and fluctuation

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. ADV7103 (taken in two daily administrations) provided an alkalising coverage equivalent to SoC coverage, taking into account that SoC is taken 3 to 6 times per day by 86.5% of the patients and even during the night for 27% of the patients whereas ADV7103 is only two intakes per day) [47].

Table 40: Mean differences between ADV7103 and SoC for AUC0-12h, AUC0-24h, Cmin, and fluctuation

	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
Cmin (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

Source: B21CS CSR. Abbreviations: AUC = area under curve, ITT = intention-to-treat, PP = per protocol, SD = standard deviation, SOC = standard of care, SP = study period.

Number of patients with hypokalaemia after 4 to 5 days of treatment at steady state

Overall, the normalisation of blood potassium was achieved with both ADV7103 and SoC. However, in the PP and ITT sets, the mean (SD) blood potassium levels were higher with ADV7103 than with SoC at each time point. Similar results were obtained for each age subset, except for adults at day 2 t0 with SoC, when the mean (SD) blood potassium level was below the median low normal value of 3.5 mmol/L in the PP and ITT sets (i.e. 3.31 [0.540] mmol/L for both analysis sets) [47].

In average, considering that median normal values of blood potassium range from 3.5 to 5.1 mmol/L, the normalisation of blood potassium was achieved with both ADV7103 and SoC [47].

Table 41: B21CS Number of patients with hypokalaemia after 4 to 5 days of treatment at steady state

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		1.000	1.000

Source: B21CS CSR. Abbreviations: ITT=intent-to-treat, PP=per protocol, SoC=standard of care, SP=study period – No=responder, Yes=non-responder
*: exact p-value obtained from a McNemar's test
n=number of patients per combination of treatment responses (No/No, No/Yes, Yes/No or Yes/Yes); N=total number of patients for whom data are available, %=proportion with N as the denominator for calculation of proportions.
Note 1: Haemolysed and post-dose samples were excluded from the analysis
Note 2: During study, three patients received chronic potassium supplements: two during SPI and one during SPI, SPII, SPIII. Note 3: No data on day 5 t0]

Number of patients with a hypercalciuria after 4 to 5 days of treatment at steady state

Patients with hypercalciuria were those for whom at least one value of UCa/UCr was superior to the age-specific upper normal limit on day 4 t0 or day 5 t0 during treatment with SoC and ADV7103 [47].

For both the PP and ITT sets, 1 (3.6% PP set; 3.3% ITT set) patient had hypercalciuria when SoC but did not experience hypercalciuria when on ADV7103, and 1 (3.6% PP set; 3.3% ITT set) patient had hypercalciuria when on ADV7103 but did not experience hypercalciuria when on SoC. According to the McNemar's test, there were no statistically significant differences between treatment groups (p=1.000 for both analysis sets). Overall, only three patients presented hypercalciuria, one after SoC, one 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 [47].

Table 42: Number of patients with hypercalciuria after 4 to 5 days of treatment at steady state

PP set			**ITT set**		
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

Source: B21CS CSR. Abbreviations: ITT=intent-to-treat, PP=per protocol, SoC=standard of care, SP=study period – No=responder, Yes=non-responder
*: exact p-value obtained from a McNemar's test
n=number of patients per combination of treatment responses (No/No, No/Yes, Yes/No or Yes/Yes); N=total number of patients for whom data are available, %=proportion with N as the denominator for calculation of proportions.

Number of patients with a hypocitraturia after 4 to 5 days of treatment at steady state

Patients with hypocitraturia were those for whom at least one value of UCi/UCr was inferior to the age-specific lower normal limit on day 4 t0 or day 5 t0 during treatment with SoC and ADV7103 [47].

In the PP set, 6 (38%) patients had hypocitraturia when on SoC but did not experience hypocitraturia when on ADV7103, whereas only 1 (6.3%) patient had hypocitraturia when on ADV7103 but did not have any hypocitraturia event when on SoC. Similarly, in the ITT set, 7 (41%) patients had hypocitraturia when on SoC but did not experience hypocitraturia event when on ADV7103, whereas only 1 (5.9%) patient had hypocitraturia when on ADV7103 but did not have any hypocitraturia event with SoC. The McNemar's test revealed no statistically significant differences between the two treatments in favour of SoC (p=0.125 for the PP set and p=0.070 for the ITT set), but this was believed to be mainly attributed to the low number of patients included in this analysis, rather than the lack of heterogeneity between the two groups [47].

Overall, all patients had hypocitraturia either after SoC, or ADV7103 or both treatments. However, most patients presented hypocitraturia after SoC: 15 (94%) patients in the PP set and 16 (94%) patients in the ITT set vs. 10 (62.3%) patients in the PP set and 10 (58.9%) in the ITT set after ADV7103. The proportion of non-responder patients lacking normalisation of citraturia after SoC treatment relative to ADV7103 treatment (41% versus 5.9% in ITT set), suggests an important trend of the benefit of ADV7103 treatment compared to SoC treatment [47].

Table 32: Number of patients with a hypocitraturia after 4 to 5 days of treatment at steady state [47]

PP Set			**ITT Set**		
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

Source: B21CS CSR. Abbreviations: ITT=intent-to-treat, PP=per protocol, SoC=standard of care, SP=study period – No=responder, Yes=non-responder
*: exact p-value obtained from a McNemar's test
n=number of patients per combination of treatment responses (No/No, No/Yes, Yes/No or Yes/Yes); N=total number of patients for whom data are available, %=proportion with N as the denominator for calculation of proportions.

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).

In both the PP and ITT sets, 9 (47% PP set; 45% ITT set) patients had abnormally high UCa/UCi values when on SoC but did not experience abnormally high UCa/UCi values when on ADV7103, whereas only 1 (5.3% PP set; 5.0% ITT set) patient had abnormally high UCa/UCi values when

ADV7103 but did not experience abnormally high UCa/UCi values when on SoC. The McNemar's test reached statistical significance for the ITT and PP sets (p=0.021 for both analysis sets), suggesting heterogeneity in the non-responder rates and indicating better responder rates in ADV7103 over SoC.

Table 43: 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

Source: B21CS CSR. Abbreviations: ITT=intent-to-treat, PP=per protocol, SoC=standard of care, SP=study period – No=responder, Yes=non-responder
*: exact p-value obtained from a McNemar's test
n=number of patients per combination of treatment responses (No/No, No/Yes, Yes/No or Yes/Yes); N=total number of patients for whom data are available, %=proportion with N as the denominator for calculation of proportions.

It is relevant to measure calciuria and citraturia to assess the value of ADV7103 in dRTA patients since hypercalciuria and hypocitraturia are considered the most common identifiable metabolic risk factor for nephrocalcinosis, nephrolithiasis and CKD [47].

Compliance

In Europe, there are no registered medications specifically indicated for the treatment of patients with dRTA yet. Therefore, medicinal alkalising hospital/pharmacy compounded preparations are generally used. These preparations induce immediate and full release of alkalising salt(s); however, their therapeutic effect is of limited duration necessitating multiple administrations during the day and night, and ultimately generating gastrointestinal discomfort and AEs [7]. These preparations are inappropriate for children due to difficulties in setting the correct dosage, their undesirable bitter taste, or the size of the tablets available through compassionate use in some countries. Overall, these drawbacks result in poor compliance of dRTA patients to their treatment regimens [47].

Untreated dRTA carries a poor outcome, often progressing to end-stage kidney failure from nephrocalcinosis [7]. Compliance is key to controlling metabolic acidosis and avoiding dRTA complications, CKD is said to usually occur in patients with a long disease history and to be explained by the combination of nephrocalcinosis and persistent hypokalaemia, leading to progressive tubulointerstitial damage, or by kidney damage following repeated episodes of dehydration and acute kidney injury. Based on the information provided by the investigators and according to the CSR requirements to assess treatment compliance of patients involved in Study B21CS, treatment compliance was quite good. Indeed 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 [47].

Acceptability

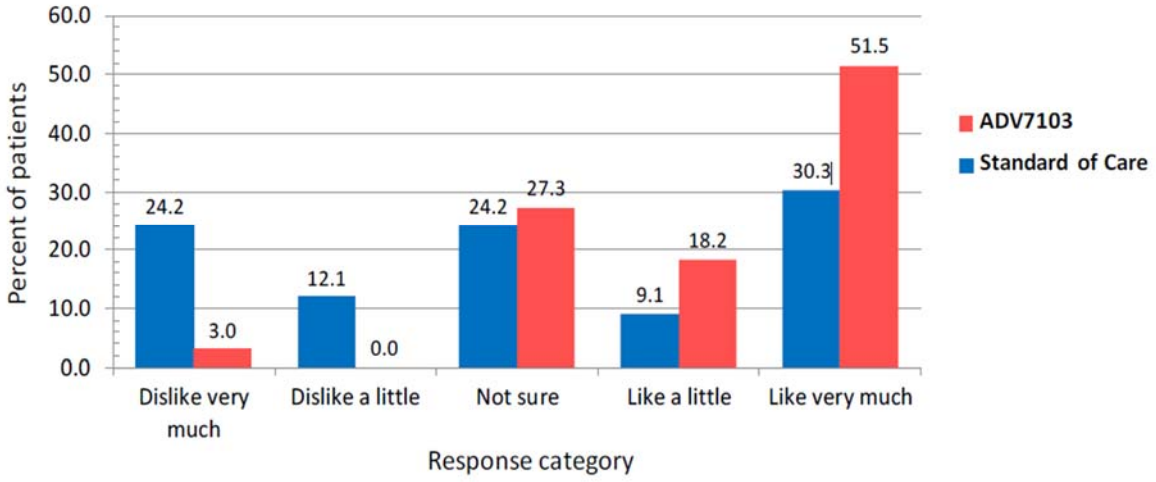
Palatability, ease of administration and ease of swallowing of ADV7103 and SoC useful as evaluation points, as acceptability is known to bring issues hindering treatment compliance in patients with dRTA[47].

Using reliable and well-established scales to accommodate patients' age, most results showed ADV7103 was favoured over SoC. Despite some differences as shown for palatability where children did not notice any difference between SoC and ADV7103 for ease of administration and ease of swallowing where children favoured SoC, all other age subsets highly favoured ADV7103 over SoC[47].

In summary, in the overall population palatability was improved with ADV7103 relative to SoC; similarly ease of administration was improved relative to SoC including in infants or at least similar to SoC in children, showing the value of the granule formulation and its acceptability relative to SoC.

Although ADV7103 is a multi-particular formulation (hundreds of granules to swallow per intake), overall ease of swallowing was preserved compared to SoC formulated as powder diluted in water or single monolithic form [47].

Table 34: Study B21CS Palatability of ADV7103 vs SoC



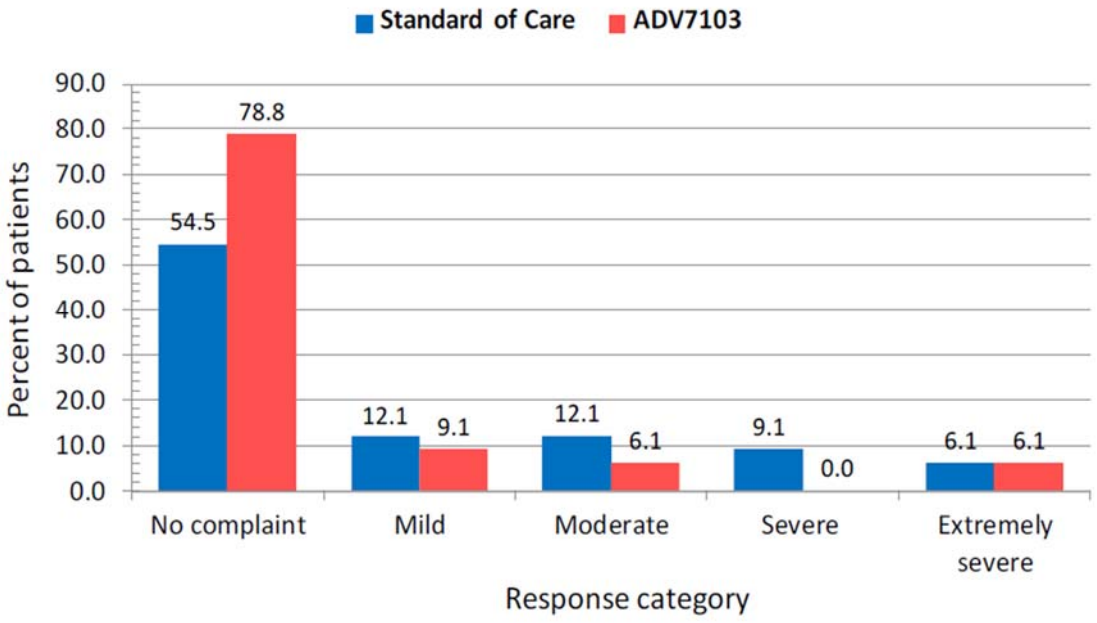
Effect on GI tolerability

GI tolerability is a relevant efficacy parameter to be assessed due to the effect it has on compliance, and therefore treatment effect [47].

Overall, in Study B21CS, improved GI tolerability was reported for ADV7103 compared to SoC. Adults, adolescents and infants reported a GI discomfort lower with ADV7103 than with SoC, while children reported equivalent and rather low GI discomfort for ADV7103 and SoC. 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) [47].

Gastrointestinal tolerability was significantly improved over SoC: 75% of patients rated no GI complaint with ADV7103 vs 51% with SoC (despite patients being on their SoC long-term versus only using ADV7103 for a few days).

Table 35: Gastrointestinal tolerance of ADV7103 vs SoC



B22CS

The long-term efficacy of ADV7103 on correcting metabolic acidosis as measured by bicarbonataemia

Overall, when blood tests were done before study drug intake, thirteen patients (52.0%) at baseline, 21 patients (91.3%) at M3, 12 patients (63.2%) at M6, 14 patients (77.8%) at M12, 16 patients (84.2%) at M18, 14 patients (60.9%) at M24, 18 patients (81.8%) at M36, and thirteen patients (68.4%) at M48 had plasma bicarbonate levels in the normal range (Table 44). Two patients had levels above the range: one adult at M24 and one child at baseline, both with NCS values.

Eleven patients (44.0%) had plasma bicarbonate levels below the normal range at baseline, when the blood test was done before study drug intake. This was less frequent at subsequent visits. There were 1 to 2 patients per age subgroup except for the child group at M48 who were below the normal range.

Ten of the abnormal results were CS. One adult had a CS value of 18.2 mmol/L at month 24 + 10 weeks. One adult had two CS values of 19.0 mmol/L at M18 and at M24. This level dipped to a CS value of 14.4 mmol/L at M24 + 10 weeks. The plasma bicarbonate level increased to an NCS level of 18.0 mmol/L at M30, decreased again to a CS level of 15.4 mmol/L at M36, and then increased to NCS levels of 21.6 mmol/L at M42 and 19.1 mmol/L at M48. One adolescent had a CS level of 16.2 mmol/L at M30, and two CS values of 17.5 and 17.7 mmol/L taken at two timepoints at an unscheduled visit at M36. Levels had returned to normal levels (23.3 mmol/L) at M48. One child had a level of 18.1 mmol/L at M36. Levels had risen to an NCS level (21.1 mmol/L) by M42. One child had a level of 12.0 mmol/L at M48. These changes correspond to mild metabolic acidosis.

The age group with the highest incidence of abnormally low plasma bicarbonate at baseline was the child group (54.5%), but this group showed the largest improvement at M3, M6, M12 and M18 (with 9.1%, 22.2%, 0% and 11.1% with abnormally low levels, respectively), although the incidence returned to 50.0% at M24 before decreasing again to 44.4% at M48.

The abnormal plasma bicarbonate values were, in most cases, limited to a slight decrease post-baseline (i.e. not below eighteen mmol/L, which corresponds to a level of mild metabolic acidosis), but three patients (one adult, 1 adolescent, and 1 child) each had values of as low as 12.0 mmoL/L at a

single time point. The abnormal plasma bicarbonate values were followed by normal values at the next scheduled visit (excluding one patient which was recorded at the M48 visit).

For one patient, the abnormally low plasma bicarbonate values could be related to the limited treatment compliance (<50% for most of the time during the study).

For two infants (2 years old and 3 years old), the abnormally low plasma bicarbonate values could be related to the decrease of the dose. Indeed, the initial daily dose of ADV7103 in mEq was maintained or not sufficiently increased resulting in a decrease of the daily dose in mEq/kg over time of 2.0 and 1.5 mEq/kg, respectively, considering the weight gain during the 48-month study. The treatment compliance was correct for both patients, i.e., >90% throughout the study, except for 75 to 90% for a 3-month period (M3 to M6) and 50 to 74% for a 6-month period (M12 to M18 for one patient and >90% or 75 to 90% throughout the study, except for 50 to 74% for a total of 12 months (M6 to M12, and M18 to M24) for one patient. In addition, the proximal signs associated in infancy with a transient proximal leak of bicarbonate due to immaturity of the physiological renal function and contributing to a more decreased plasma bicarbonate than in older patients.

Table 44: B22CS Bicarbonataemia Status by Visit – Blood Tests Done Before Drug Intake

Age Group	Analysis Visit	n	Low n (%)	Normal n (%)	High n (%)
Overall (N=30)	Baseline	25	11 (44.0)	13 (52.0)	1 (4.0)
	Month 3	23	2 (8.7)	21 (91.3)	0
	Month 6	19	7 (36.8)	12 (63.2)	0
	Month 12	18	4 (22.2)	14 (77.8)	0
	Month 18	19	3 (15.8)	16 (84.2)	0
	Month 24	23	8 (34.8)	14 (60.9)	1 (4.3)
	Month 36	22	4 (18.2)	18 (81.8)	0
	Month 48	19	6 (31.6)	13 (68.4)	0

Source: B22CS CSR. Abbreviations: N, n = number of patients; Y = years.

The long-term effects of ADV7103 on kalaemia

Overall, when blood tests were done before study drug intake for non-haemolysed samples,16 patients (84.2%) at baseline, 20 patients (95.2%) at M3, 19 patients (95.0%) at M6, 17 patients (94.4%) at M12, 17 patients (89.5%) at M18, 21 patients (91.3%) at M24, 20 patients (90.9%) at M36, and seventeen patients (89.5%) at M48 had clinically normal plasma potassium levels.

Three patients overall (15.8%) had abnormally low plasma potassium at baseline, and this figure was reduced in following visits (Table 45). The single age group with regular incidence of hypokalaemia was the adult group. There were very few CS values. One adult had a CS low level at M24 and M24 + 10 weeks visits. Three paediatric patients had NCS low values of plasma potassium: one adolescent at M6, M36, and M48, one adolescent at M24 + 10 weeks, and one child at baseline.

Similar results were seen for kalaemia results from blood tests done before study drug intake, including haemolysed and non-haemolysed samples, where overall, 21 patients (87.5%) at baseline, 23 patients (95.8%) at M3, 19 patients (95.0%) at M6, 18 patients (94.7%) at M12, 17 patients (89.5%) at M18, 22 patients (91.7%) at M24, 20 patients (90.9%) at M36, and seventeen patients (89.5%) at M48 had clinically normal plasma potassium levels.

For the larger group of patients, including blood tests not done before morning dose, nineteen patients (86.4%) at baseline, 24 patients (92.3%) at M3, 25 patients (83.3%) at M6, 24 patients (85.7%) at M12, 23 patients (82.1%) at M18, 23 patients (82.1%) at M24, 22 patients (84.6%) at M36, and 25 patients (92.6%) at M48 had clinically normal plasma potassium levels for non-haemolysed samples (Table 14.2.1.2.2.1) and 26 patients (89.7%) at baseline, 28 patients (93.3%) at M3, 25 patients (83.3%) at M6, 26 patients (86.7%) at M12, 23 patients (82.1%) at M18, 24 patients (82.8%) at M24, 22 patients (84.6%) at M36, and 25 patients (92.6%) at M48 had clinically normal plasma potassium levels for haemolysed and non-haemolysed samples.

Overall, most patients (between 82.1% and 93.3%) had normalised plasma potassium for the 48 months of follow-up on treatment with ADV7103.

Table 45: Non-haemolysed Kalaemia Status by Visit – Blood Tests Done Before Drug Intake

	Analysis Visit	n	Low n (%)	Normal n (%)	High n (%)
Overall (N=30)	Baseline	19	3 (15.8)	16 (84.2)	0
	Month 3	21	1 (4.8)	20 (95.2)	0
	Month 6	20	1 (5.0)	19 (95.0)	0
	Month 12	18	1 (5.6)	17 (94.4)	0
	Month 18	19	2 (10.5)	17 (89.5)	0
	Month 24	23	2 (8.7)	21 (91.3)	0
	Month 36	22	2 (9.1)	20 (90.9)	0
	Month 48	19	2 (10.5)	17 (89.5)	0

Source: B22CS CSR. Abbreviations: N, n = number of patients; Y = year.

The long-term effects of ADV7103 on hypocitraturia

Overall, seven patients (35.0%) had citraturia in the normal ranges at baseline, 10 patients (52.6%) at M3, nine patients (40.9%) at M6, seven patients (29.2%) at M12, 14 patients (51.9%) at M18, 10 patients (41.7%) at M24, nine patients (42.9%) at M36, and four patients (20.0%) at M48.

Overall, 13 patients (65.0%) had hypocitraturia at baseline, nine patients (47.4%) at M3, 13 patients (59.1%) at M6, 17 patients (70.8%) at M12, 13 patients (48.1%) at M18, 14 patients (58.3%) at M24, 12 patients (57.1%) at M36, and sixteen patients (80.0%) at M48.

The general trend on treatment with ADV7103 was maintenance of the number of patients with

UCi/UCr in the normal ranges between 29 and 53% throughout the 48 months of treatment except at the M12 and M48 timepoints.

Table 46: Urine Citrate/Creatinine Ratio Status by Visit

	Analysis Visit	n	Low n (%)	Normal n (%)
Overall (N=30)	Baseline	20	13 (65.0)	7 (35.0)
	Month 3	19	9 (47.4)	10 (52.6)
	Month 6	22	13 (59.1)	9 (40.9)
	Month 12	24	17 (70.8)	7 (29.2)
	Month 18	27	13 (48.1)	14 (51.9)
	Month 24	24	14 (58.3)	10 (41.7)
	Month 36	21	12 (57.1)	9 (42.9)
	Month 48	20	16 (80.0)	4 (20.0)

Source: B22CS CSR. Abbreviations: N, n = number of patients; UCi/UCr = urinary ratio of citrate to creatinine.

Normal values for UCi/UCr in mmol/mmol: boys 2-<7 years ≥0.142; boys 7-<13 years ≥0.082; boys 13-<18 years ≥0.052; boys≥18 years ≥0.052; girls 2-<7 years ≥0.171; girls 7-<13 years ≥0.154; girls 13-<18 years ≥0.127; girls ≥18 years ≥0.127 [49].

The long-term effects of ADV7103 on hypercalciuria

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 up to M48, when there were four patients with abnormally high values of UCa/UCr.

There was a stable pattern in the number of patients with UCa/UCr in the normal range, and a slight trend of decreased UCa/UCr values throughout the 48 months of treatment. However, the study was not statistically powered on this parameter.

Table 47: Urine Calcium/Creatinine Ratio Status by Visit

	Analysis Visit	n	Normal n (%)	High n (%)
Overall (N=30)	Baseline	27	27 (100.0)	0
	Month 3	27	26 (96.3)	1 (3.7)
	Month 6	26	25 (96.2)	1 (3.8)
	Month 12	29	27 (93.1)	2 (6.9)
	Month 18	27	25 (92.6)	2 (7.4)
	Month 24	28	26 (92.9)	2 (7.1)
	Month 36	27	26 (96.3)	1 (3.7)
	Month 48	26	22 (84.6)	4 (15.4)

Source: B22CS CSR. Abbreviations: N, n = number of patients

Urine calcium/citrate ratio

Low urinary citrate excretion is a known another known risk factor for nephrolithiasis. Nine patients overall (45.0%) at baseline, 11 patients (57.9%) at M3, nine patients (47.4%) at M6, patients (43.5%) at M12, 10 patients (38.5%) at M18, nine patients (37.5%) at M24, nine patients (42.9%) at M36, and five patients (25.0%) at M48 had UCa/UCi in the normal range.

Eleven patients overall (55.0%) at baseline, seven patients (36.8%) at M3, nine patients (47.4%) at M6, 12 patients (52.2%) at M12, 14 patients (53.8%) at M18, 12 patients (50.0%) at M24, 10 patients

(47.6%) at M36, and fifteen patients (75.0%) at M48 had UCa/UCi above the normal range.

Table 48: Urine Calcium/Citrate Ratio Status by Visit

	Analysis Visit	n	Low n (%)	Normal n (%)	High n (%)
Overall (N=30)	Baseline	20	0	9 (45.0)	11 (55.0)
	Month 3	19	1 (5.3)	11 (57.9)	7 (36.8)
	Month 6	19	1 (5.3)	9 (47.4)	9 (47.4)
	Month 12	23	1 (4.3)	10 (43.5)	12 (52.2)
	Month 18	26	2 (7.7)	10 (38.5)	14 (53.8)
	Month 24	24	3 (12.5)	9 (37.5)	12 (50.0)
	Month 36	21	2 (9.5)	9 (42.9)	10 (47.6)
	Month 48	20	0	5 (25.0)	15 (75.0)

Abbreviations: N, n = number of patients; UCa/UCi = urinary ratio of calcium to citrate. Normal values for UCa/UCi in mmol/mmol: boys 2-<7 years 0.24-2.31; boys 7-<13 years 0.24-2.88; boys 13-<18 years 0.29-3.84; boys ≥18 years 0.29-3.84; girls 2-<7 years 0.14-2.02; girls 7-<13 years 0.19-2.26; girls 13-<18 years 0.24-2.88; girls ≥18 years 0.24-2.88 [49].

Nine patients overall (45.0%) at baseline, 12 patients (63.2%) at M3, 10 patients (52.6%) at M6, patients (47.8%) at M12, 13 patients (50.0%) at M18, 12 patients (50.0%) at M24, 12 patients (57.1%) at M36, and six patients (30.0%) at M48 had UCa/UCi below the threshold associated with risk of lithogenesis.

Eleven patients overall (55.0%) at baseline, seven patients (36.8%) at M3, nine patients (47.4%) at M6, 12 patients (52.2%) at M12, 13 patients (50.0%) at M18, 12 patients (50.0%) at M24, nine patients (42.9%) at M36, and fourteen patients (70.0%) at M48 had UCa/UCi above the threshold associated with risk of lithogenesis.

The trend was a stabilisation of the number of patients with a UCa/UCi below the threshold used to evaluate the risk of lithogenesis at about 50% throughout the 48 months of follow-up, although this was lower at M48.

Table 49: BB2CS Risk of Lithogenesis over Time

Risk of lithogenesis n (%)				
	Visit	n	No	Yes
Overall (N=30)	Baseline	20	9 (45.0)	11 (55.0)
	Month 3	19	12 (63.2)	7 (36.8)
	Month 6	19	10 (52.6)	9 (47.4)
	Month 12	23	11 (47.8)	12 (52.2)
	Month 18	26	13 (50.0)	13 (50.0)
	Month 24	24	12 (50.0)	12 (50.0)
	Month 36	21	12 (57.1)	9 (42.9)
	Month 48	20	6 (30.0)	14 (70.0)

Source: B22CS CSR. Abbreviations: N, n = number of patients.

The long-term effects of ADV7103 on crystalluria

In this section, it's important to note that a considerable amount of data was missing, and the analytical conditions for crystalluria were not always respected (i.e. analysis performed >2 hours after urination) leading to questionable crystalluria data in some cases (as crystals appear with time).

Table 50: Urine Chemistry Crystalluria by Visit

Analysis Visit		Adults >=18Y (N=6)	Adolescents [12-18Y] (N=8)	Children [4-12Y] (N=13)	Infants [0.5-4Y] (N=3)	Overall (N=30)
Baseline	n	4	5	5	3	17
	Presence	4 (100.0)	2 (40.0)	2 (40.0)	1 (33.3)	9 (52.9)
	ACCP	4 (100.0)	2 (40.0)	2 (40.0)	0	8 (47.1)
	Unknown	0	0	0	1 (33.3)	1 (5.9)
Month 12	n	4	8	10	3	25
	Presence	1 (25.0)	5 (62.5)	3 (30.0)	0	9 (36.0)
	ACCP	1 (25.0)	3 (37.5)	2 (20.2)	0	6 (24.0)
	Amorph urate crystals	0	1 (12.5)	0	0	1 (4.0)
	Amorphous salts	0	1 (12.5)	0	0	1 (4.0)
	Brushite	0	0	1 (33.3)	0	1 (4.0)
Month 24	n	3	8	12	3	26
	Presence	3 (100.0)	4 (50.0)	5 (41.7)	1 (33.3)	13 (50.0)
	ACCP	3 (100.0)	2 (25.0)	2 (16.7)	0	7 (26.9)
	Brushite	0	0	0	1 (33.3)	1 (3.8)
	Calcium oxalate	0	0	1 (8.3)	0	1 (3.8)
	Struvite	0	0	1 (8.3)	0	1 (3.8)
	Urate acid ammonium	0	2 (25.0)	1 (8.3)	0	3 (11.5)
Month 36	n	2	6	11	3	22
	Presence	2 (100.0)	2 (33.3)	3 (27.3)	0	7 (31.8)
	ACCP	2 (100.0)	2 (33.3)	2 (18.2)	0	6 (27.3)
	Struvite	0	0	1 (9.1)	0	1 (4.5)
Month 48	n	2	7	8	3	20
	Presence	1 (50.0)	3 (42.9)	2 (25.0)	0	6 (30.0)
	ACCP	1 (50.0)	3 (42.9)	2 (25.0)	0	6 (30.0)

Source: B22CS CSR. Abbreviations: ACCP = amorphous carbonated calcium phosphate; N, n = number of patients; Y = years.

Overall, 25 (83.3%) patients had crystals during the 48-months study, 16 out of these 25 patients (64.0%) had amorphous carbonated calcium phosphate (ACCP) crystals in the study.

At baseline (M1), nine patients overall (52.9% of the seventeen assessed) had a positive crystalluria result, including four adults, two adolescents, two children and one infant). The ACCP crystals were reported in eight out of seventeen patients (47.1%), semi-quantitative analysis was performed for four of the patients, three adults had rare crystals and one adolescent had numerous crystals. An unknown type of crystal was reported in one infant.

At M12, nine patients overall (36.0% of the 25 assessed, including one adult, five adolescents, and three children) had a positive result. ACCP crystals were reported in six out of 25 patients (24.0%), in four patients, the crystals were rare. Rare amorphous uric acid crystals, amorphous salts and brushite were reported in one patient (4.0%) each).

At M24, 13 patients overall (50.0% of the 26 assessed, including three adults, four adolescents, five children and one infant) had a positive result. ACCP crystals were reported in seven patients (26.9%), in a numerous, quite numerous or 0.600 cells/mm^3 quantity in the three patients analysed for quantity.

Urate acid ammonium were reported in three cases (11.5%). Brushite (with

5.000 cells/mm^3), rare calcium oxalate crystals and struvite (with 4.000 cells/mm^3) were reported in one patient each (3.8%).

At M36, seven patients overall (31.8% of the 22 assessed, including two adults, two adolescents, and three children) having a positive result. ACCP crystals were reported in six cases (27.3%), and struvite was reported in one child (4.5%).

At M48, six patients overall (30.0% of the twenty assessed, including one adult, three adolescents, and two children) having a positive result. ACCP crystals were reported in all six cases.

Other crystals, amorphous uric acid, amorph urate, amorphous salts, and calcium oxalate were reported sporadically (between one and three occurrences) during the 48-month study.

The incidence of urine crystals was stable during the 48-month study, between 30% and 50% of the patients had positive crystalluria depending on the study yearly visit, and the incidence did not increase in line with exposure. Most patients had ACCP crystals, and the incidence of ACCP crystals did not increase with exposure.

Most patients overall had urine pH between 7.0 and 8.0; 16/23 (69.6%) at baseline, 16/21 (76.2%) at M3, 13/17 (76.5%) at M6, 16/25 (64.0%) at M12, 16/28 (57.1%) at M18, 20/26 (76.9%) at M24, 16/25 (64.0%) at M36, and 12/18 (66.7%) at M48.

Five patients overall (21.7%) had urine pH >8.0 at baseline, four (19.0%) at M3, three (17.6%) at M6, six (24.0%) at M12, 11 (39.3%) at M18, six (23.1%) at M24, nine (36.0%) at M36, and five (27.8%) at M48. Two patients overall (8.7%) had urine pH <7.0 at baseline, one (4.8%) at M3, one (5.9%) at M6, three (12.0%) at M12, one (3.6%) at M18, none at M24 or M36, and one (5.6%) at M48.

Together, crystalluria and urine pH were stable, no increase of the occurrence of ACCP crystals and of urine pH were observed with ADV7103 treatment or with increased exposure.

For specific gravity results, in the adolescent group there was only one abnormal result (low) at M18 and in the infant group there was only one abnormal result (high) at M3. In the child group, one or two patients had abnormal results (low) at each visit. Overall, many patients (>55%) had normal specific gravity at all study visits, but the dataset was limited, with data only available for up to eight patients at each visit.

The long-term effects of ADV7103 on hypermagnesuria

Adult patients are not included as no normal range was available for this group.

Most paediatric patients overall had UMg/UCr in the normal range from M1 to M48. Five patients overall (23.8%) had UMg/UCr above the normal range at baseline, one patient (5.9%) at M3, one patient (5.6%) at M6, three patients (16.7%) at M12, four patients (23.5%) at M18, two patients (9.5%) at M24, three patients (18.8%) at M36, and three patients (20.0%) at M48. These patients were all in the adolescent and child groups except for one infant with UMg/UCr above range at M18.

Table 51: Urinary Ratio of Magnesium/Creatinine by Visit

	Analysis Visit	n	Normal n (%)	High n (%)
Overall (N=24)	Baseline	21	16 (76.2)	5 (23.8)
Paediatric patients only	Month 3	17	16 (94.1)	1 (5.9)
	Month 6	18	17 (94.4)	1 (5.6)
	Month 12	18	15 (83.3)	3 (16.7)
	Month 18	17	13 (76.5)	4 (23.5)
	Month 24	21	19 (90.5)	2 (9.5)
	Month 36	16	13 (81.3)	3 (18.8)

	Month 48	15	12 (80.0)	3 (20.0)

Source: B22CS CSR. Abbreviations: N, n = number of patients.

The long-term effects of ADV7103 on hyperphosphaturia

Twenty paediatric patients (90.9%) overall had UPh/UCr in the normal range at baseline, 19 patients (95.0%) at M3, 20 patients (90.9%) at M6, 22 patients (95.7%) at M12, 21 patients (100%) at M18, 20 patients (95.2%) at M24, 18 patients (94.7%) at M36, and fifteen patients (100%) at M48.

Two paediatric patients overall (9.1%) had UPh/UCr above the normal range at baseline, one patient (5.0%) at M3, two patients (9.1%) at M6, one patient (4.3%) at M12, one patient (4.8%) at M24, and one patient (5.3%) at M36. These patients were all in the adolescent and child groups; none of the infants with data available had results above the normal range. Overall, all paediatric patients had a normal phosphaturia over time.

Table 52: Urine Phosphate and Creatinine Ratio Status by Visit

	Analysis Visit	**n**	**Normal n (%)**	**High n (%)**
Overall (N=24)	Baseline	22	20 (90.9)	2 (9.1)
Paediatric patients only	Month 3	20	19 (95.0)	1 (5.0)
	Month 6	22	20 (90.9)	2 (9.1)
	Month 12	23	22 (95.7)	1 (4.3)
	Month 18	21	21 (100.0)	0
	Month 24	21	20 (95.2)	1 (4.8)
	Month 36	19	18 (94.7)	1 (5.3)
	Month 48	15	15 (100.0)	0

Source: B22CS CSR. Abbreviations: N, n = number of patients.

Tubular reabsorption of phosphate results are summarised at each visit (as below or in range according to defined normal range). All values assessed in all age groups and at all visits were within the normal range apart from one adult at M12.

Overall, TRP levels were normal for all patients, when considering both the plasma phosphate level, (which was normal for all patients, except for some isolated and NCS low or high values).

Table 53: Tubular Reabsorption of Phosphate Status by Visit

	Analysis Visit	**n**	**Low n (%)**	**Normal n (%)**
Overall (N=30)	Baseline	20	0	20 (100.0)
	Month 3	25	0	25 (100.0)
	Month 6	26	0	26 (100.0)
	Month 12	28	1 (3.6)	27 (96.4)
	Month 18	24	0	24 (100.0)
	Month 24	26	0	26 (100.0)
	Month 36	25	0	25 (100.0)
	Month 48	19	0	19 (100.0)

Source: B22CS CSR. Abbreviations: N, n = number of patients.

Overall, most patients had values in the normal range or above. Some patients had values below the normal range: one patient (5.0%) at baseline, three patients (12.0%) at M3, two patients (7.7%) at M6, three patients (10.7%) at M12, two patients (8.3%) at M18, three patients (11.5%) at M24, three

patients (12.0%) at M36, and two patients (10.5%) at M48. There were no patients with abnormally low values at the M24 + 10 weeks, M30, or M42 visits.

In the adult group, five patients had low TmP/GFR values at one or more timepoints. In the adolescent group, three had low TmP/GFR values at one or more timepoints. All patients in the child and infant groups had TmP/GFR in the normal range at all visits.

Table 54: Tubular Maximum Reabsorption of Phosphate over Glomerular Filtration Rate by Visit

	Analysis Visit	n	Low n (%)	Normal n (%)	High n (%)
Overall (N=30)	Baseline	20	1 (5.0)	18 (90.0)	1 (5.0)
	Month 3	25	3 (12.0)	21 (84.0)	1 (4.0)
	Month 6	26	2 (7.7)	22 (84.6)	2 (7.7)
	Month 12	28	3 (10.7)	25 (89.3)	0
	Month 18	24	2 (8.3)	22 (91.7)	0
	Month 24	26	3 (11.5)	21 (80.8)	2 (7.7)
	Month 36	25	3 (12.0)	22 (88.0)	0
	Month 48	19	2 (10.5)	16 (84.2)	1 (5.3)

Source: B22CS CSR. Abbreviations: N, n = number of patients.

The long-term effect of ADV7103 on eGFR

By M48, the mean±SD eGFR (mL/min/1.73m2) was 115.5±12.3 in the adult group (n=5), 105.5±18.4 in the adolescent group (n=7), 124.0±28.4 in the child group (n=12), 130.1±10.9 in the infant group (n=3) and 118.3±23.0 overall (n=27). There was a mean±SD change from baseline in eGFR of -6.8±28.5 at M48 overall, with decreases seen at most visits in all the age groups. The largest decreases were in the adult group.

The overall percentage of patients with abnormally low levels of eGFR (only mildly decreased eGFR; Grade 2 according to KDIGO 2013 [50] was 4.3% at baseline, 6.7% at M3, 6.9% at M6, 13.3% at M12, 3.4% at M18, 3.4% at M24, 11.1% at M36, and 7.4% at M48. There were no cases of moderately or severely (Grades 3 to 5) decreased eGFR. Three patients had a decreased eGFR through at least some months of the study: two children and one adolescent during the study. Some other patients had an isolated abnormally low value at some or single timepoint(s) during the study: one adult, two adolescents and three children. There were no cases in the infant group. There was no obvious pattern in the decreased eGFR over time apart for two paediatric patients.

The long-term compliance to ADV7103

When boxes of treatment (i.e., box of 60 sachets of 24 mEq or box of 60 sachets of 8 mEq) were not retrieved, the compliance was estimated as far as possible by questioning the patient and/or his/her family, and in accordance with laboratory results. Following this, the non-retrieved boxes were considered not taken by the patient, which is the worst-case scenario for the ADV7103 compliance evaluation.

At M3, compliance for the first 3 months was >90% for 22 patients (73.3%) overall, 75 to 90% for six patients (20.0%), 50 to 74% for one patient (3.3%) and <50% for one patient (3.3%). At M6, the corresponding figures for the last 3 months were >90% for nineteen patients (65.5%) overall, 75 to 90% for seven patients (24.1%), 50 to 74% for two patients (6.9%) and <50% for one patient (3.4%). At M12, compliance for the previous six months was >90% for 22 patients (73.3%) overall, 75 to 90% for three patients (10.0%), 50 to 74% for four patients (13.3%) and <50% for one patient (3.3%). At M18, the corresponding figures for the last 6 months were nineteen patients (65.5%), four patients (13.8%), five patients (17.2%) and one patient (3.4%), respectively. At M24, compliance for the previous six months was >90% for eighteen patients (62.1%), 75 to 90% for five patients (17.2%), and 50 to 74% for six patients (20.7%). At M36, compliance for the previous six months was >90% for

twelve patients (44.4%), 75 to 90% for ten patients (37.0%), and 50 to 74% for five patients (18.5%). At M48, compliance for the previous six months was >90% for thirteen patients (48.1%), 75 to 90% for five patients (18.5%), 50 to 74% for seven patients (25.9%), and below 50% for two patients (7.4%). Overall, during the 48 months of the study, compliance was generally good (≥75%) in all age groups: for 28 patients (93.3%) at M3, 26 patients (89.7%) at M6, 25 patients (83.3%) at M12,23 patients (79.3%) at M18 and M24, 22 patients (81.5%) at M36, and eighteen patients (66.7%) at M48. Only four patients had treatment compliance below 50% recorded.

Table 55: B22CS Compliance over Time by Age Group and Overall

Visit	Compliance	Adult [≥18Y] (N=6)	Adolescent [12-18Y] (N=8)	Child [4-12Y] (N=13)	Infant [0.5-4Y] (N=3)	Overall (N=30)
Month 3	n	6	8	13	3	30
	>90%	4 (66.7)	3 (37.5)	12 (92.3)	3 (100.0)	22 (73.3)
	75-90%	2 (33.3)	3 (37.5)	1 (7.7)	0	6 (20.0)
	50-74%	0	1 (12.5)	0	0	1 (3.3)
	<50%	0	1 (12.5)	0	0	1 (3.3)
Month 6	n	5	8	13	3	29
	>90%	2 (40.0)	5 (62.5)	11 (84.6)	1 (33.3)	19 (65.5)
	75-90%	2 (40.0)	1 (12.5)	2 (15.4)	2 (66.7)	7 (24.1)
	50-74%	1 (20.0)	1 (12.5)	0	0	2 (6.9)
	<50%	0	1 (12.5)	0	0	1 (3.4)
Month 12	n	6	8	13	3	30
	>90%	5 (83.3)	5 (62.5)	11 (84.6)	1 (33.3)	22 (73.3)
	75-90%	1 (16.7)	0	2 (15.4)	0	3 (10.0)
	50-74%	0	2 (25.0)	0	2 (66.7)	4 (13.3)
	<50%	0	1 (12.5)	0	0	1 (3.3)
Month 18	n	5	8	13	3	29
	>90%	5 (100.0)	2 (25.0)	11 (84.6)	1 (33.3)	19 (65.5)
	75-90%	0	2 (25.0)	1 (7.7)	1 (33.3)	4 (13.8)
	50-74%	0	3 (37.5)	1 (7.7)	1 (33.3)	5 (17.2)
	<50%	0	1 (12.5)	0	0	1 (3.4)
Month 24*	n	5	8	13	3	29
	>90%	4 (80.0)	2 (25.0)	10 (76.9)	2 (66.7)	18 (62.1)
	75-90%	1 (20.0)	3 (37.5)	1 (7.7)	0	5 (17.2)
	50-74%	0	3 (37.5)	2 (15.4)	1 (33.3)	6 (20.7)
Month 36	n	5	7	12	3	27
	>90%	2 (40.0)	1 (14.3)	8 (66.7)	1 (33.3)	12 (44.4)
	75-90%	2 (40.0)	3 (42.9)	3 (25.0)	2 (66.7)	10 (37.0)
	50-74%	1 (20.0)	3 (42.9)	1 (8.3)	0	5 (18.5)
Month 48	n	5	7	12	3	27
	>90%	2 (40.0)	0	10 (83.3)	1 (33.3)	13 (48.1)
	75-90%	2 (40.0)	2 (28.6)	0	1 (33.3)	5 (18.5)
	50-74%	1 (20.0)	4 (57.1)	2 (16.7)	0	7 (25.9)
	<50%	0	1 (14.3)	0	1 (33.3)	2 (7.4)

Source: B22CS CSR. Abbreviations: M = month; N, n = number of patients; Y = years. *Or Early Termination visit. At M24 and M36, no compliance <50% was reported.

Exploratory objectives

The long-term effects of ADV7103 on nephrocalcinosis

It should be noted that after review of the medical dossier of a 3-year patient, the nephrocalcinosis reported at M24, but not at M1, M36 and M48, was corrected by the investigator, and confirmed as

also not observed at M24. Overall, most patients evaluated presented with nephrocalcinosis at baseline (25 patients; 86.2%), M24 (28 patients; 96.6%, corrected to 27 patients; 93.1%), M36 (24 patients; 92.3%), and M48 (20 patients; 90.9%).

One adolescent developed nephrocalcinosis during the 48 months of follow-up while they were fully compliant to treatment. For the patient, nephrocalcinosis was not seen at baseline but at M24, M36 and M48 with renal ultrasonography. However, a positive nephrocalcinosis result was already identified in this patient's dRTA medical history. The investigator confirmed that nephrocalcinosis was present before study enrolment.

Table 56: B22CS the long-term effects of ADV7103 on nephrocalcinosis

Analysis Visit	Nephrocalcinosis	Adults >=18Y (N=6)	Adolescents [12-18Y] (N=8)	Children [4-12Y] (N=13)	Infants [0.5-4Y] (N=3)	Overall (N=30)
Baseline	n	6	8	13	2	29
	No	1 (16.7)	2 (25.0)	0	1 (50.0)	4 (13.8)
	Yes	5 (83.3)	6 (75.0)	13 (100.0)	1 (50.0)	25 (86.2)
Month 24	n	5	8	13	3	29
	No	0	1 (12.5)	0	0*	1 (3.4)*
	Yes	5 (100.0)	7 (87.5)	13 (100.0)	3 (100.0)*	28 (96.6)*
Month 36	n	5	7	12	2	26
	No	0	1 (14.3)	0	1 (50.0)	2 (7.7)
	Yes	5 (100.0)	6 (85.7)	12 (100.0)	1 (50.0)	24 (92.3)
Month 48	n	4	7	8	3	22
	No	0	0	1 (12.5)	1 (33.3)	2 (9.1)
	Yes	4 (100.0)	7 (100.0)	7 (87.5)	2 (66.7)	20 (90.9)

Source: B22CS CSR. Abbreviations: n = number; y = years.

The long-term effects of ADV7103 on nephrolithiasis

Overall, nephrolithiasis was only seen in small numbers of patients, and the number/percentage of patients presenting with nephrolithiasis was similar at baseline (six patients; 20.7%), M24 (five patients; 17.2%), M36 (seven patients; 26.9%), and M48 (seven patients; 31.8%). Cases of nephrolithiasis were reported in each group of age. Five patients had nephrolithiasis at baseline then during the study (two adults, one adolescent, one child: one infant.

Nine patients had events of kidney stones during the study (one adult, three adolescents, four children and one infant. One child had kidney stones only at baseline.

Table 57: Number (Percentage) of Patients Presenting Nephrolithiasis, by Visit, Age Group and Overall

Analysis Visit	Nephrolithiasis	Adults >=18Y (N=6)	Adolescents [12-18Y] (N=8)	Children [4-12Y] (N=13)	Infants [0.5-4Y] (N=3)	Overall (N=30)
Baseline	n	6	8	13	2	29
	No	4 (66.7)	7 (87.5)	11 (84.6)	1	23 (79.3)
	Yes	2 (33.3)	1 (12.5)	2 (15.4)	1	6 (20.7)
Month 24	n	5	8	13	3	29
	No	3 (60.0)	7 (87.5)	12 (92.3)	2 (66.7)	24 (82.8)
	Yes	2 (40.0)	1 (12.5)	1 (7.7)	1 (33.3)	5 (17.2)
Month 36	n	5	7	12	2	26

	No	5 (100.0)	4 (57.1)	9 (75.0)	1	19 (73.1)
	Yes	0	3 (42.9)	3 (25.0)	1	7 (26.9)
Month 48	n	4	7	8	3	22
	No	4 (100.0)	5 (71.4)	5 (62.5)	1 (33.3)	15 (68.2)
	Yes	0	2 (28.6)	3 (37.5)	2 (66.7)	7 (31.8)

Source: B22CS CSR. Abbreviations: N, n = number of patients; Y = years.*

The long-term effects of ADV7103 on bone remodelling and BMD

1α,25-dihydroxy-vitamin D

Overall, most patients had blood 1α,25-dihydroxy-vitamin D levels in the normal range: 12 patients (80.0%) at baseline and eighteen patients (100%) at M48.

25-hydroxy-vitamin D

Overall, approximately half the patients had blood 25-hydroxy-vitamin D levels in the normal range: six patients (60.0%) at baseline and six patients (31.6%) at M48

Overall, 12 patients (80.0%) at baseline and fourteen patients (77.8%) at M48 had blood bone ALP levels in the normal range.

Overall, 27 patients (96.4%) at baseline and 21 patients (84.0%) at M48 had blood phosphate levels in the normal range.

Overall, 26 patients (100%) at baseline and 27 patients (100%) at M48 had blood calcium levels in the normal range. Overall, all patients had normal calcium levels, except two: one adult had a NCS low value once at M12, and one adolescent had NCS high values at M3, M12, M18 and M24.

Overall, all patients had blood PTH levels in the normal range or with isolated and NCS abnormal values. One child had consistently high blood PTH levels, and one adolescent had persistently low blood PTH levels from baseline to M24.

Overall, five patients (83.3%) at baseline and thirteen patients (100%) at M48 had blood calcitonin levels in the normal range.

Dual-energy X-ray absorptiometry (DXA)-scans were performed with the same equipment (including reference databases) and adjustment as baseline for ten patients (35.7%) at M24, six patients (25.0%) at M36, and six patients (27.3%) at M48. However, there was generally a single DXA-scan in each of the investigator centres. The same radiologist as baseline was used for fifteen patients (53.6%) at M24, 13 patients (54.2%) patients at M36, and thirteen patients (59.1%) at M48. The same radiologist as baseline performed DXA-scans with the same equipment (including reference databases) and adjustment for four patients (14.3%) at M24, five patients (20.8%) is at M36, and four patients (18.2%) at M48.

Spine

The Z-score of the BMD of the spine is a skeletal area relevant for evaluation of the BMD in both paediatric and adult populations.

The number/percentage of patients with normal and abnormal Z-scores (with abnormal defined as ≤-2.0 according to ISCD 2013 [24] and ≤-2.5 according to GRIO [unpublished]) for BMD of the spine (L1-L4) from baseline to M48 are presented for the overall study population in Table 58.

Many patients had normal Z-scores (> -2.0) during the 48-month study, at baseline (18 patients; 72.0%), at M24 (23 patients; 85.2%), at M36 (18 patients; 78.3%) and at M48 (18 patients; 85.7%). Spine BMD abnormalities (Z-scores ≤-2.0) were reported for seven patients (28.0%) overall at baseline and comprised one adult, two adolescents and four children. By M24, abnormalities were reported in only four patients (14.8%) overall, all children. By M36, five patients (21.7%), one adolescent and four children, had an abnormal score. By M48, abnormalities were reported in three

patients (14.3%), two children and one adolescent.

Table 58: Number (Percentage) of Patients Presenting Z-Scores for BMD of Spine by Normality Status and Visit

Reference Range ≤-2.0					Reference Range ≤-2.5	
	Analysis visit	**n**	**Low n (%)**	**Normal n (%)**	**Low n (%)**	**Normal n (%)**
Overall (N=30)	Baseline	25	7 (28.0)	18 (72.0)	1 (4.0)	24 (96.0)
	Month 24	27	4 (14.8)	23 (85.2)	1 (3.7)	26 (96.3)
	Month 36	23	5 (21.7)	18 (78.3)	1 (4.3)	22 (95.7)
	Month 48	21	3 (14.3)	18 (85.7)	1 (4.8)	20 (95.2)

Source: B22CS CSR. Abbreviations: N, n = number of patients; Y = years.*

ADV7103 could potentially have a beneficial effect over the long-term in the prevention of bone remodelling.

The long-term effects of ADV7103 on rickets and osteomalacia, respectively in the paediatric and adult population

No adults presented with osteomalacia and one infant presented with rickets with ankle pain at baseline. By M24, no paediatric patients presented with rickets. By M36, two adolescents and two children had developed rickets, and by M48, one adolescent and one child had rickets. However, the adolescent had normal and improved growth (Z-score for height of 0.89 at M1 to 1.20 at M48), did not present any rickets-specific clinical signs or AEs, any abnormal values for blood bone ALP, calcium or phosphate and spine BMD Z-score was -1.6 at M36 and -1.4 at M48. The child patient had normal and improved growth (Z-score for height of -0.72 at M1 to 0.11 at M48) did not present any rickets-specific clinical signs or any abnormal values for blood bone ALP, calcium or phosphate (except a low value for phosphate at M12) and spine BMD Z-score was -1.6 at M36 and -1.4 at M48 but a fracture of the two bones of the forearm occurred 16 months after study enrolment.

Table 59: Number (Percentage) of Patients Presenting Rickets and/or Osteomalacia by Visit, Age Group and Overall

Reported Term for the Clinical Event	Analysis Visit		Adults >=18Y (N=6)	Adolescents [12-18Y] (N=8)	Children [4-12Y] (N=13)	Infants [0.5-4Y] (N=3)	Overall (N=30)
Osteomalacia (adults and adolescents) and Rickets (adolescents, children, and infants)	**Baseline**	n	6	8	13	2	29
		No	6 (100.0)	8 (100.0)	13 (100.0)	1 (50.0)	28 (96.6)
		Yes	0	0	0	1 (50.0)	1 (4.3)
	Month 24	n	5	7	12	3	27
		No	5 (100.0)	7 (100.0)	12 (100.0)	3 (100.0)	27 (100.0)
		Yes	0	0	0	0	0
	Month 36	n	3	7	12	2	24
		No	3 (100.0)	5 (71.4)	10 (83.3)	2 (100.0)	20 (83.3)
		Yes	0	2 (28.6)	2 (16.7)	0	4 (16.7)
	Month 48	n	2	6	9	3	20
		No	2 (100.0)	5 (83.3)	8 (88.9)	3 (100.0)	18 (90.0)
		Yes	0	1 (16.7)	1 (11.1)	0	2 (10.0)

B22CS CSR. Abbreviations: n = number; y = years. “No” = patients not presenting rickets/osteomalacia; “Yes” =

patients presenting rickets/osteomalacia N, n = number of patients; Y = years. Source:

Most patients were in the ±2SD range for height for all visits (Table 60) since treatment with alkalising treatment was started a long time before study enrolment. One adult a height below -2SD at baseline, was not further improved since her growth was ended before study entry. The other patient, a 4.5-year female child, had a height below -3SD at baseline, followed by an improvement above +3SD and below -2SD at M3 and M6, then in the ±2SD range from M12 to M48.

Table 60: Z-scores for Height over Time

Analysis Visit	n	≤3SD n (%)	[-3SD;-2SD] n (%)	[-2SD;-1SD] n (%)	[-1SD;+1SD] n (%)	[+1SD;+2SD] n (%)	[+2SD;+3SD] n (%)	>+3SD n (%)
Overall								
Baseline	28	1 (3.6)	1 (3.6)	9 (32.1)	16 (57.1)	1 (3.6)	0	0
Month 3	30	0	2 (6.7)	8 (26.7)	18 (60.0)	2 (6.7)	0	0
Month 6	30	0	2 (6.7)	9 (30.0)	17 (56.7)	2 (6.7)	0	0
Month 12	30	0	1 (3.3)	10 (33.3)	16 (53.3)	3 (10.0)	0	0
Month 18	29	0	0	8 (27.6)	18 (62.1)	3 (10.3)	0	0
Month 24	29	0	0	8 (27.6)	19 (65.5)	2 (6.9)	0	0
Month 36	27	0	0	6 (22.2)	18 (66.7)	3 (11.1)	0	0
Month 48	27	0	0	7 (25.9)	17 (63.0)	3 (11.1)	0	0

Most patients were in the ±2SD range for weight for all visits (Table 61). Two children were below the ±2SD range for weight at baseline but was in the ±2SD range from M6 and from M18. There were also some patients above range for weight: three children at baseline. Two of the children remained above the ±2SD range for the whole study, but one child and one adult were in the normal range from M24 onwards. One infant was in the ±2SD range at M36 and M48, and one child was in the ±2SD range at M48. One adolescent had an isolated value in the ±2SD range at M36 but was in the normal range at M48. In addition, one adult female was in the ±2SD range at M18 and M36, and in the ±3SD range at M48.

Table 61: Weight (kg) over Time for Overall Patient Group

Visit	n	≤3SD n (%)	[-3SD;-2SD[n (%)	[-2SD;+2SD] n (%)	[+2SD;+3SD] n (%)	>+3SD n (%)
Overall						
Baseline	29	0	2 (6.9)	23 (79.3)	3 (10.3)	1 (3.4)
Month 3	30	0	2 (6.7)	24 (80.0)	3 (10.0)	1 (3.3)
Month 6	30	0	1 (3.3)	25 (83.3)	4 (13.3)	0
Month 12	30	0	1 (3.3)	25 (83.3)	3 (10.0)	1 (3.3)
Month 18	28	0	0	24 (85.7)	3 (10.7)	1 (3.6)
Month 24	28	0	0	26 (92.9)	1 (3.6)	1 (3.6)
Month 36	27	0	0	22 (81.5)	4 (14.8)	1 (3.7)
Month 48	27	0	1 (3.7)	21 (77.8)	4 (14.8)	1 (3.7)

Most patients also had a normal BMI (Table 62_bookmark155). One adolescent from M6 onwards, one child throughout the study except in M12 and two additional were below the ±2SD range for BMI

for at least one visit. In addition, four adults (three female and one male), two adolescents (one male and one female), four children (two female and two male) and two infants (both male) had high BMI for at least one visit.

Table 62: BMI (kg/m^2) over Time for Overall Patient Group

Number of patients, n (%)						
Visit	**n**	**≤3SD**	**[-3SD;-2SD]**	**[-2SD;+1SD]**	**[+1SD;+3SD]**	**>+3SD**
Overall						
Baseline	28	0	1 (3.6)	18 (64.3)	8 (28.6)	1 (3.6)
Month 3	30	0	1 (3.3)	19 (63.3)	9 (30.0)	1 (3.3)
Month 6	30	0	2 (6.7)	19 (63.3)	8 (26.7)	1 (3.3)
Month 12	30	0	2 (6.7)	19 (63.3)	8 (26.7)	1 (3.3)
Month 18	28	0	3 (10.7)	16 (57.1)	9 (32.1)	0
Month 24	28	0	2 (7.1)	19 (67.9)	7 (25.0)	0
Month 36	27	1 (3.7)	1 (3.7)	18 (66.7)	7 (25.9)	0
Month 48	27	1 (3.7)	1 (3.7)	18 (66.7)	7 (25.9)	0

Source: Abbreviations: BMI = body mass index; N, n = number of patients; SD = standard deviation.

Patient's stature balanced by the GTS

The number/percentage of patients presenting a below normal, normal, or above normal EAS at baseline, M24, and M48 is presented by age group and overall in Table 63. _bookmark156 Overall, the majority of patients had a normal EAS. The proportion of patients with a normal EAS increased over time from twenty patients (76.9%) at baseline to 23 patients (88.5%) at M48.

Two patients had a high EAS: one adolescent from baseline to M24 (the patient completed the study at M30 and one child from M24 to M48. Five children (41.7%) (two male and three female) had abnormally short EAS at enrolment, four (30.8%) at M24 and two (16.7%) at M48. Four children achieved a normal EAS during the study: two from M24 and two at M48.

In addition, the EAS was improved for one child (approaching but not yet reaching normal level) during the study: the patient had their EAS increase from 141.5 cm when aged 4.5 years old to 151.5 cm aged 8.8 years old, for a GTS of 165 cm with a normal range of 156 to 174 cm.

One child had a decreased EAS during the study. Their EAS was 161 cm when aged 11.5 years old to 152 cm aged 16 years old, for a GTS of 165 cm (normal range 156 to 174 cm). In parallel, this patient maintained normal values of plasma bicarbonate, but compliance decreased from >90% during the first 24 months to 50 to 74% during the last 24 months.

Table 63: Estimated Adult Stature by Status by Age Group and Overall

Age Group	Analysis Visit	n	Below Average n (%)	Average n (%)	Above Average n (%)
Adults [≥18Y] (N=6)	Baseline	4	0	4 (100.0)	0
	Month 24	4	0	4 (100.0)	0
	Month 48	4	0	4 (100.0)	0
Adolescents [12-18Y] (N=8)	Baseline	7	0	6 (85.7)	1 (14.3)
	Month 24	8	0	7 (87.5)	1 (12.5)
	Month 48	7	0	7 (100.0)	0
Children [4-12Y] (N=13)	Baseline	12	5 (41.7)	7 (58.3)	0

	Month 24	13	4 (30.8)	8 (61.5)	1 (7.7)
	Month 48	12	2 (16.7)	9 (75.0)	1 (8.3)
Infants [0.5-4Y] (N=3)	Baseline	3	0	3 (100.0)	0
	Month 24	3	0	3 (100.0)	0
	Month 48	3	0	3 (100.0)	0
Overall (N=30)	Baseline	26	5 (19.2)	20 (76.9)	1 (3.8)
	Month 24	28	4 (14.3)	22 (78.6)	2 (7.1)
	Month 48	26	2 (7.7)	23 (88.5)	1 (3.8)

Growth velocity

For female patients, the growth velocity for adolescents ranged from 0.11±0.62 cm/6-month to 2.80±4.44. Growth velocity for children remained relatively constant during the study, with values between 2.17±1.39 and 3.52±2.18 cm/6-month.

For male patients, the growth velocity generally increased over time for the two adolescents. Growth velocity for children remained relatively constant during the study, with values between 2.12±1.74 and 4.11±2.39 cm/6-month. Similar results were seen in infants, with values between 2.89±1.58 and 4.51±2.27 cm/6-month.

Table 64: Growth Velocity in Paediatric Patients Normality Status by Visit

	Analysis Visit	**n**	**<3rd centile n (%)**	**[3rd;25th] centile n (%)**	**≥25th centile n (%)**
Pool of paediatric groups overall (N=24)	Month 6	24	4 (16.7)	7 (29.2)	13 (54.2)
	Month 12	23	4 (17.4)	6 (26.1)	13 (56.5)
	Month 18	23	5 (21.7)	3 (13.0)	15 (65.2)
	Month 24	22	1 (4.5)	5 (22.7)	16 (72.7)
	Month 36	19	4 (21.1)	4 (21.1)	11 (57.9)
	Month 48	19	1 (5.3)	6 (31.6)	12 (63.2)

Abbreviations: BMI = body mass index; n = number; SD = standard deviation; y = years.

The long-term effects of ADV7103 on pubertal maturity in the relevant paediatric study population.

There were two adolescents with temporary late pubertal maturity; one female patient aged 14 at study entry with late pubertal development at M18 and M24, and one male patient aged 12 at study entry with late development at M18.

There were no cases of early pubertal maturity, and overall, pubertal maturity was normal in boys and girls. ADV7103 treatment had no impact on the pubertal maturity after 48 months of follow-up.

The long-term treatment acceptability of ADV7103

The VAS questions were answered by all adults, all but one adolescent and 46.2% of the children (54.5% for improved efficacy). The questions were answered by parents for one adolescent, 53.8% of the children (45.5% for improved efficacy) and all infants.

The mean±SD VAS score of the children were similar when answered by themselves or by the parent for efficacy and number of daily dose intakes, but some differences were noted for safety, appropriateness of formulation and taste.

Improved efficacy?

A very high mean±SD improvement in efficacy of 91.2±9.9 was seen overall (regardless of answerer),

with results in the different age groups 95.8±6.6, 96.0±5.4, 87.2±11.4 and 90.0 in the adult, adolescent, child and infant groups, respectively.

All patients had an improved efficacy score of ≥75% except two patients (8.7%), both children, who had an improved efficacy score ≥50%.

Improved safety?

A high mean±SD improvement in safety of 72.2±32.4 mm was seen overall, with results in the different age groups 75.6±41.6, 74.4±30.8, 66.2±34.7 and 86.3±11.2 in the adult, adolescent, child and infant groups, respectively.

An improved safety score of ≥75% was reported for nineteen patients (65.5%) overall and a score of ≥50% up to 22 patients (75.9%). The individual groups by age showed the same trend as the overall population, except for infants where all patients had a safety score ≥75%.

More appropriate formulation?

A high mean±SD VAS score for more appropriate formulation of 83.9±24.3 mm was seen overall, with results in the different age groups 74.8±32.9, 84.3±34.5, 87.2±12.5 and 83.7±26.6 in the adult, adolescent, child and infant groups, respectively.

The majority of patients had a more appropriate formulation score ≥75% (24 patients; 82.8%) and

≥50% (26 patients; 89.7%) comprising all children and infants, all but one adolescent and two adults.

More convenient number of daily dose intakes?

A very high mean±SD VAS score for more convenient number of daily dose intakes of 90.2±15.4 mm was seen overall, with results in the different age groups 95.2±10.2, 92.9±11.2, 84.5±19.2 and 99.3±1.2 in the adult, adolescent, child and infant groups, respectively.

More convenient number of daily dose intake scores were ≥75% for all patients excluding three children and one adolescent (25 patients; 86.2%), and ≥50% for all patients excluding two children (27 patients; 93.1%).

Better taste?

A mean±SD improvement in taste of 68.6±36.1 mm was seen overall, with results in the different age groups 75.2±28.7, 51.3±43.2, 71.3±36.0 and 91.7±11.9 in the adult, adolescent, child and infant groups, respectively.

Better taste scores ≥75% were obtained for seventeen patients (58.6%), including all infants, and scores 50% were reported in 21 patients (72.4%), including all infants and all adults but one.

Other improvements in treatment acceptability were reported by eight patients, including five reports related to ease/speed of intake/swallowing/drinking/administration, one report of fewer problems with gastric system/diarrhoea, one report of waking less during the night for a drink, and one report mentioning the benefit of not needing to take treatment four times a day.

Overall, throughout the long-term treatment good acceptability of ADV7103 was confirmed, whatever the parameter or the answerer. More than 80% of the patients had a score above 75% for improvement of efficacy, formulation, and number of daily doses. About 60% of the patients had a score above 75% for improvement of safety and taste even if some discrepancies were observed between answerers (children or parents).

Table 65: Number (Percentage) of Patients with Treatment Acceptability by Score Level by Age Group and Overall

Treatment acceptability score	Statistics	Adults >=18Y (N=6)	Adolescents [12-18Y] (N=8)	Children [4-12Y] (N=13)	Infants [0.5-4Y] (N=3)	Overall (N=30)
Improvement of efficacy: score ≥50%	n (%)	4 (100.0)	6 (100.0)	11 (100.0)	2 (100.0)	23 (100.0)
Improvement of efficacy: score <75%	n (%)	0	0	2 (18.2)	0	2 (8.7)
Improvement of efficacy: score ≥75%	n (%)	4 (100.0)	6 (100.0)	9 (81.8)	2 (100.0)	21 (91.3)
Improvement of safety: score <50%	n (%)	1 (20.0)	2 (25.0)	4 (30.8)	0	7 (24.1)
Improvement of safety: score ≥50%	n (%)	4 (80.0)	6 (75.0)	9 (69.2)	3 (100.0)	22 (75.9)
Improvement of safety: score <75%	n (%)	1 (20.0)	3 (37.5)	6 (46.2)	0	10 (34.5)
Improvement of safety: score ≥75%	n (%)	4 (80.0)	5 (62.5)	7 (53.8)	3 (100.0)	19 (65.5)
More appropriate formulation: score <50%	n (%)	2 (40.0)	1 (12.5)	0	0	3 (10.3)
More appropriate formulation: score ≥50%	n (%)	3 (60.0)	7 (87.5)	13 (100.0)	3 (100.0)	26 (89.7)
More appropriate formulation: score <75%	n (%)	2 (40.0)	1 (12.5)	1 (7.7)	1 (33.3)	5 (17.2)
More appropriate formulation: score ≥75s	n (%)	3 (60.0)	7 (87.5)	12 (92.3)	2 (66.7)	24 (82.8)
More convenient number of daily dose intake: score <50%	n (%)	0	0	2 (15.4)	0	2 (6.9)
More convenient number of daily dose intake: score ≥50%	n (%)	5 (100.0)	8 (100.0)	11 (84.6)	3 (100.0)	27 (93.1)
More convenient number of daily dose intake: score <75%	n (%)	0	1 (12.5)	3 (23.1)	0	4 (13.8)
More convenient number of daily dose intake: score ≥75%	n (%)	5 (100.0)	7 (87.5)	10 (76.9)	3 (100.0)	25 (86.2)
Better taste: score <50%	n (%)	1 (20.0)	4 (50.0)	3 (23.1)	0	8 (27.6)
Better taste: score ≥50%	n (%)	4 (80.0)	4 (50.0)	10 (76.9)	3 (100.0)	21 (72.4)
Better taste: score <75%	n (%)	2 (40.0)	5 (62.5)	5 (38.5)	0	12 (41.4)
Better taste: score ≥75%	n (%)	3 (60.0)	3 (37.5)	8 (61.5)	3 (100.0)	17 (58.6)

Abbreviations: N, n = number of patients; Y = years. Source: B22CS CSR. Abbreviations: M = month; N, n = number of patients; Y = years.

The long-term effects of ADV7103 on QoL

QoL of the patient (assessed by either parents or patients)

Mean±SD VAS results for the QoL of patients at M6 and M24, and the change between these two time points are summarised by age group and overall for any answerer (e.g. study patient or parent) in Table 66.

A very high mean±SD patient's QoL of 80.7±20.7 mm at M6 was seen overall, with results in the different age groups 84.7±19.5, 76.4±27.3, 77.5±18.4 and 98.0±3.5 in the adult, adolescent, child and infant groups, respectively. Additionally, a very high mean±SD of 88.9±18.9 mm at M24 was seen overall, with results in the different age groups 98.6±2.2, 84.6±26.0, 86.5±19.0 and 94.7±6.8 in the adult, adolescent, child and infant groups respectively.

An improvement was seen at M24 compared to M6, with an overall difference of 7.0±16.3 mm, a difference of 6.2±5.0, 8.3±18.2 and 9.0±19.3 in the adult, adolescent and child groups, respectively. A change of -3.3±8.5 was observed in the infant group.

Table 66: Quality of Life Results at M6 and M24 by Age Group and Overall

QoL of the patient	Statistics	Adults >=18Y (N=6)	Adolescents [12-18Y] (N=8)	Children [4-12Y] (N=13)	Infants [0.5-4Y] (N=3)	Overall (N=30)
QoL of the patient at M6	**N**	**6**	**8**	**13**	**3**	**30**
	Mean±SD	84.7±19.5	76.4±27.3	77.5±18.4	98.0±3.5	80.7±20.7
	SEM	8.0	9.7	5.1	2.0	3.8
	Min/Median/Max	46/92.0/100	25/84.5/100	40/76.0/100	94/100.0/100	25/87.0/100
QoL of the patient at M24	N	5	8	13	3	29
	Mean±SD	98.6±2.2	84.6±26.0	86.5±19.0	94.7±6.8	88.9±18.9
	SEM	1.0	9.2	5.3	3.9	3.5
	Min/Median/Max	95/100.0/100	23/93.0/100	44/97.0/100	87/97.0/100	23/97.0/100
Change in QoL M24-M6	N	5	8	13	3	29
	Mean±SD	6.2±5.0	8.3±18.2	9.0±19.3	-3.3±8.5	7.0±16.3
	SEM	2.2	6.4	5.4	4.9	3.0
	Min/Median/Max	0/7.0/13	-21/5.5/39	-22/9.0/42	-13/0.0/3	-22/7.0/42

Source: B22CS CSR. Abbreviations: M = month; Min = minimum; Max = maximum; N, n = number of patients; QoL = quality of life; SD = standard deviation; SEM = standard error of the mean; Y = years.

QoL of the parent

Parent's QoL was 89.6±13.9 mm overall, with results in the different age groups 97.0 (no SD), 93.8±6.8, 84.6±17.2 and 98.0±2.0 in the adult, adolescent, child and infant groups, respectively.

Overall, the improvement of the QoL of the patients was very high and maintained after 24 months of follow-up. The QoL of the parents was also high.

Qualitative assessment of QoL of the patients after 48 months

A qualitative assessment was done by conducting semi-structured interviews with patients after 48 months of treatment.

The key points emerging from this analysis are summarised below.

Motivation for study participation:

The motivation of most patients (13/19 [68.4%]) to participate in Study B21CS was seeking a lower treatment burden and/or a better treatment efficiency,

The motivation of most patients (13/17 [76.5%]) to enter Study B22CS was related to their reassurance regarding both effectiveness and acceptance of the product, and their wish to continue to benefit from the treatment.

Comparisons of patients/parents' treatment experiences with SoC versus ADV7103 showed several QoL domains that evolved with a change in treatment, namely:

SoC impacted QoL in terms of:

- School/work: 100% of the participants (n=13) found difficulties at school/work due to burdensome explanations for school staff, burdensome administrative tasks, reluctance of school staff to provide treatment at school, and/or parents who stopped working to take care of the treatment regimen (repeated daily intake of SoC),
- Social/family: 31.5% of the participants (n=6) found difficulties with travel and holidays, thinking about managing treatment during day/night, impaired ability of children to participate in social activities with their peers during lunchtime recess, and/or relationship difficulties between parents,
- Emotional functioning: 68.4% of the participants (n=13) patients/parents reported they are ill at ease or uncomfortable with people's questions (such as questions about their treatment or their disease), so indicating there is an emotional burden associated with their disease,
- Physical health: 84.2% of the participants (n=16) reported bad taste, bad breath and GI disorders, 21.1% of the participants (n=4) refused to take treatment. Poor compliance leading to severe AEs or strong physical impacts was reported by 36.8% of the participants (n=7), with long-term consequences on health and well-being and possible hospitalisations.

ADV7103 improved QoL in terms of:

- School/work: 100% of the participants (n=13) found improvements at school/work as problems participants encountered with SoC disappeared altogether, explanations for school staff were no longer needed, specific administrative tasks were no longer required, issues of reluctance to provide treatment at school were no longer present, and/or ability to return to work for parents,
- Social/family: 94.7% of the participants (n=18) found that travel and holidays are easier and have become a real possibility, and reported absence of tension in the family/couple, and/or no thinking about and managing treatment during the day/night,
- Emotional functioning: 63.2% of the participants (n=12) felt relief thanks to the absence of invasive questions related to the treatment, or emotional relief linked to lower disease burden,
- Physical health: 94.7% of the participants (n=18) reported neutral taste, absence of bad breath, and absence of GI disorders, only one refused to take treatment, and overall better compliance was reported leading to less strong physical impacts (reported by 15.8% of the participants, n=3).

All patients declared they were satisfied with their current treatment, with a mean score of nine out of 10. A total of 14/17 patients (82.4%) said the treatment either met or was above their expectations.

B.2.7 Subgroup analyses

B03CS

The primary PD endpoints were analysed for each gender separately if there was enough data to support the analyses. The gender effect and gender by treatment interaction were tested on the primary endpoints using the above-mentioned analysis of covariance (ANCOVA) with additional factors for the gender and gender by treatment interactions [48].

B21CS

All variables were summarised in their respective analysis sets by treatment for each age subset separately. The primary and secondary efficacy variables were planned to be summarised in the PP and ITT sets by treatment for the following additional subgroups where possible [47]:

- Type of dRTA (primary, secondary).

- SoC type, as determined by the World Health Organisation (WHO) Drug patient treatment, (considering the full patient treatment, e.g., citrate, bicarbonate, combination citrate + bicarbonate (naming SoC alkalising - SoCA), with sodium, potassium or both as cations (naming SoC cation – SoCC), with or without potassium supplement).
- Bicarbonataemia (according to the different methods of bioanalysis) [47].

For continuous efficacy variables, the mean treatment difference (ADV7103-SoC) was reported with its 95% CI. However, no formal statistical hypothesis testing was carried out, as the study was not powered for subgroup analyses) [47].

Subgroup analyses of primary and secondary endpoints by dRTA type were not performed, since only one enrolled patient had the acquired form of dRTA. Subgroup analyses of bicarbonataemia according to the different methods of bioanalysis, was also not performed, since intra-individual comparisons were carried out (therefore, the bioanalysis method was always the same for each patient) [47].

B22CS

The following subgroups of patients were defined for analysis [46]:

Subgroups by age, according to the following categories [46]:

- Subgroup 1: adults (≥18 years old).
- Subgroup 2: adolescents (12 to 17 years old).
- Subgroup 3: children (4 to 11 years old).
- Subgroup 4: infants and children (6 months to 3 years old).

As this disease is most often diagnosed from infancy (when it is of inherited aetiology), all paediatric subgroups of age in addition to adults had to be evaluated, in accordance with the guidance on clinical investigation of medicinal products in the paediatric population. This was also endorsed by the Paediatric Committee (PDCO) at the EMA as shown by the PIP agreed in 2014 and further modified (EMEA-001357-PIP01-12-M02)

- Subgroup analyses were performed on bicarbonataemia and kalaemia values issued from venous blood tests done before the morning study drug intake, kalaemia values issued from non-haemolysed blood samples and kalaemia values issued from non-haemolysed samples and blood tests done before the morning study drug intake. Note: No normal values were provided for capillary blood bicarbonate.
- Subgroup analyses were performed on the measurements using the same DXA features (equipment and adjustment).
- Subgroup analysis of data on pregnant women was planned to be performed, if relevant, as pregnancy has specific effects on calcium and phosphate metabolism, citraturia, urinary pH, and vitamin D production
- Subgroup analysis by type of dRTA (primary or secondary) was planned to be performed.

A summary of results for the subgroups in appendix E.

B.2.8 Meta-analysis

No meta-analyses were performed.

B.2.9 Indirect and mixed treatment comparisons

An indirect comparison of the mean pre-morning dose blood bicarbonate levels after 2 to 4 days of

treatment with ADV7103 to the historical baseline data in untreated patients reported in previous studies of eighteen adult and paediatric dRTA patients [51,52]. Their mean (SD) bicarbonate level prior to treatment was 16.1 (2.5) mmol/l. ADV7103 was compared to untreated patients using a two-sample t-test. The 95% CI for the mean difference was calculated. This analysis was performed in the PP and ITT sets.

Results of the two-sample t-tests showed that there were statistically significant differences between the treatment groups (ADV7103 and reference), with an estimated mean difference (95% CI) of 6.96 (5.6033, 8.3167) mmol/L for the PP set and of 6.915 (5.5632, 8.2669) mmol/L for the ITT set. These analyses showed statistical superiority of ADV7103 to reference (i.e., untreated patients).

Table 67: 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)

Source: B21CS CSR. Abbreviations: CI=confidence interval, ITT=intent-to-treat, LS=least square, N=total number of patients, PP=per protocol, SD=standard deviation

B.2.10 Adverse reactions

All clinical trials conducted for ADV7103 collected safety data.

- Study B03CS assessed during the study, the incidence of urine pH values > 8.0 over the course of the study, vital signs and ECG parameters: mean values and changes from baseline during the study, incidence of abnormal values after treatment.
- Study B21CS assessed the number/proportion of subjects presenting AE, incidence and severity of AE during the course of the study, gastrointestinal tolerability evaluated with appropriate scales (an FHS for the youngest and a VAS for the other subjects) at inclusion, on SP I day 5 and on SP III Day 5 and incidence of abnormal values on safety parameters after 5 days of treatment at steady state.
- Study B22CS assessed AEs and SAEs, physical examination (including body weight, height, BMI, hereditary target stature and Tanner stage if appropriate), vital signs and electrocardiograms (ECGs), and urine and blood laboratory tests.

Additionally, safety data has been collected for the patients on EAP.

B03CS

AE during the study

Study B03CS demonstrated that ADV7103 was well tolerated with very few TEAEs. Overall, ADV7103 was well tolerated and TEAEs were reported in a total of 5 (31.3%) subjects. Headache was the most frequently reported TEAE (3 [18.8%] subjects). Nausea, of mild intensity, was observed only in one subject treated with the highest dose of ADV7103 (50/100 mg/kg of CK/BK) and was the only treatment related TEAE reported during the study. There were no serious or severe TEAEs [48].

In

Table 68, six columns constitute the four ADV7103 dosing regimens plus two additional analyses of ADV7103 41.5/83.0 [+2h] and combined ADV7103 33.0/66.0. [+2h] means two hours after administration of the dose. A clinical laboratory evaluation (haematology, coagulation, blood chemistry

and urinalysis) was performed at screening, day-1 and day 7 of both SPs. In addition, kalaemia was performed at day 1, day 3 and day 5 2 hours after the morning IMP administration, of both study periods, and alkaline reserve and blood pH (on arterial blood) was performed at SP II day 5 2 hours after the morning IMP administration, only in the four subjects predetermined in the randomisation table.

Table 68: B03CS AE during the study

	Placebo N=8 n (%)	ADV7103 17.0/34.0 N=4 n (%)	ADV7103 33.0/66.0 N=4 n (%)	ADV7103 41.5/83.0 [+2h]* N=4 n (%)	ADV7103 41.5/83.0 N=4 n (%)	ADV7103 33.0/66.0 and 50.0/100.0 N=4 n (%)	ADV7103 50.0/100.0 N=4 n (%)	Total N=16 n (%)
Patients with AE(s)	1 (12.5%)	2 (50.0%)				1 (25.0%)	1 (25.0%)	5 (31.3%)
Conjunctivitis							1 (25.0%)	1 (6.3%)
Dizziness		1 (25.0%)						1 (6.3%)
Headache		2 (50.0%)				1 (25.0%)		3 (18.8%)
Lymphadenitis	1 (12.5%)							1 (6.3%)
Nausea							1 (25.0%)	1 (6.3%)

Source: B03CS CSR. Source: B22CS CSR. Abbreviations: AE = adverse events; h = hours; N, n = number of patients; Y = years.

* [+2h] = [+2h] = was used to indicate that ADV7103 was taken 2h after the meal and not before a meal as done for the other arms.. In the period 1 of the study, 3 different doses were evaluated with the same way of intake. In the period 2 of the study, the same dose was tested with three different ways of intake, including one arm with intake 2 hours after a meal.

The incidence of urine pH values > 8.0 over the course of the study

The number of urine collections presenting a pH value > 8.0 is equal to thirteen out of 1750 urine collections, i.e., an incidence of 0.7%.

Among these 13 values, only four were above 8.1 points of pH, without exceeding 8.25. The other values were between 8.00 and 8.10.

Four values were measured in the 0-2 hours post-dose urine collection, eight values were measured in the 2-4 hours post-dose urine collection, and three values were measured in the 4-6 hours post-dose urine collection. Among these 15 values, 9 were found for subjects taking the high dose of treatment (50/100 mg of ADV7103-CK/BK bidaily), 4 for subjects taking the intermediate dose of treatment (41,5/83 mg of ADV7103-CK/BK bidaily) and two for subjects taking the medium dose of treatment (33/66 mg of ADV7103-CK/BK bidaily).

The low incidence of urine pH values > 8.0 and the maximum value of 8.25 seem to indicate a good safety of ADV7103 concerning the risks associated with high urinary pH (for example urinary infections). Furthermore, no adverse event possibly linked to high urinary pH has been observed during the study.

Standard laboratory parameters and special laboratory parameters (such as kalaemia, blood pH, arterial alkaline reserve, urine electrolytes): mean values and changes from baseline

during the course of the study, incidence of abnormal values after treatment.

Kalaemia

Plasma potassium levels were within the normal range (i.e., 3.5-5.1 mmol/L) at all timepoints and with all doses and regimens of ADV7103, and mean changes from baseline were minimal showing no trend of increase with increasing dose. Only for one subject (Subject #001008) treated with ADV7103 41.5/83 mg/kg bidaily) (or 1.19 mEq/kg bidaily), blood potassium values were above the normal range on day 3 (i.e. 5.5 mmol/L) but reverted to normal in the control test performed shortly after on the same day (i.e. 4.8 mmol/L) [48].

Table 69: B03CS Kalaemia Safety Analysis [48]

Venous blood potassium, mmol/L	Day -1	Day 1a	Day 3a	Day 5a	Day 7
Placebo (n)	8	8	8	8	8
Mean (SD)	4.51 (0.364)	4.28 (0.354)	4.13 (0.205)	4.19 (0.352)	4.41 (0.264)
Median (Min, Max)	4.50 (4.1, 5.2)	4.15 (3.9, 4.8)	4.15 (3.9, 4.4)	4.10 (3.8, 4.8)	4.35 (4.1, 4.9)
Mean (SD) change from baseline	-	-0.138 (0.3021)	-0.288 (0.2748)	-0.225 (0.2712)	0.000 (0.2976)
ADV7103 17/34 mg/kg BID (n)	4	4	4	4	4
Mean (SD)	(0.216)	4.15 (0.191)	4.43 (0.250)	4.38 (0.263)	4.45 (0.311)
Median (Min, Max)	4.15 (4.0, 4.5)	4.20 (3.9, 4.3)	4.45 (4.1, 4.7)	4.45 (4.0, 4.6)	4.35 (4.2, 4.9)
Mean (SD) change from baseline	-	-0.050 (0.2380)	0.225 (0.4272)	0.175 (0.3862)	0.250 (0.3873)
ADV7103 33/66 mg/kg BID (n)	4	4	4	4	4
Mean (SD)	4.38 (0.287)	4.43 (0.150)	4.55 (0.300)	4.38 (0.222)	4.38 (0.096)
Median (Min, Max)	4.45 (4.0, 4.6)	4.50 (4.2, 4.5)	4.50 (4.3, 4.9)	4.30 (4.2, 4.7)	4.35 (4.3, 4.5)
Mean (SD) change from baseline	-	0.050 (0.3000)	0.175 (0.5852)	0.000 (0.2944)	0.000 (0.2944)
ADV7103 41.5/83.0 mg/kg BID [+2h] (n)	4	4	4	4	4
Mean (SD)	4.55 (0.351)	4.12 (0.479)	4.38 (0.299)	4.55 (0.387)	4.53 (0.562)
Median (Min, Max)	4.55 (4.2, 4.9)	4.00 (3.7, 4.8)	4.40 (4.0, 4.7)	4.45 (4.2, 5.1)	4.60 (3.9, 5.0)
Mean (SD) change from baseline	-	-0.425 (0.3500)	-0.175 (0.3403)	0.000 (0.3162)	-0.025 (0.2630)
ADV7103 41.5/83.0 mg/kg BID (n)	4	4	4	4	4
Mean (SD)	4.33 (0.206)	4.40 (0.082)	4.90 (0.432)	4.45 (0.129)	4.35 (0.342)
Median (Min, Max)	4.30 (4.1, 4.6)	4.40 (4.3, 4.5)	4.80 (4.5, 5.5)	4.45 (4.3, 4.6)	4.40 (3.9, 4.7)
Mean (SD) change from baseline	-	-0.033 (0.2309)	0.300 (0.1000)	0.000 (0.2000)	-0.033 (0.4041)
ADV7103 33/66 mg/kg (AM) and 50/100 mg/kg (PM) (n)	4	4	4	4	4
Mean (SD)	4.25 (0.238)	4.38 (0.386)	4.15 (0.289)	4.43 (0.479)	4.08 (0.236)
Median (Min, Max)	4.35 (3.9, 4.4)	4.55 (3.8, 4.6)	4.15 (3.8, 4.5)	4.40 (3.9, 5.0)	4.00 (3.9, 4.4)
Mean (SD) change from baseline	-	0.12 (0.1708)	-0.100 (0.2160)	0.175 (0.3500)	-0.175 (0.2754)
ADV7103 50/100 (n)	4	4	4	4	4

Venous blood potassium, mmol/L	Day -1	Day 1a	Day 3a	Day 5a	Day 7
Mean (SD)	4.28 (0.206)	4.23 (0.330)	4.55 (0.465)	4.55 (0.412)	4.30 (0.346)
Median (Min, Max)	4.30 (4.0, 4.5)	4.20 (3.9, 4.6)	4.55 (4.1, 5.0)	4.50 (4.2, 5.0)	4.30 (4.0, 4.6)
Mean (SD) change from baseline	-	-0.050 (0.3697)	0.275 (0.3500)	0.275 (0.2872)	0.025 (0.2500)

Source: B03CS CSR. Abbreviations: AM: anti-meridiem, BID: twice daily, Max: maximum, Min: minimum, n: number of subjects, PM: post meridiem, SD: standard deviation

Blood pH

Overall, mean (SD) arterial blood pH was within the normal range (i.e., 7.35-7.45), and similar at Baseline and Day 5 with either dose of ADV7103:

- 7.405 (0.0071) vs. 7.435 (0.0212) with ADV7103 41.5/83.0 mg/kg BID.
- 7.425 (0.0354) vs. 7.435 (0.0071) with 33/66 mg/kg (morning) and 50/100 mg/kg (evening) [48].

Table 70: B03CS Arterial blood pH [48]

	Day 1	Day 5
ADV7103 41.5/83.0 mg/kg BID (n)	2	2
Mean (SD)	7.405 (0.0071)	7.435 (0.0212)
Median (Min, Max)	7.405 (7.40, 7.41)	7.435 (7.42, 7.45)
Mean (SD) change from baseline	-	0.030 (0.0141)
ADV7103 33/66 mg/kg (AM) and 50/100 mg/kg (PM) (n)	2	2
Mean (SD)	7.425 (0.0354)	7.435 (0.0071)
Median (Min, Max)	7.425 (7.40, 7.45)	7.435 (7.43, 7.44)
Mean (SD) change from baseline	-	0.010 (0.0283)

Source: B03CS CSR. Abbreviations: AM: anti-meridiem, BID: twice daily, Max: maximum, Min: minimum, n: number of subjects, PM: post meridiem, SD: standard deviation. [a] at 2 hours after the morning dose

Alkaline reserve

Arterial alkaline reserve (assessed in subjects treated with medium or high doses of ADV7103 at Days -1 and 5 at 2 hours after the morning dose), and corresponding mean changes from baseline are presented in Table 71.

Overall, mean (SD) arterial alkaline reserve was similar at Baseline and Day 5 with either doses of ADV7103:

- 25.15 (2.192) mmol/L vs. 26.30 (4.243) with ADV7103 41.5/83.0 mg/kg BID
- 26.15 (1.768) mmol/L vs. 26.75 (1.909) mmol/L with 33/66 mg/kg (morning) and 50/100 mg/kg (evening) [48].

Table 71: B03CS Arterial alkaline reserve[48]

mmol/L	Day -1	Day 5 [a]
ADV7103 41.5/83.0 mg/kg BID (n)	2	2
Mean (SD)	25.15 (2.192)	26.30 (4.243)
Median (Min, Max)	25.15 (23.6, 26.7)	26.30 (23.3, 29.3)
Mean (SD) change from baseline	-	1.15 (2.051)
ADV7103 33/66 mg/kg (AM) and 50/100 mg/kg (PM) (n)	2	2

mmol/L	Day -1	Day 5 [a]
Mean (SD)	26.15 (1.768)	26.75 (1.909)
Median (Min, Max)	26.15 (24.9, 27.4)	26.75 (25.4, 28.1)
Mean (SD) change from baseline	-	0.60 (0.141)

Source: B03CS CSR. Abbreviations: AM: anti-meridiem, BID: twice daily, Max: maximum, Min: minimum, n: number of subjects, PM: post meridiem, SD: standard deviation
[a] at 2 hours after the morning dose

Urine electrolytes, citraturia and creatininuria

Compared to baseline increases were observed for:

- Urine citric acid (normal values: 1.5-4.58 mmol/24h), with mean (SD) values ranging from 2.438 (0.1624) mmol/24h at baseline to 4.465 (0.6223) mmol/24h at day 4 and 5.148 (0.4861) mmol/24h at day 5 (i.e. approximately a 2-fold increase), in line with the PD of the product [48].
- Urine potassium (normal values: 25-125 mmol/24h), with mean (SD) values ranging from 79.3 (45.81) mmol/24h at baseline to 185.8 (15.44) mmol/24h at day 4 and 195.5 (43.44) mmol/24h at day 5 (i.e. approximately a 2 to 2.5-fold increase), in line with the PD of the product [48].

Compared to baseline, decreases were observed for:

- Urine calcium (normal values: 2.5-7.5 mmol/24h), from 4.893 (1.4951) mmol/24h at baseline to 2.813 (1.0025) mmol/24h at day 4 and 3.133 (0.6965) mmol/24h at day 5 (i.e. approximately a 1.5 to 2-fold decrease), in line with the PD of the product [48].
- Urine phosphate (normal values: 13-42 mmol/24h), from 40.05 (36.866) mmol/24h at baseline to 19.98 (2.900) mmol/24h at day 4 and 20.28 (3.514) mmol/24h at day 5 (i.e. approximately a 2-fold decrease) [48].
- Urine sodium (normal values: 40-220 mmol/24h), from 199.3 (111.33) mmol/24h at baseline to 151.5 (37.61) mmol/24h at day 4 and 153.3 (61.78) mmol/24h at day 5 (i.e. approximately a 1.3-fold decrease) [48].

Overall, urine creatinine remained stable throughout the study and urine chloride stayed within the normal range (110-250 mmol/24h) [48].

Table 72: B03CS 24-hour urine chemistry with ADV7103 50/100 mg/kg BID [48]

Urine parameter	Day -1	Day 4	Day 5
Calcium (mmol/24h)	n=4	n=4	n=4
Mean (SD)	4.893 (1.4951)	2.813 (1.0025)	3.133 (0.6965)
Median (Min, Max)	5.435 (2.70, 6.00)	2.790 (1.94, 3.73)	2.975 (2.47, 4.11)
Mean (SD) change from	-	-2.080 (1.4100)	-1.760 (1.6404)
Chloride (mmol/24h)	n=4	n=4	n=4
Mean (SD)	176.0 (95.22)	149.8 (36.72)	162.8 (58.50)
Median (Min, Max)	178.5 (71, 276)	144.0 (112, 199)	164.5 (100, 222)
Mean (SD) change from	-	-26.3 (87.79)	-13.3 (109.04)
Citric acid (mmol/24h)	n=4	n=4	n=4
Mean (SD)	2.438 (0.1624)	4.465 (0.6223)	5.148 (0.4861)
Median (Min, Max)	2.420 (2.26, 2.65)	4.285 (3.99, 5.30)	5.330 (4.43, 5.50)
Mean (SD) change from	-	2.028 (0.6874)	2.710 (0.4715)
Creatinine (mmol/24h)	n=4	n=4	n=4
Mean (SD)	11965.0 (3818.83)	11895.0 (2785.26)	12695.5 (3037.07)
Median (Min, Max)	12036.0 (7218, 16570)	12257.0 (8368, 14698)	12306.0 (9754, 16416)
Mean (SD) change from	-	-70.0 (1600.03)	730.5 (1772.12)
Phosphate (mmol/24h)	n=4	n=4	n=4
Mean (SD)	40.05 (36.866)	19.98 (2.900)	20.28 (3.514)
Median (Min, Max)	25.45 (14.5, 94.8)	19.45 (17.5, 23.5)	20.35 (15.9, 24.5)
Mean (SD) change from	-	-20.075 (38.6394)	-19.775 (39.6447)
Potassium (mmol/24h)	n=4	n=4	n=4
Mean (SD)	79.3 (45.81)	185.8 (15.44)	195.5 (43.44)
Median (Min, Max)	70.0 (37, 140)	189.0 (166, 199)	189.5 (149, 254)
Mean (SD) change from	-	106.5 (55.94)	116.3 (72.56)
Sodium (mmol/24h)	n=4	n=4	n=4
Mean (SD)	199.3 (111.33)	151.5 (37.61)	153.3 (61.78)
Median (Min, Max)	208.5 (80, 300)	150.0 (107, 199)	147.0 (89, 230)
Mean (SD) change from baseline	-	-47.8 (117.60)	-46.0 (142.79)

Source: B03CS CSR. Abbreviations: BID: twice daily, Max: maximum, Min: minimum, n: number of subjects, SD: standard deviation

Vital signs

Vital signs (SBP, DBP, HR, RR and body temperature) were either normal or NCS abnormal, and changes from baseline were minimal. ECG readings were either normal of NCS abnormal, and changes from baseline were small [48].

B21CS

Number/proportion of patients with TEAEs, incidence and severity of these TEAEs during the study.

Regardless of the SP, TEAEs were reported in a total of 24 (64.9%) patients, with gastrointestinal disorders being the most common SoC for TEAEs [47].

Overall, regardless of the SP, the most frequently reported TEAEs (in >10% of the patients) were

abdominal pain (in 8 [21.6%] patients), headache (in 6 [16.2%] patients), abdominal pain upper (in 5 [13.5%] patients), and fatigue (in 4 [10.8%] patients). Apart from abdominal pain and abdominal pain upper, other TEAEs from the Gastrointestinal Disorders SoC reported in >1 patient included diarrhoea and vomiting (each in 3 [8.1%] patients), and nausea (in 2 [5.4%] patients) [47].

Abdominal pain was the most frequently reported TEAE in adults and adolescents (overall in 4 [57.1%] and 3 [30.0%] patients, respectively) and in the overall population as well (in 8 [21.6%] patients).

Table 73: Number/proportion of patients with TEAEs

	SPI SoC steady state	**SPII ADV7103 titration**	**SPIII ADV7103 steady state**	**Total**
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%)

Abbreviations: n: number of patients with at least one adverse event, N: number of patients by study period or overall, SoC: system organ class, PT: preferred term, SP: study period, TEAE: treatment-emergent adverse event. A patient with multiple occurrences of a TEAE is counted only once in the PT category. A patient with multiple TEAEs within a SoC was counted only once in the "Total" row.

A summary of TEAEs is presented for each SP and overall, by age subset in Table 74.

Table 74: TEAEs (SA set)

	SP I[a] n (%)	SP II[b] n (%)	SP III[c] n (%)	Total n (%)
Adults, ≥18, years old	**N=7**	**N=7**	**N=7**	**N=7**
TEAEs	2 (28.6%)	5 (71.4%)	1 (14.3%)	6 (85.7%)
Serious TEAEs	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Treatment-related TEAEs	2 (28.6%)	3 (42.9%)	0 (0.0%)	4 (57.1%)
Severe TEAEs	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TEAEs leading to discontinuation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Adolescents, from 12-17 years inclusive	**N=10**	**N=10**	**N=8**	**N=10**
TEAEs	3 (30.0%)	7 (70.0%)	0 (0.0%)	8 (80.0%)
Serious TEAEs	0 (0.0%)	1 (10.0%)	0 (0.0%)	1 (10.0%)
Treatment-related TEAEs	2 (20.0%)	3 (30.0%)	0 (0.0%)	4 (40.0%)
Severe TEAEs	0 (0.0%)	1 (10.0%)	0 (0.0%)	1 (10.0%)
TEAEs leading to discontinuation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Children, from 4-11 years inclusive	**N=15**	**N=14**	**N=14**	**N=15**
TEAEs	1 (6.7%)	5 (35.7%)	3 (21.4%)	6 (40.0%)
Serious TEAEs	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Treatment-related TEAEs	0 (0.0%)	3 (21.4%)	1 (7.1%)	3 (20.0%)
Severe TEAEs	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TEAEs leading to discontinuation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Infants, from 6 months-3 years old inclusive	**N=5**	**N=3**	**N=3**	**N=5**
TEAEs	1 (20.0%)	2 (66.7%)	2 (66.7%)	4 (80.0%)
Serious TEAEs	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Treatment-related TEAEs	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe TEAEs	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TEAEs leading to discontinuation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Overall	**N=37**	**N=34**	**N=32**	**N=37**
AEs	7 (18.9%)	19 (55.9%)	6 (18.8%)	24 (64.9%)
Serious TEAEs	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.7%)
Treatment-related TEAEs	4 (10.8%)	9 (26.5%)	1 (3.1%)	11 (29.7%)
Severe TEAEs	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.7%)
TEAEs leading to discontinuation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: B21CS CSR. Abbreviations: N = number, TEAE = treatment emergent adverse events.

The TEAEs reported in SP I and SP III are presented together, as during these SPs treatments were taken in the same conditions (5-day steady state periods). The TEAEs reported during SP II are presented separately, as this SP was a dose finding period of flexible duration (up to 30 days) for which more TEAEs were expected.

Overall, a total of 24 (64.9%) patients experienced at least one TEAE during the study.

- SP I and SP III – The proportion of patients experiencing TEAEs was similar in SP I and SP III (7 [18.9%] and 6 [18.8%] patients, respectively).
- SP II – 19 (55.9%) patients experienced TEAEs.

Overall, 11 (29.7%) patients were reported with treatment-related TEAEs:

- SP I and SP III – The proportion of patients with treatment-related TEAEs was lower in SP III (1 [3.1%] patient) than in SP I (4 [10.8%] patients).
- SP II – 9 (26.5%) patients experienced treatment-related TEAEs.

Severe TEAEs were reported in only 1 (2.9%) patient during SP II. A serious TEAE was reported in 1 (2.9%) patient during SP II, and it was not considered as related to the treatment. There were no TEAEs leading to discontinuation and no deaths during the study.

Age subsets

Table 75 presents TEAEs associated with ADV7103 in study B21CS, according to age subset.

Table 75: B21CS TEAEs according to subset of treatment population

Subset	SPI and SPIII	SPII	Comment
Adult	As in the overall study population, the proportion of patients experiencing TEAEs was similar in SP I and SP III (2 [28.6%] patients and 1 [14.3%] patient, respectively). Treatment-related TEAEs were reported only in SP I, in 2 (28.6%) patients.	TEAEs were reported in 5 (71.4%) patients, and treatment related TEAEs in 3 (42.9%) patients.	There were no serious TEAEs or severe TEAEs reported in this age subset.
Adolescents	TEAEs and treatment related TEAEs were reported only in SP I in 3 (30.0%) patients and 2 (20.0%) patients, respectively.	TEAEs were reported in 7 (70.0%) patients, and treatment related TEAEs in 3 (30%) patients. One (10.0%) patient experienced two severe TEAEs (one possibly related and the other unlikely related to the treatment), and 1 (10.0%) patient experienced a serious TEAE (unrelated to the treatment). These events accounted for all serious and severe TEAEs reported during the study.	
Children	The proportion of patients experiencing TEAEs was higher in SP III (3 [21.4%] patients) than SP I (1 [6.7%] patient). Treatment-related TEAEs were reported only in 1 (7.1%) patient in SP III.	TEAEs were reported in 5 (35.7%) patients, and treatment related TEAEs in 3 (21.4%) patients.	There were no severe or serious TEAEs reported in this age subset.
Infants	The proportion of patients experiencing TEAEs was slightly lower in SP I than in SP III (1 [20.0%] patient vs. 2 [66.7%] patients).	TEAEs were reported in 2 (66.7%) patients.	There were no treatment related TEAEs, and no severe or serious TEAEs reported in this age subset.
TEAE = Treatment Emergent Adverse Events, SP = Study Period			

Gastrointestinal tolerability

Gastrointestinal tolerability evaluated with age-appropriate scales: a FHS for the 4-11-year-old children and a 100mmVisual Analogue Scale (VAS) ranging from zero “no complaint” to 100

“extremely severe complaint” for the other patients) at inclusion, on SP I Day 5 (Visit 2) and SP III Day 5 (Visit 3).

Overall, ADV7103 had a very good gastrointestinal tolerability. A higher number of patients had no gastrointestinal complaint with ADV7103 treatment in SPIII than with SoC treatment in SPI (24 [75.0%] vs. 18 [51.4%] patients). On the other hand, patients with gastrointestinal discomfort of any severity were fewer with ADV7103 treatment in SPIII than with SoC treatment in SPI: 8 (25.0%) patients vs. 17 (48.6%) patients [47].

According to a mixed model with treatment as a fixed factor and patient as a random effect in the acceptability analysis set, there was a statistically significant decrease in severity of intestinal discomfort with ADV7103 compared to SoC, with a mean score difference of -14.237 mm (95% CI: -25.9196, -2.5545) [47].

Incidence of abnormal values of: Venous blood chemistry, at the screening visit (visit 1, day 1) and day 5 of SP I and SP III (Urea/Blood Urea Nitrogen, urate, creatinine, creatinine clearance, total protein, albumin, serum electrolytes (potassium, sodium, chloride, calcium, magnesium, bicarbonate, phosphorus). Bone alkaline phosphatases, 25-hydroxy-vitamin D, 1α,25-dihydroxy-vitamin D, parathormone, new bone marker).

Overall, the assessed safety blood chemistry parameters of safety did not change in a CS manner from Screening to Day 5 of SPI and SPIII [47].

Urine chemistry

Urine chemistry, at the screening visit (visit 1, day 1) and day 5 of SP I and SP III: pH, specific gravity, bicarbonate, creatinine, urea, citrate, potassium, sodium, chloride, calcium, magnesium and phosphate and crystalluria.

Overall, only small differences could be observed between the mean (SD) levels of the tested safety urine chemistry parameters at t0h day 5 of SPI and SPIII. Urine potassium increased with ADV7103 but not after SoC treatment, due to the higher load of potassium provided with ADV7103 (mean (SD) dose: 105.41 (59.151) mmol/day) than with SoC (mean (SD) dose: 63.9 (58.54) mmol/day) to maintain normal kalaemia [47].

Urine sodium level was lower with ADV7103 treatment than with SoC treatment, as expected, since SoC includes sodium salts, particularly in infants who were treated exclusively with sodium bicarbonate, while ADV7103 is devoid of sodium [47]**.**

Table 76: B21CS Urine chemistry [47]

Overall (N=37)			
	Screening	**SPI SoC steady state t0h day 5**	**SPIII ADV7103 steady state t0h day 5**
Bicarbonate (mmol/L)	n=11	n=10	n=11
Mean (SD)	21.25 (12.431)	18.54 (8.279)	23.73 (10.537)
Median (Min, Max)	15.00 (11.0, 53.0)	19.50 (4.6, 32.0)	18.00 (15.0, 43.0)
Sodium (mmol/L)	n=32	n=31	n=31
Mean (SD)	78.58 (34.109)	85.28 (39.654)	66.65 (29.599)
Median (Min, Max)	79.50 (31.0, 155.0)	84.00 (5.0, 151.0)	64.00 (11.0, 135.1)
Potassium (mmol/L)	n=32	n=34	n=31
Mean (SD)	65.19 (29.296)	50.37 (25.974)	87.25 (45.726)
Median (Min, Max)	61.00 (18.6, 123.0)	46.50 (1.0, 100.0)	83.00 (30.0, 213.6)
Magnesium (mmol/L)	n=30	n=31	n=29
Mean (SD)	1.88 (0.930)	2.25 (0.971)	2.46 (1.169)

Overall (N=37)			
	Screening	**SPI SoC steady state t0h day 5**	**SPIII ADV7103 steady state t0h day 5**
Median (Min, Max)	1.76 (0.2, 4.9)	2.10 (0.8, 4.9)	2.17 (1.0, 5.8)
Urea (mmol/l)	n=30	n=34	n=30
Mean (SD)	157.86 (72.077)	152.49 (58.274)	163.34 (57.784)
Median (Min, Max)	139.00 (58.0, 373.0)	144.55 (70.0, 295.0)	156.50 (42.0, 331.0)
Creatinine (µmol/L)	n=32	n=34	n=29
Mean (SD)	4438.72 (2469.601)	4368.66 (2377.423)	4423.99 (2071.062)
Median (Min, Max)	3850.00 (1040.0, 9850.0)	3700.00 (1178.0, 9170.0)	3680.00 (1440.0, 8800.0)

Source: B21CS CSR. Abbreviations: Max: maximum, Min: minimum, SD: standard deviation, SP: study period

With regards to missing observations for blood bicarbonate data, the pre-analytical procedure to handle urine sample in the aim to analyse urine bicarbonate is very sensitive, as anaerobic conditions are key to measure accurately the level of bicarbonate, very instable parameter that turns into carbon dioxide gas quickly. Therefore, a urine collection under paraffin or in a vacuum sterile container is required. When collected under oil, any remaining oil in the aliquot risks to damage the equipment used for the urine analysis. In any case, air bubbles must be avoided in the aliquot used for analysis. Nowadays, this analysis is rarely performed in current practice. For these reasons, the laboratories of the investigator's sites were reluctant or not able to perform this analysis.

If one or several of the three bicarbonate blood levels at Day2 t0, day 3 t0 and day 4 t0 were missing, the following replacement procedure was used:

- Identify a possible replacement set for the missing data. This set included any additional bicarbonate blood levels on day 1 t0, day 5 t0, or day 5 t24h, in the same SP, that was not missing if it was quantified strictly in the same conditions as for the primary timepoints. This means, using the same analysis laboratory, the same analysis method, the same equipment, and the same normal ranges as for day 2 t0, day 3 t0 and day 4 t0.
- Replace any missing value(s) from the primary set in their order of appearance (i.e., first day 2 t0, then day 3 t0 and finally day 4 t0) by the first available values in the replacement set. The order of priority for the replacement set is day 1 t0, day 5 t0, day 5 t24h.

After the replacement procedure, any remaining missing samples were skipped when calculating the mean. If all the three samples were still missing, the average was reported as missing.

The individual differences (ADV7103 – SoC) in the mean of the three-pre-morning dose blood bicarbonate levels on day 2 (t0), day 3 (t0) and day 4 (t0) were analysed in the PP set with a one-sided one-sample t-test.

Urine analysis (pH, leucocytes, glucose, ketones, protein, blood) at the screening visit (Visit 1, Day 1) and Day 5 of SP III (end of study).

Results of urinalysis were either negative or abnormal NCS in all cases. Overall mean (SD) urine pH values were always >7: 7.61 (0.557) at screening, 7.60 (0.602) at t0h day 5 of SPI and 7.78 (0.599) at t0h day 5 of SPIII. Similar results were obtained in each age subset.

A complete physical examination was performed at screening (visit 1, day 1) and day 5 of SP III (end of study). Physical examination findings were either normal or NCS abnormal [47].

B22CS

The primary endpoint in this study was the number/percentage of patients presenting AEs during the study, including the incidence and severity of these events. AE were reported throughout the study up to the point of database lock for this analysis, from baseline (visit 1, M1 [Inclusion]) to M48.

A single AE was not a TEAE; an abdominal pain judged as not related to study drug started in the B21CS study before entry into the B22CS extension study, and for which the intensity did not change.

Table 77 presents a summary of AEs. There were no TEAEs leading to permanent study drug discontinuation or withdrawal. There were three temporary discontinuations of treatment during the study. These were associated with eight TEAEs, and these discontinuations were limited to three to seven days. All discontinuations were all related to an occurrence of an episode of vomiting, irrespective if other AEs occurred at the same time.

Table 77: Study B22CS Summary of Adverse Events

	Adults >=18Y (N=6)		**Adolescents [12-18Y] (N=8)**		**Children [4-12Y] (N=13)**		**Infants [0.5-4Y] (N=3)**		**Overall (N=30)**	
	n (%)	**nae**	**n (%)**	**nae**	**n (%)**	**nae**	**n (%)**	**nae**	**n (%)**	**nae**
At least one TEAE	4 (66.7)	23	8 (100.0)	66	12 (92.3)	72	3 (100.0)	27	27 (90.0)	188
At least one TEAE by intensity										
Mild	4 (66.7)	17	8 (100.0)	43	11 (84.6)	57	3 (100.0)	18	26 (86.7)	135
Moderate	2 (33.3)	6	4(50.0)	22	6 (46.2)	13	2 (66.7)	8	14 (46.7)	49
Severe	0	0	1 (12.5)	1	1 (7.7)	2	1 (33.3)	1	3 (10.0)	4
At least one related TEAE	1 (16.7)	1	2 (25.0)	6	2 (15.4)	4	0	0	5 (16.7)	11
At least one SAE	1 (16.7)	1	4 (50.0)	6	3 (23.1)	4	2 (66.7)	2	10 (33.3)	13
At least one related SAE	0	0	0	0	0	0	0	0	0	0
TEAE leading to study drug interruption	0	0	2 (25.0)	8	0	0	0	0	2 (6.7)	8
AE leading to death	0	0	0	0	0	0	0	0	0	0

Source: Study B22CS CSR. Abbreviations: 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. (%): (n/N)*100.

A summary of all TEAEs reported in the 48 months of the OLE is presented overall and for all SoC per 6-month period in Table 78. Overall, during the 48 months of study, and per 6-month period, between 9 (33.3%) and 17 (56.7%) patients reported TEAEs, between 4 (14.8%) and 1 (3.3%) patient reported GI disorders, and between 0 (0.0%) and 2 (6.7%) patients reported treatment-related TEAEs all GI disorders. There is no pattern of increasing TEAES (treatment-related or not) with increasing duration of exposure to ADV7103.

Table 78: Study B22CS TEAEs Affecting ≥2 patients Overall by System Organ Class and Preferred Term

	Adults >=18Y (N=6)		Adolescents [12-18Y] (N=8)		Children [4-12Y] (N=13)		Infants [0.5-4Y] (N=3)		Overall (N=30)	
SoC/PT	**n (%)**	**nae**	**n (%)**	**nae**	**n (%)**	**nae**	**n (%)**	**nae**	**n (%)**	**nae**
All All	4 (66.7)	23	8 (100.0)	66	12 (92.3)	72	3 (100.0)	27	27 (90.0)	188
GI disorders										
All	2 (33.3)	3	7 (87.5)	22	6 (46.2)	13	1 (33.3)	6	16 (53.3)	44
Abdominal pain	1 (16.7)	2	1 (12.5)	1	2 (15.4)	3	1 (33.3)	1	5 (16.7)	7
Abdominal pain upper	0	0	2 (25.0)	2	1 (7.7)	1	0	0	3 (10.0)	3
Diarrhoea	0	0	2 (25.0)	6	2 (15.4)	2	1 (33.3)	1	5 (16.7)	9
Dyspepsia	1 (16.7)	1	1 (12.5)	1	1 (7.7)	1	0	0	3 (10.0)	3
Nausea	0	0	1 (12.5)	1	2 (15.4)	2	1 (33.3)	2	4 (13.3)	5
Vomiting	0	0	4 (50.0)	6	3 (23.1)	4	1 (33.3)	2	8 (26.7)	12
General disorders and administration site conditions										
All	1 (16.7)	2	0	0	0	0	1 (33.3)	1	2 (6.7)	3
Pyrexia	1 (16.7)	2	0	0	0	0	1 (33.3)	1	2 (6.7)	3
Infections and infestations										
All	2 (33.3)	4	1 (12.5)	6	6 (46.2)	22	2 (66.7)	11	11 (36.7)	43
Bronchitis	1 (16.7)	1	1 (12.5)	2	0	0	0	0	2 (6.7)	3
Gastro-enteritis	0	0	0	0	0	0	2 (66.7)	4	2 (6.7)	4
Influenza	0	0	1 (12.5)	2	0	0	1 (33.3)	2	2 (6.7)	4
Naso-pharyngitis	1 (16.7)	1	0	0	3 (23.1)	3	1 (33.3)	1	5 (16.7)	5
Rhinitis	0	0	1 (12.5)	1	2 (15.4)	2	0	0	3 (10.0)	3
Tinea infection	0	0	0	0	2 (15.4)	2	0	0	2 (6.7)	2
Urinary tract infection	1 (16.7)	1	0	0	1 (7.7)	1	0	0	2 (6.7)	2
Vitamin D deficiency										
All	2 (33.3)	2	6 (75.0)	19	8 (61.5)	9	2 (66.7)	5	18 (60.0)	35
Decreased appetite	0	0	2 (25.0)	2	0	0	0	0	2 (6.7)	2
Hypokalaemia	1 (16.7)	1	3 (37.5)	3	1 (7.7)	1	0	0	5 (16.7)	5
Iron deficiency	0	0	0	0	3 (23.1)	3	1 (33.3)	1	4 (13.3)	4

	Adults >=18Y (N=6)		Adolescents [12-18Y] (N=8)		Children [4-12Y] (N=13)		Infants [0.5-4Y] (N=3)		Overall (N=30)	
Vitamin D deficiency	1 (16.7)	1	6 (75.0)	12	4 (30.8)	4	2 (66.7)	2	13 (43.3)	19

Abbreviations: N, n = number of patients; nae = number of adverse events; PT = preferred term; SoC = system organ class; TEAE = treatment-emergent adverse event; Y = years.

A total of 188 TEAEs were experienced by 27 patients overall (90.0%); 23 TEAEs in four adult patients (66.7%), 66 TEAEs in eight adolescents (100.0%), 72 TEAEs in twelve children (92.3%) and 27 TEAEs in three infants (100.0%) (Table 78).

The most common TEAEs were metabolism and nutrition disorders; 35 TEAEs in eighteen patients (60.0%) overall. Of the eighteen patients reporting TEAEs in this body system, 13 (43.3%) had vitamin D deficiency (one adult, six adolescents, four children and two infants). There were also five patients with hypokalaemia (one adult, three adolescents, and one child), four patients with iron deficiency (three children and one infant), and two adolescents with decreased appetite.

TEAEs were common in the SoC GI disorders; 44 TEAEs in sixteen patients (53.3%) overall. The majority of these were cases of vomiting, abdominal pain, or diarrhoea. Eight (26.7%) patients (four adolescents, three children and one infant) reported twelve episodes of vomiting. Five (16.7%) patients (one adult, one adolescent, two children and one infant) reported seven episodes of abdominal pain. Five (16.7%) patients (two adolescents, two children and one infant) reported nine episodes of diarrhoea. Four (13.3%) patients (one adolescent, two children, and one infant) reported five episodes of nausea. There were also three (10.0%) patients (two adolescents and one child) with abdominal pain upper, and three (10.0%) patients (one adult, one adolescent, and one child) with dyspepsia.

TEAEs were quite common in the SoC Infections and infestations; 43 TEAEs were reported in eleven patients (36.7%) overall and were very varied. Five (16.7%) patients (one adult, three children, and one infant) reported five episodes of nasopharyngitis. Three (10.0%) patients (one adolescent and two children) reported three episodes of rhinitis. Other TEAEs of bronchitis, gastroenteritis, influenza, tinea infection, and urinary tract infection were reported in two patients each. TEAEs of the urine sphere (known as site of infections in dRTA patients) were limited, two patients (one adult and one child) had a urinary tract infection, one child had four episodes of pyelonephritis (three within four months then one a year later) and one child had an asymptomatic bacteriuria.

In the musculoskeletal and connective tissue disorders SoC there were 11 TEAEs reported in nine patients (30.0%). Four (13.3%) patients (two adults and two children) reported five episodes of back pain. Three (10.0%) patients (one adolescent, one child and one infant) reported three episodes of pain in extremity.

TEAEs were also quite common in the SoC Renal and urinary disorders; 17 TEAEs were reported in nine patients overall (30.0%). Three (10.0%) patients (one adult and two children) reported three episodes of renal colic, and two (6.7%) patients (one adult and one child) reported six episodes of nephrolithiasis. No TEAEs affecting the renal system were deemed to be related to study drug, and none resulted in a change in dose.

One adult reported five episodes of nephrolithiasis; three of which were moderate, and two were mild. All were resolved. One child reported one episode of nephrolithiasis of mild severity, and not resolved at the end of the study.

One adult reported renal colic (moderate severity) and calculus urinary (mild severity). Both events resolved without changing the dose of study drug. One child reported an episode of renal colic of moderate severity, which resolved without change to dose. The same patient reported three separate episodes of haematuria, the first one of mild severity, and then two others two years later of moderate severity. The last episode was not resolved at the end of the study. One child (Patient 013-002) also

had one episode of renal colic of moderate severity

In addition, two adolescents had one episode each of anuria (moderate severity) and hypocitraturia (mild severity), and two children had one episode each of dysuria and hypercalciuria (both mild severity). None was related to study drug.

Most of the TEAEs were of mild intensity: 26 patients overall (86.7%) reported 135 TEAEs of mild intensity.

There were 49 TEAEs of moderate severity reported in 14 (46.7%) patients overall. The TEAEs of moderate severity were most commonly from the SoC Renal and urinary disorders; nine TEAEs of moderate severity were reported in five (16.7%) patients overall. Three (10.0%) patients (one adult and two children) reported three episodes of renal colic, one adult reported three episodes of nephrolithiasis, one child reported two episodes of haematuria, and one adolescent reported one episode of anuria.

There were four severe TEAEs affecting three patients in the study: one case of decreased appetite in the adolescent group, two cases of unilateral deafness affecting one child, and one case of gastroenteritis rotavirus in the infant group. None of the severe TEAEs was considered related to study drug.

Eleven TEAEs in five patients (16.7%) were considered treatment-related, all in the SoC of GI disorders. One adolescent had three episodes of diarrhoea, one episode of GI disorder, and one episode of GI pain. One child had one episode of abdominal pain, abdominal pain upper, and dyspepsia. One child had one episode of abdominal pain. One adolescent had one episode of abdominal pain upper. One adult had one episode of dyspepsia.

All related TEAEs were all mild in severity except for the GI disorder and one of the cases of diarrhoea, which were of moderate severity. None of these related TEAEs required an IMP dose change, except for the GI disorder in an adolescent for whom the daily dose was reduced by 16 mEq while blood and renal metabolic markers were maintained in normal ranges. All these related TEAEs were resolved apart from the case of abdominal pain upper and one case of dyspepsia, both in one child for four months up to M48.

A summary of all TEAEs (not treatment-related and treatment-related) reported in the 48 months of the OLE is presented overall and for all SoC per 6-month period in Table 79. Overall, during the 48 months of study, and per 6-month period, between 9 (33.3%) and 17 (56.7%) patients reported TEAEs, between 4 (14.8%) and 1 (3.3%) patient reported GI disorders, and between 0 (0.0%) and 2 (6.7%) patients reported treatment-related TEAES all GI disorders. There is no pattern of increasing TEAES (treatment-related or not) with increasing duration of exposure to ADV7103.

Table 79: TEAEs per 6-month period – Safety Analysis Set

Overall	**M1-M6**		**M6-M12**		**M12-M18**		**M18-M24**		**M24-M30**		**M30-M36**		**M36-M42**		**M42-M48**	
N	**30**		**30**		**30**		**29**		**29**		**29**		**27**		**27**	
SoC*	**n (%)**	**nae**	**n (%)**	**nae**	**n (%)**	**nae**	**n (%)**	**nae**	**n (%)**	**nae**	**n (%)**	**nae**	**n (%)**	**nae**	**n (%)**	**nae**
ALL disorders	13 (43.3)	28	17 (56.7)	24	13 (43.3)	19	15 (51.7)	28	12 (41.4)	20	10 (34.5)	15	9 (33.3)	16	10 (37.0)	25
Ear and labyrinth	0 0.0)	0	0 0.0)	0	0 0.0)	0	0(0.0)	0	1 (3.4)	2	0 0.0)	0	0 (0.0)	0	2 (7.4)	4
Endocrine	0 (0.0)	0	0 (0.0)	0	1 (3.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
GI	4 (13.3)	6	4 (13.3)	5	3 (10.0)	3	4 (13.8)	5	4 (13.8)	4	1 (3.4)	1	3 (11.1)	6	4 (14.8)	11
General and administration site	0 (0.0)	0	0 (0.0)	0	1 (3.3)	1	0 (0.0)	0	0 (0.0)	0	1 (3.4)	1	1(3.7)	1	0(0.0)	0
Immune system	1 (3.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Infections and infestations	3 (10.0)	3	6 (20.0)	8	6 (20.0)	8	4 (13.8)	9	2 (6.9)	3	4 (13.8)	5	2 (7.4)	2	2 (7.4)	4
Injury, poisoning and procedural complications	0 (0.0)	0	1 (3.3)	1	1 (3.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Investigations	0(0.0)	0	1 (3.3)	1	0 (0.0)	0	1 (3.4)	1	0 (0.0)	0	2 (6.9)	2	1 (3.7)	1	1(3.7)	1
Metabolism and nutrition	7 (23.3)	9	4 (13.3)	4	1 (3.3)	1	4 (13.8)	4	6 (20.7)	6	2 (6.9)	2	3 (11.1)	3	3 (11.1)	3
Nervous system	1 (3.3)	1	0 (0.0)	0	0 (0.0)	0	2 (6.90	2	2 (6.9)	2	0 (0.0)	0	1 (3.7)	1	0 (0.0)	0
Psychiatric	0 (0.0)	0	0 (0.0)	0	1 (3.3)	1	0 (0.0)	0	0 (0.0)	0	0(0.0)	0	0 (0.0)	0	0(0.0)	0
Renal and urinary	2 (6.7)	2	2 (6.7)	2	1 (3.3)	1	3 (10.3)	3	2 (6.9)	2	2 (6.9)	2	0 (0.0)	0	2(7.4)	2
Reproductive system and breast	1 (3.3)	1	0 (0.0)	0	0 (0.0)	0	1 (3.4)	1	0 (0.0)	0	0 (0.0)	0	1 (3.7)	1	0(0.0)	0

Skin and subcutaneous tissue	3 (10.0)	3	1 (3.3)	1	0(0.0)	0	1 (3.4)	1	0 (0.0)	0	1 (3.4)	1	0 (0.0)	0	0(0.0)	0
Surgical and medical procedures	0 (0.0)	0	1 (3.3)	1	1(3.3)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (3.7)	1	0(0.0)	0
ALL related	2 6.7)	4	1(3.3)	1	2 6.7)	2	1 3.4)	1	1 (3.4)	1	0 0.0)	0	0 (0.0)	0	1 (3.7)	2
GI related	2 (6.7)	4	1 (3.3)	1	2(6.7)	2	1 (3.4)	1	1 (3.4)	1	0 (0.0)	0	0 (0.0)	0	1 (3.7)	2

Source: B22CS CSR. Abbreviations: GI = gastrointestinal, M = months, N, n = number of parents, nae = number of adverse events, SoC = standard of care.

Early Access Programs

Since the availability of ADV7103 in the frame of EAPs and up to July 2021 (date of the last pharmacovigilance (PV) report), 15 non-serious PV cases have been reported in the PV database (13 in France and two in Sweden), and no serious PV cases have been reported.

These 15 PV cases are describing 23 AEs in the following system organ classes:

- Gastrointestinal disorders: 6 AEs, including diarrhoea (4), dyspepsia (1) and abdominal pain (1)
- Investigations: 5 AEs, including weight increased (1), plasma potassium increased (1) or decreased (1), plasma bicarbonate increased (1) or decreased (1)
- Injury, poisoning and procedural complications: 5 AEs, including medication error (granules crunched at the first intake) (1), off label use (intake of a half sachet instead of a full sachet, (1), product administration interrupted (1), product use complaint (2)
- General disorders and administration site conditions: 4 AEs, including fatigue (1), ineffective drug (2), treatment non-compliance (1)
- Metabolism and nutrition disorders with a case of alkalosis
- Renal and urinary disorders, with a case of hypocitraturia
- Psychiatric disorders, with a case depressed mood

In addition, most patients (62) enrolled in France first in an individualised EAP have been further switched in a cohort EAP.

Since the start of the cohort EAP (January 2020) up to July 2021 (date of the last pharmacovigilance (PV) report), 8 non-serious PV cases have been reported in the PV database, and no serious PV cases have been reported.

These 8 PV cases are describing 11 AEs in the following system organ classes:

- Injury, poisoning and procedural complications: 5 AEs, including product use complaint (2), inappropriate schedule of product administration (1) and product prescribing error (1)
- Gastrointestinal disorders: 2 AEs, including gastro-oesophageal reflux disease (1) and haemorrhoids (1)
- Renal and urinary disorders: 2 AEs, including urinary calculus (1) and hypocitraturia (1)
- Investigations: 2 AEs, including plasma bicarbonate abnormal (1) or decreased (1)
- General disorders and administration site conditions, with a case of aggravated condition.

The review of these PV cases does not show new information about the safety of the product ADV7103.

Ongoing studies

Studies B23CS and B24CS, both to be carried out in the US, are on hold while a new protocol is agreed. Details of the trials are provided in Table 80.

Table 80: Ongoing studies of ADV7103 in dRTA

	B23CS	B24CS
Study name	ARENA-2 A phase 3 Multicentre, Randomised, Double-Blinded, Placebo-Controlled Withdrawal Study Evaluating ADV7103 In Paediatric and Adult Subjects	ARENA-2 A phase 3B OLE Of Study B23CS (ARENA 2) Evaluating The Continued Safety And Efficacy Of ADV7103 In Subjects With Primary

	B23CS	B24CS
	With Distal Renal Tubular Acidosis (dRTA)	Distal Renal Tubular Acidosis
Trial registry number	NCT03644706	NCT03831152
Study design	The study will target enrolling at least four subjects in each of the following age groups: 6 months - 23 months; 2-11 years, and ≥ 12 years. Subjects will be in the study for up to 21 weeks. After screening and enrolment, subjects will participate in an 8-12 week open-label period where their dose of ADV7103 will be titrated to effect, then continued for the remainder of the open-label period. Periodic measurements of bicarbonate and potassium levels will be collected during this period. Following the open-label period, subjects will enter a 6-day randomised withdrawal period. For this portion of the study, subjects will be admitted to an inpatient setting. A follow-up period up to four weeks on re-established therapy completes the trial. Subjects will have the opportunity to subsequently enter a long-term OLE	Open-label study involving longitudinal assessment of the continued safety, tolerability, and efficacy of ADV7103 in maintaining targeted serum bicarbonate levels, preventing metabolic acidosis, and preventing hypokalaemia in the following groups of subjects with primary dRTA: • Subjects who participated in Study B23CS and were adherent to the protocol; • subjects ≥ 6 months of age who are living in Europe and did not participate in Study B23CS; • Infants younger than 6 months of age
Primary endpoint	Mean change in blood bicarbonate levels [Time Frame: 6 days] Compare the efficacy of ADV7103 versus placebo in preventing metabolic acidosis, defined as two consecutive serum bicarbonate levels < 18 mEq/L for subjects ≥ 4 years old and < 17 mEq/L for subjects < 4 years old, during the Withdrawal period	The Safety of ADV7103 will be assessed by evaluating the frequency of TEAEs as compared to placebo [Time Frame: To 30 months]. Number/proportion of subjects presenting with ADV7103 treatment-related AEs during the study, by severity grade
Comparator	Placebo: Placebo is a combination of 2 mm green coated lactose granules and 2 mm white coated lactose granules	Single group assignment
Placebo	Each dose of placebo contains a fixed ratio of 1/3 of green granules and 2/3 of white granules.	Not applicable.
Sample size	Estimated enrolment 40 participants	40 participants
Estimated primary completion rate	Unknown. Not yet recruiting. On hold while a new protocol is agreed.	Unknown. Not yet recruiting. On hold while a new protocol is agreed.

B.2.12 Innovation

ADV7103 is an innovative fixed-dose combination of CK and BK, formulated as prolonged-release granules, developed to control metabolic acidosis and any hypokalaemia in dRTA patients with a safe and simplified BID dosing regimen compared with the current SoCs, which require multiple administrations and are not always well tolerated.

The following essential elements were considered when developing ADV7103/ADV7103:

- A need for one specific product containing an alkalising product and potassium supplement
- A need for one single product with no sodium intake
- A need for a BID dosing with no intake during school or at night
- A need for a product easy to swallow whatever the age and tasteless
- A need for a product allowing dose adjustment whatever the age

- A need for a product with an improved gastrointestinal tolerability
- A need for A product with a positive benefit/risk profile to control metabolic acidosis.

ADV7103 fulfils these factors for innovation.

B.2.13 Interpretation of clinical effectiveness and safety evidence

Clinical efficacy conclusion

Overall, the mean (SD) well-adapted SoC dose was 2.78 (1.808) mEq/kg/day (higher in younger patients than in adults: 1.99, 2.20, 2.70 and 5.27 mEq/kg/day for adults, adolescents, children and infants, respectively), while the mean (SD) optimal ADV7103 dose was 3.31 (1.810) mEq/kg/day (higher in younger patients than in adults: 1.74, 2.79, 3.80 and 6.11 mEq/kg/day for adults, adolescents, children and infants, respectively). The higher dose of ADV7103 compared SoC (increase of 22%) could be reached thanks to the better gastrointestinal safety profile of ADV7103 relative to its formulation features.

The primary efficacy endpoint was the average blood bicarbonate levels (Day 2 to Day 4) at steady state in SP I (SoC) and SP III (ADV7103), which was tested for non-inferiority as intra-individual comparison in the PP set. The timing of the assessment for blood bicarbonate was prior to the pre-morning dose, corresponding to 12 hours after the last ADV7103 administration. Therefore, it represents the lowest potential efficacy for ADV7103. For SoC, the timing of the assessment represented a variable time (but less than 12 hours) after the last SoC administration, as multiple intakes were generally taken (between 3 to 6 intakes were recorded in 86.5% of the patients). Overall, a greater improvement and normalisation of blood bicarbonate levels and less variability were observed with ADV7103 compared to SoC. The statistical analysis not only demonstrated the non-inferiority of ADV7103 vs. SoC but also its superiority, both in the ITT and PP sets. The superiority was shown with an adjusted mean difference (95% CI) of 1.64 (0.67, 2.60) mmol/L, p=0.0008, in the ITT set. The lower bound of the 95% CI of 0.67 mmol/L suggested also a potentially clinically relevant difference between ADV7103 and SoC. The sensitivity analyses conducted in the ITT and PP sets comparing ADV7103 with historical baseline data in untreated patients confirmed the robustness of the on-inferiority analysis.

ADV7103 greater efficacy was also highly supported by the analyses of non-responders with respect to blood bicarbonate levels, i.e. patients with blood bicarbonate levels below the lower limit of normal as defined by the local laboratories and according to three definitions (patients with at least one value of blood bicarbonate below the lower limit of normal value, patients with all non-missing values of blood bicarbonate below the lower limit of normal value, or patients with the average value of blood bicarbonate below the lower normal value, on Day 2 t0, Day 3 t0 and Day 4 t0, on SP I and on SP III). The non-responders and responders in each SP were analysed with a McNemar's test to investigate the homogeneity of the rates.

Regardless of the definition of non-responder, in both the ITT and PP sets, the McNemar's test was statistically significant, suggesting heterogeneity in the non-responder rates between SoC and ADV7103. This was in line with the investigation of the raw proportions, which clearly indicates a trend in favour of ADV7103 over SoC.

This is further supported by study B21CS whereby twice daily doses of ADV7103 were demonstrated to adequately restore normal plasma bicarbonate and potassium levels for all age groups of patients with dRTA over 47 months.

Overall, these data are of great clinical importance as they showed the ability of ADV7103 of switch non-responders with SoC to responders. In the stratified analyses of bicarbonataemia by SoC type, non-inferiority of ADV7103 vs. SoC was demonstrated for all SoCA and SoCC types, and superiority of ADV7103 vs. SoC was demonstrated for SoCA type B and SoCA type BC. The results of sensitivity analyses by SoCA and SoCC types were in line with the results of the primary analyses. The analyses

of mean differences between treatment with ADV7103 and SoC did not achieve statistical significance for bicarbonate-derived parameters after 5 days at steady state (AUC0-12h, AUC0-24h, Cmin, and fluctuation) in both the PP and ITT sets, and in the subgroups stratified by SoCA and SoCC types. These results suggest that the alkalising coverage obtained with 3-6 doses per day of SoC can be reached with only two administrations per day of the prolonged-release granules ADV7103. At 4 to 5 days of treatment at steady state (SP I and SP III), normalisation of blood potassium was achieved with both ADV7103 and SoC. Even if higher plasma potassium levels were reached with ADV7103 over SoC, there were no statistically significant differences between the two treatments in terms of probability of presenting with hypokalaemia.

Study B22CS also showed that ADV7103 allowed very good control of the metabolic acidosis with most patients showing normal values of bicarbonataemia over time up to 48 months.

ADV7103 greater efficacy was also supported by the analyses of non-responders with respect to urine parameters used as markers of risk of nephrocalcinosis and calcium nephrolithiasis. At 4 to 5 days of treatment at steady state (SP I and SP III), normalisation of calciuria was achieved for most patients for both ADV7103 and SoC, and there were no statistically significant differences between the two treatments in terms of probability of presenting with hypercalciuria. At 4 to 5 days of treatment at steady state (SP I and SP III), there were no statistically significant differences between the two treatments in terms of probability of presenting with hypocitraturia, nevertheless the proportion of non-responder patients lacking normalisation of citraturia after SoC treatment relative to ADV7103 treatment (41% versus 5.9% in ITT set) suggests an important trend of the benefit of ADV7103 treatment compared to SoC treatment, also in accordance with the difference observed for UCa/UCi. The probability of having abnormally high UCa/UCi values (in mg/mg) was statistically significantly higher with SoC than with ADV7103 in both the PP and ITT sets (p=0.021 for both analysis sets), while the risk of lithogenesis was higher with SoC than with ADV7103 (p=0.021 for both analysis sets). This is substantiated by study B22CS, whereby compared to SoC treatment, ADV7103 allowed an important and marked reduction in the number of patients with hypocitraturia, abnormally high UCa/UCi and risk of lithogenesis over 48 months.

Results from the exploratory parameters assessed in the OLE were also encouraging. In terms of bone remodelling, blood calcium, phosphate and bone ALP levels are generally normal in all age groups throughout the 48 months of follow-up. Therefore, as expected, there is no sign of increased secretion of PTH that is usually stimulated by hypocalcaemia, and there is no sign of increased secretion of 1α,25-dihydroxy-vitamin D (the active form of the 25-hydroxy-vitamin D) that is usually stimulated (via the 1-25 hydroxylase) by hypophosphoraemia and/or reduced PTH level.

Overall, most patients had blood bone ALP level in the normal range throughout the study. The blood bone ALP is a highly specific marker of the bone-forming activity of osteoblasts and is elevated with bone growth, Therefore, the blood bone ALP level increased physiologically as expected for adolescents and infants in accordance with the strong bone growth in these age groups. The bone ALP level is also abnormally high in osteomalacia (due to excessive rates of bone remodelling). This suggests there is not an excessive rate of bone remodelling that could lead to rickets/osteomalacia.

Maintaining all the blood bone parameters in the normal ranges prevent the risk of rickets/osteomalacia. Overall, the Z-score of the BMD of the spine (the relevant skeletal area for evaluating the BMD in both paediatric and adult populations) showed a continuous and significant clinical improvement after 48 months of treatment with ADV7103. ADV7103 could potentially have a beneficial effect over the long term in the prevention of bone remodelling.

Palatability, compliance and quality of life

Patients reported a statistically significant palatability improvement for ADV7103 vs. SoC in study B21CS, suggesting that the ADV7103 coated formulation masks efficaciously the bitterness of the active substances. Patients also reported a greater ease of administration for ADV7103 as compared to SoC, suggesting that a posology limited to 2 intakes a day of a single product facilitates the

administration. Patients rated both treatments similar for ease of swallowing. The ease of swallowing is preserved even though ADV7103 is a multiarticulate solid formulation (several hundreds of granules can be swallowed per intake), while SoC is provided as solution, syrup, powder or single tablet or capsule.

Throughout the OLE study, compliance was good (≥75%) in all age groups: for 18 (66.6%) patients to 28 (93.3%) patients according to the study visit. Only four patients had treatment compliance <50%. Between one (3.3%) and seven (25.9%) patients presented treatment compliance below 75% despite reminders from the Investigators and other site personnel. Some of the reasons contributing to this were: treatment boxes not returned entirely therefore the investigators gave an estimation of compliance based on questioning, and adolescents were less compliant than others due to their age and poor acceptance of their disease and the constraints of the study. The issue of patients not returning all their treatment boxes for counting was addressed during the study by amending the protocol to allow assessment of compliance to be based partly on Investigator questioning of the patient, but this approach is inevitably more subjective. However, overall, long-term treatment compliance was high with ADV7103 in patients with dRTA.

This was further supported by the OLE study, whereby mean satisfaction score with ADV7103 compared with SoC was 9 out of 10, and ADV7103 exceeded or met the expectations of 82% patients. Patients reported a marked change in four QoL domains: the perceived emotional burden of disease was relieved in the absence of treatment-related invasive questions from others; the difficulties at school due to burdensome administrative issues and need to explain disease and treatment disappeared, facilitating parents who had stopped working to return to work; the social/family issues improved with travel and holidays became easier to organise, patients/parents stopped thinking about managing treatment daily/nightly, reducing tension in the family/couple; and the physical impact improved with lessened bad taste, bad breath and fewer GI AEs with ADV7103, as well as better compliance, which led to milder physical impacts and less fear of being hospitalised. Overall, all participants were highly satisfied with ADV7103 across multiple QoL dimensions. The change in treatment had repercussions on several aspects of their QoL which were “life-changing” for all patients/parents.

Conclusions of clinical safety

During study B21CS, ADV7103 was well tolerated, and no safety concerns were raised for ADV7103 compared to the SoC in terms of TEAEs and laboratory parameters. TEAEs were reported with similar frequency when treatments were taken in the same conditions: in 7 (18.9%) patients during SP I (SoC steady state, well-adapted dose) and in 6 (18.8%) patients during SP III (ADV7103 steady state, optimal dose). TEAEs were reported in 19 (55.9%) patients during SP II (ADV7103 titration period when the treatment was generally taken at doses lower than the optimal dose). Notably, TEAEs from the Gastrointestinal Disorders SOC were reported less frequently during SP III than during SP I. In addition, the proportion of patients with treatment related TEAEs was lower in SP III (1 [3.1%] patient) than in SP I (4 [10.8%] patients). In line with these results, the gastrointestinal tolerability based on patients’ evaluations was statistically significantly better with ADV7103 than with SoC.

In terms of long-term safety in the 48-month study, a total of 188 TEAEs were reported by 27 patients overall (90.0%), including 11 TEAEs in five patients (16.7%) that were considered treatment-related. The most common TEAEs were metabolism and nutrition disorders (35 TEAEs in 18 patients [60.0%] overall, including 13 patients with vitamin D deficiency, five patients with hypokalaemia, four patients with iron deficiency, and two with decreased appetite, and GI disorders (44 TEAEs in 16 patients (53.3%) overall, mainly cases of abdominal pain, vomiting or diarrhoea).

Overall, 135 TEAEs were of mild intensity and reported in 26 patients (86.7%), 49 TEAEs were of moderate severity and reported in 14 patients (46.7%), and four severe TEAEs were reported in three patients (10.0%): a decreased appetite in one adolescent, two episodes of unilateral deafness in one child and a gastroenteritis rotavirus in one infant. None of the severe TEAEs was considered related to treatment.

Five patients (16.7%) had 11 treatment related TEAEs including diarrhoea, GI disorder, GI pain, abdominal pain, abdominal pain upper, and dyspepsia.

Thirteen SAEs were reported in 10 patients overall (33.3%), all considered unrelated to treatment. All SAEs were resolved/recovered within the following days. The SAEs included deafness unilateral, sudden hearing loss, food poisoning, gastritis, vomiting, gastroenteritis rotavirus, gastroenteritis viral, migraine, renal colic, and wisdom teeth removal.

There were no TEAEs leading to study drug discontinuation or death, and no SUSARs. The AE profile seen in the study was generally as expected for this population and the cases of GI events, known to be related to the drug mechanism, were infrequent, and mostly mild in severity.

No episodes of hyperkalaemia were reported and, importantly, there were no observed abnormalities known to be linked to hyperkalaemia or hypokalaemia on the ECG.

The higher increase of bicarbonate in urine observed in infants compared to other age groups could be related to the physiological immaturity of the renal function leading to a bicarbonate leak in urine The lower urine potassium level observed in the adult group is congruent with the cases of hypokalaemia described in this subgroup of age.

Presence of potassium in urine signals an effective control of the hypokalaemia, with the elimination of the potassium in excess in urine, according to the severity of the hypokalaemia. The lower urine potassium level observed in the study in the adult group is congruent with the cases of hypokalaemia described in this subgroup of age.

Conclusion

Study B21CS showed the sustained effect over 24 hours of ADV7103 as an alkalising therapy in controlling hyperchloremic metabolic acidosis is known to be critical and directly related to clinical outcomes. For example, impaired growth in children with dRTA is due to a lower growth hormone secretion which is maximal during night and is promoted with physiological blood pH conditions. ADV7103 normalised kalaemia. ADV7103 had significantly better palatability and better ease of administration than SoC. Both ADV7103 and SoC, were safe and well tolerated, though ADV7103 resulted in fewer TEAEs of gastrointestinal nature and exhibited a significant greater gastrointestinal tolerability than SoC. In conclusion, and in accordance with the observations made in the 48 months OLE study, it can be concluded that greater clinical efficacy and benefit of ADV7103 compared to the SoC therapy was demonstrated and had no safety concern.

B.3 Cost-effectiveness

B.3.1 Published cost-effectiveness studies

A systematic literature review was conducted on 26th August 2021 (see Appendix D). The review included the identification of studies assessing patients with dRTA reporting data regarding:

- o Efficacy and safety of pharmacological treatments
- o Treatment options covering guidelines and patterns
- o Epidemiology covering incidence and prevalence
- o Economic evidence covering evaluations, and cost burden
- o Utility and quality of life evidence
- o Consequences of disease

Searching Medline, Embase and EBMR databases. The SLR followed the standard methodology for conducting systematic reviews as per guidelines provided by the National Institute for Health and Care Excellence (NICE) [53] and the Cochrane handbook. The results of this review are reported as per the PRISMA guidelines. The data collection was performed using inclusion/exclusion criteria guided by the PICOS approach. Two investigators independently reviewed the full texts. The search resulted on 63 studies from 81 publications, which consisted of 20 studies from 33 publications from Europe.

No studies were found giving detail of economic evaluations of current standard of care. There is very limited literature on the economic evaluation of dRTA, with no evaluations being found on previous cost effectiveness studies for dRTA.

Cost burden evidence is limited to one study by Mumford et al 2020[54] that concluded that there is high variability in costs of managing dRTA, depending on disease severity, age and treatment strategies. Interventional procedures and costs related to late diagnosis were identified as the main cost drivers for patients. Thus, there may be a strong argument that early diagnosis and management strategies that focus on patient compliance for dRTA could lead to a decrease in potentially unnecessary resource utilisation costs and burden upon the healthcare system.

For the purposes of the HTA submission, further targeted searching of the literature was required to source utility and disutility values associated with each health state, and to identify transition values not available from clinical trial data or dRTA specific literature. These values were verified with a dRTA health care professional.

B.3.2 Economic analysis

dRTA is a chronic, progressive disease leading to kidney failure. Kidney complications associated with dRTA may result in CKD, and in the long-term, chronic metabolic acidosis can lead to end-stage renal disease. The aim of the analysis was to extrapolate and explore the long-term effects of ADV7103 versus SoC on cost-effectiveness. As such, a Markov model approach was adopted in order to appropriately reflect the patient heterogeneity of CKD patients.

Patient population

As this disease is most often diagnosed from infancy (when it is of inherited aetiology), in accordance with the guidance on clinical investigation of medicinal products in the paediatric population, all paediatric subgroups (infants from 1 year to 3 years old, children from 4 to 11 years old, adolescents from 12 to 17 years old) in addition to adults (18+) have been evaluated. This reflects the population included in the B21CS and B22CS trials, and the marketing authorisation for ADV7103.

Patients are stratified based on the age at the start of the model into four age groups as illustrated in the Table 81 below. Due to limited data on epidemiology, a conservative approach was taken, and the patients were equally split into adults (18+) and under-aged patients (<18). The under-aged patients (<18) were split into proportions based on the number of years within each age group.

Table 81: Patients' composition at model entry

Age groups	Composition (%)	Mean age	Mean weight (kg)	Source (weight)
1-3	8.8	2.00	12.78	So et al [55]
4-11	23.5	8.00	32.00	Tinning and Acworth 2007 [56]
12-18	17.6	15.00	59.70	Linear interpolation between weight at fifteen from Tinning and Acworth [56] and weight at 18 years
>18	50.0	25.00	70.80	Walpole et al, 2012 [57]

The mean weight estimates were calculated as follows.

The mean age is equal to 2 from age group of 1-3. The model implements the Theron formula which is a weight estimation method, introduced by So et al 2009. This formula is demonstrated as follows: weight (Kg)=exp[(0.175571* age in years)+2.197099]. Therefore, the mean weight of 12.78 can be obtained by inputting a mean age of 2 into the equation.

The mean age is equal to 8 from age group of 4-11. According to Tinning and Acworth 2007, the authors stated that the simplified linear equation for the patients fall into this age group. The following formula helped derived the mean weight: Weight (kg)= 4*age in years, this reflected a linear relationship between age and weight, when age increase by 1, the corresponding weight will increase by 4kg. The input value of age in years is 8, therefore, using the formula as shown above, average weight can be derived as weight(kg)=4*8=32.

The calculation of average weight for age group between 12 and 18 consisted of two parts. The first part focuses on the patient in age group of 14 where the corresponding weight can be calculated by applying the same equation stated in Tinning and Acworth 2007. As above using the formula, this led us to Weight (kg)= 4*age in years= 4*14=56. The average weight of an adult is 70.8 is retrieved from Walpole et al. 2012, we can calculate how much average weight gain there is for patients between the

age group of 14-18. The equation of average weight is (70.8-56) /(18-14)=3.7. Thus, the result can be derived by summing the average weight for patient at age of 14 and the average weight gain each year between 14 to 18. The result is 56+3.7=59.7.

The average weight for age group over 18 years old is retrieved from Walpole et al. 2012 table 3, the figure reflects the average weight in Europe.

Model structure

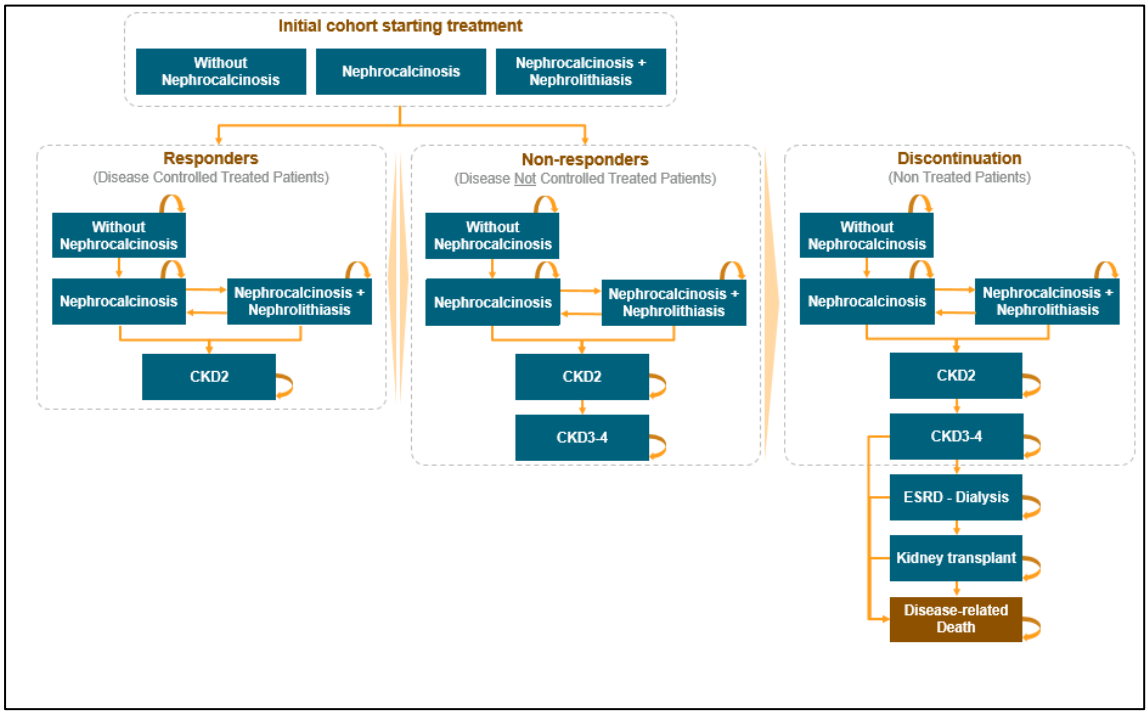
The cost-effectiveness model is a cohort Markov model designed to reflect the clinical pathway for patients with dRTA. Figure 19 illustrates the schematic for this decision analytic model.

Markov modelling is the most appropriate for use in modelling disease where recursive events occur, and patients move among a finite number of health states over the time horizon. All clinically important events are modelled as transitions from one state to another state. Due to its versatility in adopting different types of health states, ease of implementation and short computational times, a Markov model approach was used for this analysis.

In the first two years of the model, the cycle length is six months and one year thereafter, to reflect the clinical trial and relevant treatment and resource utilisation e.g., physician visits. A half-cycle correction was applied in the model using the Trapezoidal method.

In line with NICE recommendations, the NHS and Personal and Social Services (PSS) perspective was used for the base-case analysis. Only direct healthcare costs incurred by the NHS, such as drug costs, adverse event costs and disease management costs were included.

Figure 19: dRTA model schematic



The model structure and main assumptions described below were validated by a working group of clinicians comprising of adult and paediatric nephrologists and urologists from the UK including

Ireland and Scotland. The assumptions applied were used to balance the natural history of disease with appropriate simplifications to modelling approaches.

In the model, all patients in age groups 1 to 3 (1 to 3 years old, 4 to 11 years old and 12 to 17 years old respectively at the start of the model) are assumed to be affected by primary dRTA. All patients starting in age group 4 (over 18 years old at the start of the model) are assumed to be affected by acquired dRTA. Those patients in age group 4 incur a fixed utility decrement associated with acquired dRTA.

Patients enter the model in one of three health states: without nephrocalcinosis, with nephrocalcinosis, and with nephrocalcinosis+nephrolithiasis, as responders or non-responders. The split is based on the repartition at baseline from the trial and differs for children and adults.

There are three response status groups within the model:

- Responders
    - Disease-controlled and receiving treatment
- Non-responders
    - Disease-uncontrolled and receiving treatment
- Discontinuation
    - SoC arm: disease-uncontrolled and untreated
    - ADV7103 arm:
        - Proportion X receive SoC to be responder, non-responder or discontinue as per SoC arm
        - Proportion (1-X) disease-uncontrolled and untreated

Disease progression depends on the response status (responders versus non-responders) and on the treatment group. Within each treatment and response status group, patients can transition to different health states reflecting varying CKD severity. There are 24 transition matrixes in the model reflecting differences in age groups (children and adults), type of treatment (ADV7103 versus SoC), and time period (model cycle). Further detail on the model assumptions is presented in Section B.3.6.

<u>Responders</u>

Responders are defined as disease-controlled patients with sufficient alkali therapy and metabolic acidosis is absent. Responders cannot progress to health states worse than CKD2, and progression from Nephrocalcinosis or Nephrocalcinosis+Nephrolithiasis to CKD2 is not reversible.

Responders can remain in the responder health states or stop responding and transition to non-responder health states. All responders receive treatment and are assigned drug related costs. Responders cannot transition directly to the discontinued health states.

<u>Non-responders</u>

Non-responders are defined as disease-uncontrolled patients with insufficient alkali therapy and metabolic acidosis is present. Non-responders cannot progress to health states worse than CKD3-4. Progression to CKD2 or CKD3-4 is not reversible.

Non-responders can remain in the non-responder health states, transition to the responder health states, or can transition to the discontinued treatment health states based on an annual discontinuation rate. The response rate (transition to a responder state) is treatment

dependent but is assumed to be the same for the patients without nephrocalcinosis, with nephrocalcinosis, nephrocalcinosis+ nephrolithiasis.

Treatment disease control (probability of remaining a responder) and treatment disease recovery (probability of transitioning from non-responder to responder) are derived from the patient level data of the clinical trial (B21CS) at specific follow-up periods (6 months, 12, months, 18 months, 24 months, and 36 months).

Discontinuation

For the ADV7103 arm, a proportion of patients who discontinue ADV7103 will receive SoC (as either a responder or non-responder), and the remaining are assumed to be discontinued without treatment (disease-uncontrolled and untreated).

For the SoC arm, all patients who discontinue SoC are assumed to be discontinued without treatment (disease-uncontrolled and untreated).

All patients who discontinue and do not receive treatment can progress to end of stage renal disease (ESRD) which requires dialysis at home or in hospital. Kidney transplant is only possible for patients with ESRD.

At any cycle in the model, non-responders and discontinued patients in any health state excluding transplant patients can experience hypokalaemia, gastrointestinal (GI) disorders, and/or musculoskeletal transitory events. Musculoskeletal events include fracture, bone deformities, osteomalacia, and failure to thrive (FTT). All transitory events incur a decrement in quality of life and incur additional health care resources.

FFT can occur only before a threshold age for patients in non-responder health states. At each cycle, the number of patients recovering from faltering growth in each age group is determined by a fixed annual recovery rate determined by the number of years left before reaching the age threshold past which patients could not develop faltering growth.

General age-related mortality (UK specific) has been adjusted and applied per cycle to all patients included in the model. Disease-related mortality is only applied to severe health states (CKD3-4, ESRD and kidney transplant) and after a hypokalaemia, GI or musculoskeletal event. The same risk is applied to children and adults. Patients experiencing a fracture or hypokalaemia event have an additional, event-related risk of mortality [58].

Mortality estimates for a fracture event, hypokalaemia, CKD3-4, ESRD and transplant are from the general population and not from dRTA specific cohort.

Table 82: Features of the economic analysis

	Current appraisal	
Factor	**Chosen values**	**Justification**
Time horizon	75 years (lifetime)	dRTA is a chronic disease, however if metabolic acidosis is controlled, there is no decrease in life expectancy and renal failure is uncommon. As the new intervention could affect mortality, a lifetime horizon is considered appropriate to capture all the differences in health benefits and costs between the two technologies.

Treatment waning effect	No	The treatment effect is present as long as the treatment is administered and stops when discontinued (and off treatment)
Source of utilities	Literature	Health utilities were not collected during the trial
Source of costs	Literature and National Cost Collection	Resources used were not collected during the trial

Intervention technology and comparators

The dRTA treatment aims at restoring physiological blood pH (blood bicarbonate levels greater than or equal to 22 mM) and requires individual adjustment of the dose.

The comparator is represented by the standard treatment for dRTA, alkali therapy, as recommended in the BMJ best practice patient guidelines. Paediatric patients are generally treated with higher doses/kg because their bicarbonate needs are greater than adults. Currently, the standard treatment for dRTA involves alkali agents, which are used to neutralise excess acid in the blood. Paediatric patients are generally treated with higher doses/kg because their bicarbonate needs are greater than adults. Potassium supplementation is required for patients with hypokalaemia [18].

Current SoC treatments are generally immediate release alkalising products, and their effect is short-lived. Treatment is administered in several daily doses to compensate for short duration of action and induces potential gastrointestinal (GI) side effects due to a peak of alkali loading on the stomach, which may encourage clinicians to prescribe a lower and less efficient dose to negate these side effects. The consequence of this is the need to take the treatment at night; during school; during work; with considerable impact on patients' QoL with the outcome of poor compliance [59].

Several alkalising salts have been authorised in the EU for indications that may include partial treatment of dRTA although none of them are indicated for the global treatment of dRTA. Some of them may include partial treatment of dRTA (such as metabolic acidosis, hypokalaemia or nephrolithiasis), but without any clinical evidence. Indeed, these authorised medications are used off label in dRTA, and in children (except Alcaphor – Disodium Hydrogen Citrate) since there is usually no data to support their efficacy in these populations. These include, among others sodium citrate and sodium bicarbonate, each as single active substance or in different product combinations. [47]

The range and percentage of alkali products used to define SoC treatment in the model is derived from the B21CS trial and is illustrated in the Table 83.

Table 83: SoC therapies consumption based on B21CS trial

	SoC breakdown	**Percentage of users (n=37)**	**Source**
1 product		**51.40%**	
	potassium bicarbonate	8.10%	B21CS CSR: Table 9 pg. 68
	potassium citrate	21.70%	B21CS CSR: Table 9 pg. 68
	modified Shohl's solution	2.70%	B21CS CSR: Table 9 pg. 68
	sodium bicarbonate	18.90%	B21CS CSR: Table 9 pg. 68
2 products		**48.6%**	
	potassium bicarbonate+ potassium citrate	8.10%	B21CS CSR: Table 9 pg. 68

	potassium bicarbonate+ sodium bicarbonate	13.50%	B21CS CSR: Table 9 pg. 68
	potassium citrate+ sodium bicarbonate	24.30%	B21CS CSR: Table 9 pg. 68
	modified Shohl's solution + sodium bicarbonate	2.70%	B21CS CSR: Table 9 pg. 68

ADV7103 for the treatment of dRTA

The test product in this study is ADV7103 prolonged-release granules taken orally approximately every 12 hours (prior to both the morning and evening meals/snacks/feedings) at a dose titrated to achieve desired serum bicarbonate levels. An ADV7103 fixed-dose is 1/3 potassium citrate (green granules, ADV7103-CK) and 2/3 potassium bicarbonate (white granules, ADV7103-BK) by weight.

ADV7103 offers a product with better gastrointestinal tolerance. It achieves stable metabolic control, therefore potentially reducing the consequences of dRTA.

Dosages for ADV7103 treatment and SoC

All patients receiving treatment are assumed to receive the full dose as required by age and weight with patients' mean weight depending on age group and country. The following tables (Table 84 and Table 85 illustrate the varying dosages provided to dRTA patients in both trial B21CS and B22CS.

Table 84: Treatment dosage based on B21CS trial

Mean age	**ADV7103 (dose mEq/kg/day)**	**SoC (dose mEq/kg/day)**	**Source**
3	6.11	5.27	CSR table 2.7.3-29
11	3.80	2.70	CSR table 2.7.3-29
17	2.79	2.20	CSR table 2.7.3-29
18	1.74	1.99	CSR table 2.7.3-29

Table 85: Treatment dosage based on B22CS trial

Mean age	**ADV7103 (dose mEq/kg/day)**
3	4.806
11	3.413
17	2.606
18	2.260

B.3.3 Clinical parameters and variables

The clinical data from the B21CS trial (up to 24 months) and B22CS trial (from 24 months up to 48 months) were used to derived transition probabilities in the model as shown in Table 86, Table 87 and Table 88**.** As the number of patients past the 36 months' time point was limited, the efficacy for months 36-48 was considered the same as in the previous time interval (24-36 months). This assumption was validated by key opinion leader in a modified Delphi panel. The modified Delphi panel aimed at recruiting expert adult and paediatrician nephrologists and urologists from England, Ireland, Scotland and Wales to validate the model input and assumptions. 23 invitations were sent, and 11 experts participated.

Table 86: Initial Health State

Age group	Without Nephrocalcinosis	Nephrocalcinosis	Nephrocalcinosis + Nephrolithiasis	Source/Justification
Children	6.66%	86.67%	6.67%	B21CS trial data
Adults	0.00%	85.71%	14.29%	B21CS trial data

Table 87: Initial Disease control

Age group	ADV7103	Source/Justification	SoC	Source/Justification
Children	90.00%	CSR table 2.7.3-21	43.00%	CSR table 2.7.3-21
Adults	90.00%	CSR table 2.7.3-21	43.00%	CSR table 2.7.3-21

Table 88: Disease control and Recovery across treatment arms

ADV7103							
Disease control (%)	**0-6 months**	**6-12 months**	**12-18 months**	**18-24 months**	**24-36 months**	**36-48 months**	**Source**
Children	84.20%	100.00%	92.00%	72.00%	80.00%	80.00%	*PLD up to 24 months, assume the same disease control values for 36 to 48 months*
Adults	84.20%	100.00%	92.00%	72.00%	80.00%	80.00%	
Disease recovery							
Children	63.64%	28.60%	40.00%	50.00%	67.00%	67.00%	*PLD up to 24 months, assume the same disease control values for 36 to 48 months*
Adults	63.64%	28.60%	40.00%	50.00%	67.00%	67.00%	

ADV7103							
Disease control (%)	**0-6 months**	**6-12 months**	**12-18 months**	**18-24 months**	**24-36 months**	**36-48 months**	**Source**
SoC							
Disease control (%)							
Children	45.00%	53.00%	49.00%	42.00%	41.00%	41.00%	*Assumes same relative efficacy of ADV7103 versus SoC across time*
Adults	45.00%	53.00%	49.00%	42.00%	41.00%	41.00%	
Disease recovery							
Children	10.00%	10.00%	10.00%	10.00%	10.00%	10.00%	*Assumes same relative efficacy of ADV7103 versus SoC across time*
Adults	10.00%	10.00%	10.00%	10.00%	10.00%	10.00%	

**PLD up to 48 months for disease control and disease recovery. Post 36 months, assumes the same disease control or recovery as trial data was limited. Assumption validated with KOL*

Disease progression is considered independent from treatment; following an initial response that is treatment-based efficacy, the proportion of patients who are responders is determined by treatment disease control and treatment disease recovery. There are two parameters (for children and for adults) of treatment disease control (defined as the probability of patients in the responder health state at the beginning of a cycle to remain in the responder state) with user definable threshold age. Similarly, there are two parameters (for children and for adults) of treatment disease recovery (defined as the probability of patients in the non-responder health state at the beginning of a cycle to transition to the responder state) with user definable threshold age. Treatment disease control and treatment disease recovery are derived from the PLD of the clinical trial at specific follow-up (6 months, 12 months, 18 months, 24 months, 36 months).

Data for all patients from the 24-month patient level data were used to estimate the values for efficacy. As the number of patients in the B21CS trial were small, the efficacy for adults and children has been assumed equivalent. The ratio of efficacy between ADV7103 and SoC at each cycle is the same as the initial levels of efficacy observed after the first 5 days of treatment (for both children and adults).

Patients in the non-controlled health state are assumed to discontinue treatment with a set probability (discontinuation rate). During a modified Delphi panel (October 2020), key opinion leaders were asked about typical treatment compliance to SoC for children and adults with dRTA. As no data informing discontinuation rates in SoC for people with dRTA could be identified in literature, discontinuation rates have been assumed from compliance. If a patient is not compliant to therapy this was assumed to be an equivalent to discontinuation, i.e., the patients were no longer receiving treatment that delivers metabolic control.

Table 89: Treatment discontinuation for non-responders (1yr Probability at each cycle)

Age group	**Treatment arm**			
	ADV7103	**Source/ Justification**	**SoC**	**Source/ justification**
Children	0.00%	B22CS CSR because this was the extension trial B21CS trial period too short	39.00%	KOL opinion Research October 2020
Adults	3.30%	B22CS CSR because this was the extension trial B21CS trial period too short	45.00%	KOL opinion Research October 2020

KOL= Key opinion leader, SoC= Standard of Care

Transition between health states, probability of transitory events and mortality probabilities are presented in Table 90, Table 91 and Table 92 below. There is reliance on clinical opinion for transitory adverse events used in the model due to lack of information in the trial. Age-standardised mortality rates for disease and event related mortality estimates have not been used in the model.

In the absence of data in the literature on the probability of CKD2 in dRTA patients, the model integrated a solver using the prevalence of CKD2 and CKD3-4 in patients with dRTA at 11 years old. [7] The solver will determine the value of the transition probability to CKD2 that will result in a prevalence of CKD2 of 31.8% and prevalence of CKD3-4 of 2.90% in the cohort of the SoC arm reaching the age of 11 years old (mean age of the studied population of Lopez-García [2019]). [7]

There are 24 transition matrixes in the model reflecting differences in age groups (children and adults), type of treatment (ADV1703 versus SoC), and time period (model cycle).

Table 90: Transition probabilities used in the model – health state transitions

Health state transitions – Annual probabilities							
Transition from	**Transition to**	**Responders*** ***ADV7103 and SoC***	**Source**	**Non-responders*** ***ADV7103 and SoC***	**Source**	**Discontinuation*** ***Patients not on any treatment***	**Source**
w/NC	NC	12.56%	Clinical opinion 1/2x risk of non-respondents	25.13%	Palazzo et al.[15]	100.00%	Clinical opinion 100% in 2 years
NC	NC+NL	4.66%	Clinical opinion 1/2x risk of non-respondents	9.23%	Lopez-García et al.[7]	40.00%	Clinical opinion
NC+NL	NC	20.00%	Clinical opinion	20.00%	Clinical opinion	20.00%	Clinical opinion
NC	CKD2	3.82%	Clinical opinion 7.5% at 2 years	SOLVER 3.98%	Lopez-García et al.[7]	7.96%	Clinical opinion 2x risk of non-respondents
NC+NL	CKD2	3.82%	Clinical opinion 7.5% at 2 years	SOLVER 3.69%	Lopez-García et al.[7]	7.37%	Clinical opinion 2x risk of non-respondents
CKD2	CKD3-4	n/a		3.00%	Clinical opinion	7.80%	Clinical opinion 2.6x risk of non-respondents
CKD3-4	ESRD	n/a		3.00%	Clinical opinion	7.80%	Clinical opinion 2.6x risk of non-respondents
ESRD	Transplant	n/a		n/a		5.50%	Sugrue et al.,2019[60]
Abbreviations: w/NC, without nephrocalcinosis; NC, nephrocalcinosis; NL, nephrolithiasis; CKD, chronic kidney disease; ESRD, end-stage renal disease							

*1-year probabilities applied at each cycle.

Table 91: Transitory events – annual probabilities

Transitory event transitions – Annual probabilities				
Transitory Event	**Non-responders** ***ADV7103 and SoC***	**Source**	**Discontinuation** ***Patients not on any treatment***	**Source**
Hypokalaemia	9.39%	Clinical opinion	72.00%	Clinical opinion
FTT	12.91%	Palazzo et al[15]	12.91%	Clinical opinion Same risk as non-responders
FTT recovery	10.00%	Assumption	10.00%	Clinical opinion Same risk as non-responders
Fracture	0.17%	Zhang et al.[16]	0.34%	Clinical opinion 2x risk of non-responders
Osteomalacia	40.00%	Clinical opinion	80.00%	Clinical opinion 2x risk of non-responders
Bone deformities	8.09%	Jha et al.[27]	16.17%	Clinical opinion 2x risk of non-responders
Abbreviations: FTT, failure to thrive				

Transitory events are applied to patients with the following health states: Without Nephrocalcinosis, Nephrocalcinosis, Nephrolithiasis, CKD2, CKD3-4, and ESRD.

Table 92: Mortality – annual probabilities

Disease and Event related mortality – Annual probabilities		
Health state	**Annual probability**	**Source**
CKD3-4	13.83%	Ayav et al [61]
ESRD	17.70%	Sugrue et al 2019[60]
Transplant	5.30%	Sugrue et al 2019[60]
Hypokalaemia: No CKD; CKD; ESRD;	 0.67% 2.28% 5.82%	 Collins et al.[62] Collins et al. [62] Ohnishi et al. [63]
Fracture	3.54%	Centre et al. [64]
Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease		

*1-year probabilities applied at each cycle.

B.3.4 Measurement and valuation of health effects

Health-related quality of life studies

A systematic literature review was conducted to summarise the key published data on dRTA and any comorbidities with the objective to inform the health economic modelling. In cases where dRTA specific results were lacking the search was broadened for the co-morbidity to find generic utility/ disutility values. The results and methodology of the SLR can be found in Appendix D.

HRQoL data used in the cost-effectiveness analysis

Patients with dRTA have a poor HRQoL and are often burdened with significant complications from the disorder. It is well established that dRTA can significantly impact HRQoL if left untreated, leading to fatigue, muscle weakness, growth failure, osteomalacia, rickets and even renal insufficiency.[16] However, published material specifically on dRTA and HRQoL is very limited.

Utility is a generic measure of health, ranging from 0 (health state equivalent to death) to 1 (full health). dRTA associated health states are deemed to have detrimental effects on HRQoL. Health utility values were obtained from a targeted literature search. Due to a lack of directly relevant data, utility loss values were derived from varying literature sources.

Table 93: Health state utility values for cost-effectiveness analysis

Health states	Utility/year	Standard Error	Distribution	Source
w/NC	0.856	0.171	Beta	Szende et al 2004 [65] (Taken from EQ-5D general population value set, assumed responders will have same utility value as general population)
NC+NL	0.830	0.166	Beta	Polotti et al, 2020[66]
NC	0.850	0.170	Beta	assumed as CKD2
CKD2	0.850	0.170	Beta	Jesky et al, 2016[67] (EQ-5D index score)
CKD3-4	0.770	0.154	Beta	Jesky et al, 2016[67] (average stage 3b/ 4)
ESRD	0.530	0.106	Beta	Neri et al 2012[68] (Assumed the same as CKD5)
Transplant first year	0.830	0.166	Beta	Li et al 2017[69]
Transplant subsequent years	0.700	0.140	Beta	Wyld et al 2012[70] cites Laupacis et al. 1996 [71] (Post-transplant utility 13-24m)
Abbreviations: w/NC, without nephrocalcinosis; NC, nephrocalcinosis; NL, nephrolithiasis; CKD, chronic kidney disease; ESRD, end-stage renal disease				

Each transitory adverse event is associated with detrimental effects on patient HRQoL. Table 94 displays the utility decrement for each adverse event. Similar to the utility values above, the disutility values were derived from the literature. Where specific values could not be obtained from the literature, suitable proxy values were used based on similarities between the diseases.

Clinical opinion suggested that long bone and rib fracture were the most common types of fracture for dRTA patients. However, no robust utility data could be identified. As such, a conservative approach was adopted, and a disutility associated with post-hip fracture in year 1 was applied in the model.

Table 94: Health disutility associated with transitory events

Transitory events	Disutility/event	Standard Error	Distribution	Source
Osteomalacia and fracture	0.170	0.034	Gamma	Schousboe et al 2007[72] cites Borgström et al 2007 (post-hip fracture in year 1)
Faltering growth	0.130	0.026	Gamma	NICE guideline on Faltering Growth: recognition and management of faltering growth in children [NG75] [73]
Bone deformities	0.352	0.070	Gamma	Yanes et al 2019[74]
GI event	0.001	0.0002	Gamma	de Groot et al, 2018[75] Using renal carcinoma as a proxy as this relates to detriments in kidney function. Average of disutilities for diarrhoea, constipation, nausea and vomiting
Hypokalaemia	0.050	0.010	Gamma	Palaka et a 2019[76], utility decrement assumed the same as Hyperkalaemia calculated using utility difference between those with and without HK.
Loss of QoL in Acquired dRTA	0.180	0.036	Beta	Åhlström et al, 2005[77]. The proxy used was the mean QoL decrement from patients with acute renal failure. Difference in utility values between general and study population. Assumed detriment will be the same.

HRQoL assumptions

- HRQoL for any health state and adverse event has not been age-adjusted across time.
- No adjustment has been made between the health state utility values for responders, non-responders, and discontinued patients. For example, patients in the CKD2 health state will have a utility score of 0.850 with no adjustment for treatment response status.
- HRQoL associated with the kidney transplant health state are different for patients entering (cycle of transplant occurrence) or remaining in health state (post-transplant)
- HRQoL of adult patients incurs fixed decrement associated to underlying condition because they are assumed to have acquired dRTA. Acquired forms of the disease are usually

associated with autoimmune diseases, such as Sjögren's syndrome, systemic lupus erythematosus or autoimmune chronic liver disease.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Resource identification, measurement and valuation studies

Costs were calculated from the National Health service perspective (NHS) UK and PSS perspective. The cost components consisted of treatment costs, and disease management costs. A discount rate of 3.5% per annum has been applied to all costs as per NICE guidelines [78].

As no health care resource use data was recorded in the trials, and given the paucity of data in published literature, key opinion leaders' input was used to estimate values for health care resource use.[79,80] The majority of costs were based on the National Cost Collection 2019/20. Other cost sources included the British National Formulary (BNF) for drug acquisition costs, and NICE guidance for health state or adverse event costs. Detailed unit costs are presented in Table 95.

Costs assumptions

- Costs associated with the kidney transplant health state are different for patients entering (cycle of transplant occurrence) or remaining in health state (maintenance)
- No drug wastage is considered for SoC as it includes different medications
- Drug wastage is only considered for ADV7103; it is taken into account in the calculation of the mEq per day, rounding-up the total number of packets needed (of either 8 or 24 mEq).

Intervention and comparators' costs and resource use

The intervention and comparator's costs are based on milliequivalent (mEq) as dosage is adjusted based on patient's weight. The drugs' acquisition costs per mEq are shown in the Table 95 below.

As both the intervention and SoC are oral drugs, there are no costs associated with treatment administration. Flexibility to add treatment administration costs has been built into the model.

Given that there is no existing recommended guidance on SoC, the cost for a mEq of SoC in the model was calculated based on a weighted average between the costs of each drug and the proportion of patients being administered (see Table 95 and Table 81). Unit drug costs were taken from the BNF and used to estimate a costs per mEq. Where two products were used, an average cost was calculated between the two components.

Table 95: SoC unit costs

	SoC breakdown	Unit cost/mEq (£)	Source
1 product	potassium bicarbonate	£0.0384	BNF Sodium Alginate with Potassium Bicarbonate, Acidex Advance Oral Suspension, Accessed November 2021

	SoC breakdown	Unit cost/mEq (£)	Source
	potassium citrate	£0.0023	BNF Citric Acid With Potassium Citrate, Potassium Citrate Mixture Oral Solution, Accessed November 2021
	modified Shohl's solution	£0.0775	BNF Sodium Citrate, Sodium citrate 0.3M Oral Solution, Accessed November 2021, calculated here as average of potassium citrate and sodium citrate
	sodium bicarbonate	£0.3980	BNF Sodium Bicarbonate, S-Bicarb 420mg/5ml (1mmol/ml) Oral Solution, Accessed November 2021
2 products	potassium bicarbonate+ potassium citrate	£0.0204	Average unit cost of potassium bicarbonate and potassium citrate
	potassium bicarbonate+ sodium bicarbonate	£0.2182	Average unit cost of potassium bicarbonate and sodium bicarbonate
	potassium citrate+ sodium bicarbonate	£0.2002	Average unit cost of potassium citrate and sodium bicarbonate
	modified Shohl's solution + sodium bicarbonate	£0.0775	BNF Sodium Citrate, Sodium citrate 0.3M Oral Solution, Accessed November 2021, calculated here as average of potassium citrate and sodium citrate

Table 96: Drug acquisition costs

Treatment	Unit cost / mEq
ADV7103	0.2500
ADV7103 PAS price ([redacted]	[redacted]
Average SoC	0.1628

Health state unit costs and resource use

The resources used and the number of units per health state have been validated by clinicians in a modified Delphi panel (October 2020). Where available costs were derived from the 2019/2020 National Cost Collection and from relevant literature. Costs captured in literature were uplifted to 2019/2020 prices using the NHS cost inflation index (NHSCII). Annual percentage increases for the HSHC and NHSCII pay and price index values for years from 2009/2010 to 2019/2020 are reported in the most recent Personal Social Services Research Unit (PSSRU) unit costs of health and social care (2019/2020) report [81].

Table 97and Table 98 summarise the annual costs associated with each health state included in the

model. Patients under the discontinued treatment status are assumed to incur the same health state costs as for non-responder patients.

Table 97: Responder status costs

Response states	Resource use (Units/years)	Unit costs (£)	Sub-total (£)	Source	Description/ Comments
Responders					
Doctor/visit	2.00	£180.77	£361.54	2019/20 National Cost Collection	WF02A, Nephrology Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up
Blood test	2.00	£6.94	£13.87	NICE guideline appendices 2015 [82] Inflated using NHSCII	Full blood count test 2015 price: £6.42
Urine test	2.00	£4.41	£8.81	NICE guideline appendices 2015 Inflated using NHSCII	Urine test (using urinalysis analyser) 2015 price: £4.08
Radiography (CT scan)	1.00	£106.42	£106.42	2019/20 National Cost Collection	Diagnostic imaging code RD23Z+RD24Z Computerised Tomography Scan of Two Areas, with or without Contrast (Outpatient weighted average)
DEXA scan	0.10	£66.34	£6.63	2019/20 National Cost Collection	Diagnostic imaging Code: RD50Z: Imaging: DEXA scan (Outpatient weighted average)
Ultrasound	0.50	£32.50	£16.25	2019/20 National Cost Collection	Diagnostic imaging code: RD40Z & RD41Z Ultrasound Scan with duration of less than 20 minutes, with or without Contrast (Outpatient weighted average)
Total (cost per year)			£513.53		
Non-Responders					
Doctor/visit	4.00	£180.77	£723.08	2019/20 National Cost Collection	WF02A, Nephrology Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up
Blood test	4.00	£6.94	£27.74	NICE guideline appendices 2015 Inflated using NHSCII	Full blood count test 2015 price: £6.42
Urine test	4.00	£4.41	£17.63	NICE guideline appendices 2015 Inflated using	Urine test (using urinalysis analyser) 2015 price: £4.08

				NHSCII	
Radiography (CT scan)	2.00	£106.42	£212.85	2019/20 National Cost Collection	Diagnostic imaging code RD23Z+RD24Z Computerised Tomography Scan of Two Areas, with or without Contrast (Outpatient weighted average)
DEXA scan	0.50	£66.34	£33.17	2019/20 National Cost Collection	Diagnostic imaging Code: RD50Z: Imaging: DEXA scan (Outpatient weighted average)
Ultrasound	1.00	£32.50	£32.50	2019/20 National Cost Collection	Diagnostic imaging code: RD40Z & RD41Z Ultrasound Scan with duration of less than 20 minutes, with or without Contrast (Outpatient weighted average)
Urine infection treatment (adults)	0.50	£2.70	£1.35	Cephalosprins Cefalexin 250mg BNF, Accessed November 21	Assumed to be examined during doctors' visit (using urine test)
Total (cost per year)			£1,048.32		

*The resource utilisation listed above was validated by a panel of nephrologists and urologists

Table 98: Health state costs

Health states	Cost per year (£)	Source	Description/ Comments
Nephrolithiasis	£6,240.93	2019/20 National Cost Collection	LB75A & B: Percutaneous Nephrolithotomy with CC Score 0-1 & 2 (weighted average)
Nephrocalcinosis	£1,211.41	Kent et al [83] Inflated using NHSCII	Mean hospital cost per person-year of follow-up 2010 cost: £1,055
CKD2	£1,211.41	Kent et al [83] Inflated using NHSCII	Mean hospital cost per person-year of follow-up 2010 cost: £1,055
CKD3-4	£4,241.65	Kent et al [83] Inflated using NHSCII	Mean hospital cost per person-year of follow-up 2010 cost: £3,694
ESRD	£32,360.40	NICE NG107 [84] Inflated using NHSCII	NG107 renal replacement therapy and conservative management 2016 cost: £30,591

Transplant first year	£14,631.12	2019/20 National Cost Collection	Weighted average of codes LA01A, LA01B, LA02A, LA02B, LA03A, LA03B Plus weighted average of codes LA11Z, LA12A, LA12B Plus weighted average of codes LA13A, LA13B, LA14Z
Transplant subsequent years	£5,913.50	NHS Blood and Transplant fact sheet 7 (2009) Inflated using NHSCII	Immuno-suppression required by a patient with a transplant

Total health state costs are computed by summing the cost associated with the responder status (i.e. responder, non-responder or discontinued), the cost associated with the health state (i.e. NC, NC+NL, CKD2 etc.) and the additional cost of any transitory events occurring during the cycle.

The annual health state costs used in the model, and reported by Kent et al., reflect hospital care costs including inpatient admissions, day cases and some outpatient attendances [83]. To reflect the additional care costs associated with CKD, costs including doctor visits was assigned to the responder status. No additional cost is incurred for patients without-nephrocalcinosis.

The costs associated with kidney transplantation include the initial cost of the transplant procedure and subsequent first year cost, and ongoing maintenance costs applied to years post-transplant. The failure of kidney transplant procedure is not modelled. Costs for the first year of transplant have been obtained from the National Cost Collection 2019/2020, and costs for the post-transplant state have been obtained from the NHS Blood and Transplant fact sheet (2009) and inflated using the NHSCII index.

Adverse reaction unit costs and resource use

Costs related to the management of transient events are presented in Table 99. The costs of an osteomalacia/fracture, FFT or bone deformity event are applied as a cost per year. The costs of a GI or hypokalaemia event are applied per cycle.

Table 99: Transitory event costs

Transitory events	Cost per year (£)	Source	Description/Comments
Osteomalacia/fracture	£2,125.56	2019/20 National Cost Collection	Weighted average of Pathological Fractures HD39D, HD39E, HD39F, HE39G, HD39H
Faltering growth	£2,089.39	2019/20 National Cost Collection	Weighted average of Paediatric Faltering Growth (Failure to Thrive) with CC Score 0, 1 & 2+

			PX30A, PX30B, PX30C
Bone deformities	£3,182.68	Zipitis et al, 2006 Inflated using NHSCII	Cost of treating Vitamin D deficiency 2006 cost: £2,500
	Cost per event (£)		
GI event	£148.12	2019/20 National Cost Collection	WF01A Non-admitted face-to face attendance, follow-up, Gastroenterology
Hypokalaemia	£ 1,329.93	2019/20 National Cost Collection	Weighted average of Fluid or Electrolyte Disorders, with and without interventions KC05G, KC05H, KC05J, KC05K, KC05L, KC05M, KC05N

Miscellaneous unit costs and resource use

No miscellaneous resource used were included in the analysis.

B.3.6 Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

The mean values used in the base-case are presented in the table below (Table 100)

Table 100: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: standard error (distribution)	Reference to section in submission
Population composition	8.8% (1-3 years old age group) 23.5% (4-11 years old) 17.6% (12-17 years old) 50% (>18 years old)		B.3.2 Economic Analysis – patient population
Mean Age	2 years old (1-3 years old) 8 years old (4-11 years old) 15 years old (12-17 years old) 25 years old (>18 years old)		B.3.2 Economic Analysis – patient population
Mean Weight	12.78 (2 years old) 32 (8 years old) 59.70 (15 years old) 70.80 (25 years old)		B.3.2 Economic Analysis – patient population
Adult age threshold (years)	18	Normal SE+-20%	B.3.2 Economic Analysis – patient population
Failure to thrive age limit (years)	15	Normal SE+-20%	B.3.2 Economic Analysis – patient population
Discount rate for costs and outcomes	3.5%		B.3.5 Cost and healthcare resource use identification, measurement and valuation
Initial Health State (%)			
w/NC Children Adults NC Children	 6.66% 0.00% 86.67%	 Dirichlet Assumed SE+-20%	B.3.3 Clinical parameters and variables

Adults NC+NL Children Adults CKD2 Children Adults	85.71% 6.67% 14.29% 0.00% 0.00%		
Disease Control - Initial Efficacy (%)			
ADV7103 Children Adults SoC Children Adults	 90% 90% 43% 43%	Dirichlet Assumed SE+-20%	B.3.3 Clinical parameters and variables
Disease Control 0 to 6 month (%)			
ADV7103 Children Adults SoC Children Adults	 84.20% 84.20% 45.00% 50.00%	Dirichlet Assumed SE+-20%	B.3.3 Clinical parameters and variables
Disease Recovery 0 to 6 month (%)			
ADV7103 Children Adults SoC Children Adults	 63.64% 63.64% 10.00% 10.00%	Dirichlet Assumed SE+-20%	B.3.3 Clinical parameters and variables
Disease Control 6 to 12 month (%)			
ADV7103 Children Adults SoC Children Adults	 100% 100% 53.00% 59.00%	Dirichlet Assumed SE+-20%	B.3.3 Clinical parameters and variables
Disease Recovery 6 to 12 month (%)			

ADV7103 Children Adults SoC Children Adults	 28.60% 28.60% 10.00% 10.00%	Dirichlet Assumed SE+-20%	B.3.3 Clinical parameters and variables
Disease Control 12 to 18 month (%)			
ADV7103 Children Adults SoC Children Adults	 92.00% 92.00% 49.00% 54.00%	Dirichlet Assumed SE+-20%	B.3.3 Clinical parameters and variables
Disease Recovery 12 to 18 month (%)			
ADV7103 Children Adults SoC Children Adults	 40.00% 40.00% 10.00% 10.00%	Dirichlet Assumed SE+-20%	B.3.3 Clinical parameters and variables
Disease Control 18 to 24 month (%)			
ADV7103 Children Adults SoC Children Adults	 72.00% 72.00% 42.00% 42.00%	Dirichlet Assumed SE+-20%	B.3.3 Clinical parameters and variables
Disease Recovery 18 to 24 month (%)			
ADV7103 Children Adults SoC Children Adults	 50.00% 50.00% 10.00% 10.00%	Dirichlet Assumed SE+-20%	B.3.3 Clinical parameters and variables
Disease Control 24 to 36 month (%)			
ADV7103 Children	 80.00%	Dirichlet Assumed SE+-20%	B.3.3 Clinical parameters and variables

Adults SoC Children Adults	80.00% 41.00% 41.00%		
Disease Recovery 24 to 36 month (%)			
ADV7103 Children Adults SoC Children Adults	 67.00% 67.00% 10.00% 10.00%	Dirichlet Assumed SE+-20%	B.3.3 Clinical parameters and variables
Disease Control 36 to 48 month (%			
ADV7103 Children Adults SoC Children Adults	 80.00% 80.00% 41.00% 41.00%	Dirichlet Assumed SE+-20%	B.3.3 Clinical parameters and variables
Disease Recovery 36 to 48 month (%)			
ADV7103 Children Adults SoC Children Adults	 67.00% 67.00% 10.00% 10.00%	Dirichlet Assumed SE+-20%	B.3.3 Clinical parameters and variables
Treatment Discontinuation for non-responders (1 year probability)			
ADV7103 Children Adults SoC Children Adults	 0.00% 3.30% 39.00% 45.00%	Dirichlet Assumed SE+-20%	B.3.3 Clinical parameters and variables
Treatment after discontinuation			
ADV7103 Average SoC No treatment	 50.00% 50.00%	ADV7103 only Dirichlet Assumed SE+-20%	

SoC Average SoC No treatment		0.00% 100.00%				
Discontinuation of CKD3b or CKD4 (% amongst CKD3-4)						
ADV7103 SoC		20.00% 20.00%			Dirichlet Assumed SE+-20%	
GI (events/dose [mEq]) rate						
ADV7103 SoC		0.0000021 0.0000028			Gamma Assumed SE+-20%	B.3.3 Clinical parameters and variables
Health State transitions 1 year probability						
From	**To**	**Responders**	**Non-responders**	**Discontinuation**	**Measurement of uncertainty and distribution: standard error (distribution)**	**Reference to section in submission**
w/NC NC NC+NL NC NC+NL CKD2 CKD3-4 ESRD	NC NC+NL NC CKD2 CKD2 CKD3-4 ESRD Transplant	12.56% 4.66% 20.00% 3.82% 3.82% n/a n/a n/a	25.13% 9.23% 20.00% SOLVER SOLVER 3.00% 3.00% n/a	100.00% 40.00% 20.00% 7.96% 7.37% 7.80% 7.80% 5.50%	Dirichlet Assumed SE+-20%	B.3.3 Clinical parameters and variables
Transitory events 1-year probability		**Non-Responders**	**Discontinuation**		**Measurement of uncertainty and distribution: standard error (distribution)**	**Reference to section in submission**
Hypokalaemia Failure to thrive Failure to thrive recovery Fracture Osteomalacia Bone deformities		9.39% 12.91% 10.00% 0.17% 40.00% 8.09%	72.00% 12.91% 10.00% 0.34% 80.00% 16.17%		Gamma Assumed SE+-20%	B.3.3 Clinical parameters and variables
Disease and Event related Mortality 1-year probability					**Measurement of uncertainty and distribution: standard error (distribution)**	**Reference to section in submission**
CKD3-4 ESRD Transplant Hypokalaemia No CKD CKD ESRD Fracture		13.83% 17.70% 5.30% 0.67% 2.28% 5.82% 3.54%			Gamma Assumed SE+-20%	B.3.3 Clinical parameters and variables
Treatment costs (unit cost/mEq)		**Cost**			**Measurement of uncertainty and distribution: standard error (distribution)**	**Reference to section in submission**
ADV7103 Acquisition		£0.2500			Gamma Assumed SE+-20%	B.3.5 Cost and healthcare resource use

Average SoC Acquisition	£0.1628	*not varied in PSA	identification, measurement and valuation
Management costs (per year)			
Health states Responders Non-responders Nephrolithiasis Nephrocalcinosis CKD2 CKD3-4 ESRD Transplant (first year) Transplant (subsequent years) Transitory event Osteomalacia/fracture Failure to thrive Bone deformities GI event Hypokalaemia	 £513.53 £1,048.32 £6,240.93 £1,211.41 £1,211.41 £4,241.65 £32,360.40 £14,631.12 £5,913.50 £2,125.56 £2,089.39 £3,182.68 £148.12 £1,329.93	Gamma Assumed SE+-20%	B.3.5 Cost and healthcare resource use identification, measurement and valuation
HRQoL (per year)	**Utility**	**Measurement of uncertainty and distribution: standard error (distribution)**	**Reference to section in submission**
w/NC NC+NL NC CKD2 CKD3-4 ESRD Transplant first year Transplant subsequent years	0.856 0.830 0.850 0.850 0.770 0.530 0.830 0.700	Beta Assumed SE+-20%	B.3.5 Measurement and valuation of health effects
HRQoL decrement			
Transitory Events Disutility/year Osteomalacia/fracture Failure to thrive Bone deformities Disutility/event GI event Hypokalaemia Loss of QoL in Acquired dRTA	 0.170 0.130 0.352 0.001 0.050 0.180	Gamma Assumed SE+-20%	B.3.5 Measurement and valuation of health effects
Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease, GI, gastrointestinal			

Key model assumptions

- Patients are stratified based on the age at the start of the model into 4 age groups (1 to 3 years old, 4 to 11 years old, 12 to 17 years old and over 18 years old).
- All patients in age groups 1 to 3 (1 to 3 years old, 4 to 11 years old and 12 to 17 years old respectively at the start of the model) are assumed to be affected by primary dRTA.
- All patients starting in age group 4 (over 18 years old at the start of the model) are assumed to be affected by acquired dRTA.
- Patients can enter the model without Nephrocalcinosis, with Nephrocalcinosis, or with Nephrocalcinosis+Nephrolithiasis.
- No transition allowed from patients Without Nephrocalcinosis to CKD2. Only patients with Nephrocalcinosis or Nephrocalcinosis + Nephrolithiasis are at risk of progressing to CKD2.
- No transition allowed from Nephrocalcinosis or Nephrocalcinosis + Nephrolithiasis to CKD3-4 or ESRD as these patients must first experience CKD2
- All age groups progress independently, and in each age group, patients have same age and weight, and these are updated at any cycle.
- The response rate (% of disease controlled) is treatment dependent but is assumed to be the same for the patients without Nephrocalcinosis, with Nephrocalcinosis, and Nephrocalcinosis+Nephrolithiasis
- Patients receiving ADV7103 have to stop treatment when eGFR levels equal, or fall below, 44 ml/min/1.73m^2. Thus, the patients in the non-responder (disease-uncontrolled) group reaching the stages CKD3b-4 (defined as a fixed proportion among the health state CKD3-4) will discontinue treatment, and patients on ESRD will automatically stop treatment
- Disease-related mortality is only applied to severe health states (CKD3-4, ESRD and kidney transplant) and after a hypokalaemia or musculoskeletal event. The same risk is applied to children and adults.
- No adjustment has been made between the health state utility values for responders, non-responders, and discontinued patients. For example, patients in the CKD2 health state will have a utility score of 0.850 with no adjustment for treatment response status.
- Age specific background mortality is included in the model and applied equally across all health states.
- Age-standardised mortality rates for disease and event related mortality estimates have not been used in the model.
- No age-related HRQoL adjustment is made in the model.

B.3.7 Base-case results

The deterministic base case cost-effectiveness analysis results of ADV7103 compared with SoC over a lifetime horizon are summarised in Table 101 (list price) and Table 102 (PAS price).

Treatment with ADV7103 compared with SoC was associated with increased life years (7.95 per patient) and increased QALYs (9.44 per patient) at an incremental cost of £206,104 per patient at list price and [redacted] per patient at PAS price.

Treatment with ADV7103 is cost-effective compared with SoC at a willingness-to-pay threshold of £30,000/QALY at list price with an ICER of £21,828, and at a willingness-to-pay threshold of £20,000/QALY at PAS price with an ICER of [redacted].

The incremental QALYs were driven by an increase in life years and longer duration spent without CKD, and in earlier stages of CKD. The Markov traces, displaying the distribution of patients across health states and responder status are presented in Appendix J.

Table 103 and Table 104 provide a summary of the disaggregated costs associated with ADV7103 and SoC. The additional costs associated with ADV7103, and main driver of the difference in costs, were due to the higher acquisition costs compared with SoC treatment. Treatment with ADV7103 was associated with a reduction in total management costs as a result of fewer adverse events, and fewer ESRD and transplant patients.

Table 101: Base case deterministic results – list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	£164,593.34	17.04	8.43					
ADV7103	£370,697.65	24.99	17.87	£206,104.31	7.95	9.44	£21,827.49	£21,827.49
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 102: Base case deterministic results – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	£164,593.34	17.04	8.43					
ADV7103	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 103: Base case disaggregated costs (per person) – list price

Per person costs	ADV7103	SoC	Incremental
Total cost	£370,698.65	£164,593.34	£206,104.31
Treatment costs	£291,713.20	£20,814.72	£270,898.47
Management costs	£78,984.45	£143,778.62	-£64,794.16
w/NC, NC, NC+NL costs	£47,279.49	£52,448.90	-£5,169.41
CKD costs	£17,518.48	£18,701.62	-£1,183.14
ESRD costs	£1,036.91	£11,852.85	-£10,815.94
Transplant costs	£237.65	£3,109.98	-£2,872.33
Musculoskeletal costs	£11,222.01	£43,463.73	-£32,241.73
Other costs (GI/hypokalaemia)	£1,689.92	£14,201.53	-£12,511.61

Table 104: Base case disaggregated costs (per person) - PAS price

Per person costs (PAS price)	ADV7103	SoC	Incremental
Total cost	[redacted]	£164,593.34	[redacted]
Treatment costs	[redacted]	£20,814.72	[redacted]
Management costs	£78,984.45	£143,778.62	-£64,794.16
w/NC, NC, NC+NL costs	£47,279.49	£52,448.90	-£5,169.41
CKD costs	£17,518.48	£18,701.62	-£1,183.14
ESRD costs	£1,036.91	£11,852.85	-£10,815.94
Transplant costs	£237.65	£3,109.98	-£2,872.33
Musculoskeletal costs	£11,222.01	£43,463.73	-£32,241.73
Other costs (GI/hypokalaemia)	£1,689.92	£14,201.53	-£12,511.61

B.3.8 Sensitivity analyses

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed to explore the effect of uncertainty associated with all model inputs. PSA results for 1,000 iterations are presented in Table 105(list price) and Table 106 (PAS price). The mean incremental costs and QALYs of ADV7103 compared with SoC were calculated to estimate the probabilistic ICER.

The probabilistic results were highly comparable with the deterministic results. Using the list price, the incremental per patient QALYs and costs in the probabilistic analysis results were 9.35 QALYs and £203,652, compared to 9.44 QALYs and £206,104 in the deterministic analysis results. Using the PAS price, the incremental per patient QALYs and costs in the probabilistic analysis results were 9.33 QALYs and £111,438, compared to 9.44 QALYs and £115,889 in the deterministic analysis results.

The ICER in the probabilistic analysis remained cost effective at list price with an ICER of £21,787.59, and at PAS price with an ICER of £11,943.31. The probabilities of cost-effectiveness at willingness-to-pay threshold of £30,000/QALY were 85.5% at list price, and 98.4% at PAS price. The PSA scatterplots and cost-effectiveness acceptability curves are shown in Figures 20-23.

Table 105: Base case probabilistic results – list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
SoC								
ADV7103				£203,652.18		9.35	£21,787.59	£21,787.59
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 106: Base case probabilistic results – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
SoC								
ADV7103				[redacted]		[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Figure 20: Cost-effectiveness plane from PSA (1,000 simulations) - list price

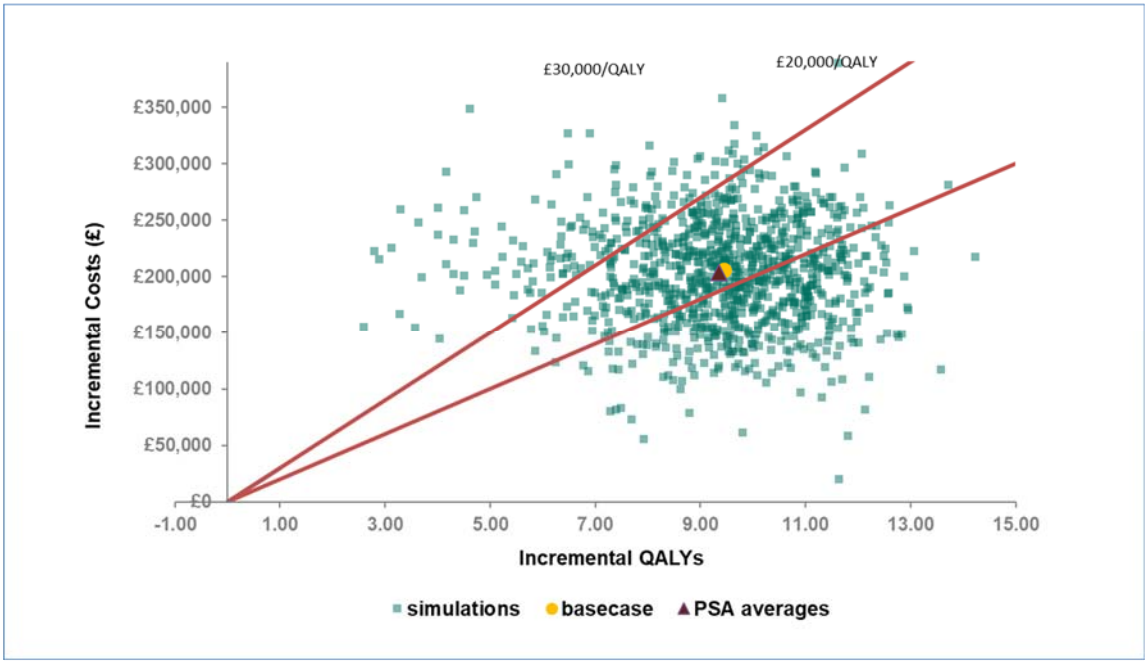


Figure 21: Cost-effectiveness acceptability curve from PSA (1,000 simulations) - list price

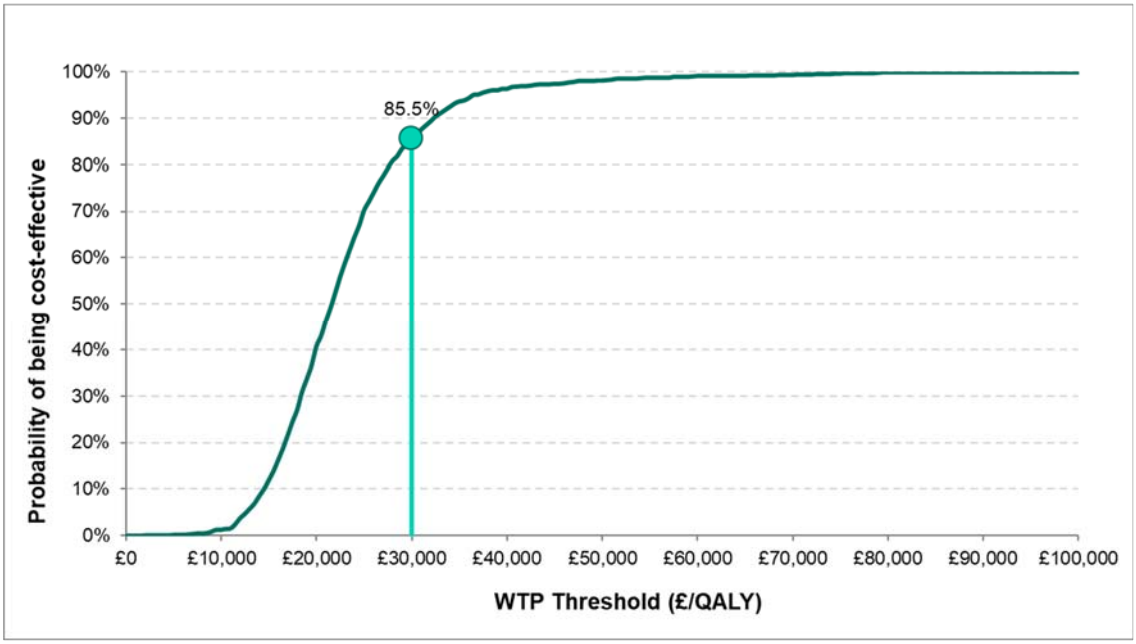


Figure 22: Cost-effectiveness plane from PSA (1,000 simulations) – PAS price

Figure 23: Cost-effectiveness acceptability curve from PSA (1,000 simulations) – PAS price

Deterministic sensitivity analysis

Deterministic sensitivity analyses (DSA) were performed to explore the effect of uncertainty

associated with varying individual model inputs. All model inputs were varied by 10%, except discount rates (lower = 1.5%, higher = 5%), and the model time horizon (lower = 40 years, higher = lifetime). The top 20 inputs with the greatest impact on the ICERs are presented in descending order as a tornado plot in Figure 24 (list price) and Figure 25 (PAS price).

In the DSA, a reduction in the discount rate of costs had the largest impact on increasing the ICER (by 15,532/QALY gained for the list price, and by [redacted] QALY gained for the PAS price), whereas a reduction in the discount rate of outcomes had the largest impact on decreasing the ICER (by -£9,700/QALY gained for the list price, and by [redacted]/QALY gained for the PAS price). These results can be explained by the increase in life years and longer duration spent without CKD, and in earlier stages of CKD for patients treated with ADV7103. For example, after 25 years in the model, there are approximately 957 patients alive in the ADV7103 treatment arm, compared with 510 in the SoC arm. By lowering the discount rate, the incremental cost of treating patients with ADV7103 compared with SoC increases. By comparison, lowering the discount rate for outcomes decreases the ICER as the longer-term ESRD and transplant costs that are more prevalent in the SoC arm, are increased.

For the list price, ADV7103 is no longer cost-effective when compared with SoC at a WTP threshold of £30,000/QALY when the lower bound discount rate for costs, or the upper bound discount rate for outcomes is used in the model. For the PAS price, ADV7103 is no longer cost-effective when compared with SoC at a WTP threshold of £20,000/QALY but remains cost-effective at a WTP threshold of £30,000/QALY when the lower bound discount rate for costs is used in the model.

Figure 24: Tornado plot of DSA (top 20) – list price

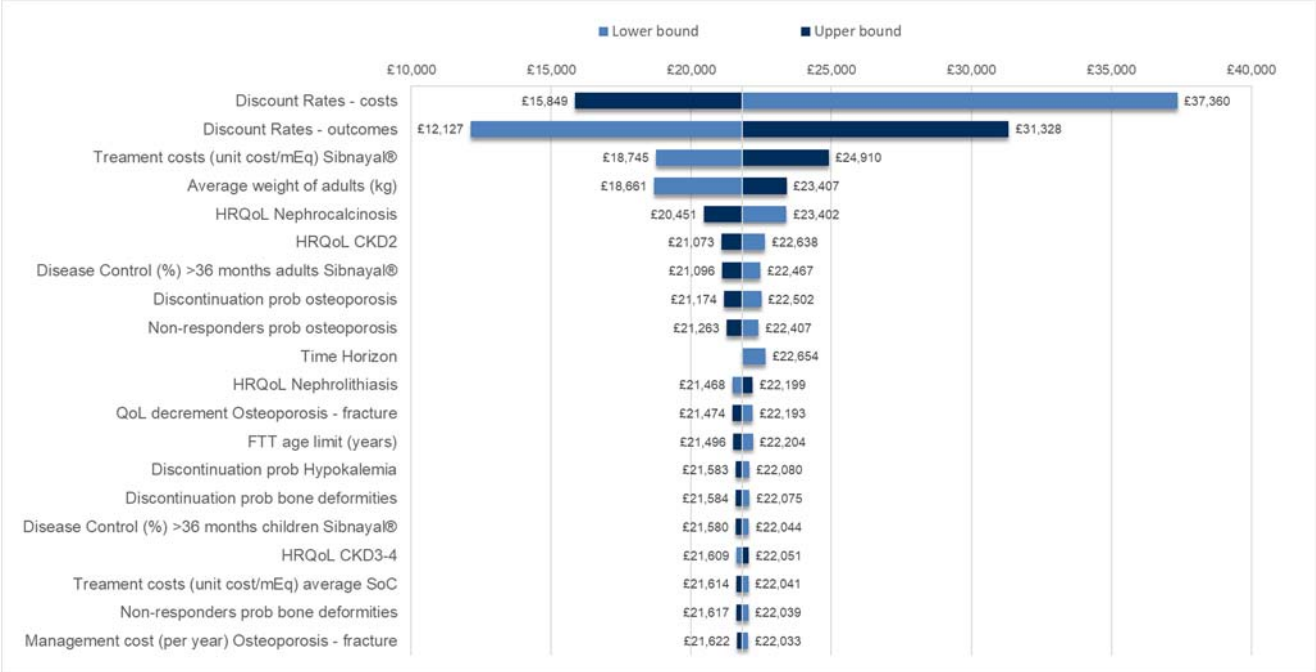


Figure 25: Tornado plot of DSA (top 20) – PAS price

Scenario analysis

A range of scenario analyses were conducted to test the robustness of the model to alternative model inputs and assumptions. The details of the undertaken scenario analyses and the results of the scenario analyses, presented as the incremental costs, QALYs and ICERs of ADV7103 compared with SoC are shown in Table 107(list price) and Table 108 (PAS price). The base case ICER has been presented for reference.

At list price, for all scenarios other than scenario 6, the ICER for ADV7103 remained below a WTP threshold of £30,000/QALY. In no scenario did the ICER fall below a WTP threshold of £20,000/QALY. Scenario 6 assumed that patients who discontinued treatment (to receive no treatment) incurred the same risk of an adverse event as patients who were receiving treatment but were non-responders.

At PAS price, the results show that the cost-effectiveness analysis is robust and ADV7103 consistently remained cost-effective with an ICER below £20,000/QALY.

Table 107: Summary of scenario analyses – list price

Scenario	Base case value		Alternative inputs		ΔCosts (£)	ΔQALYs	ICER (£/QALY)
Base case					£206,104.31	9.44	£21,827.49
1. B22CS ADV7103 alternative doses	Age	Dose (B21C)	Age	Dose (B22C)	£277,311.88	9.44	£29,370.45
	3	6.110	3	4.806			
	11	3.800	11	3.413			
	17	2.790	17	2.606			
	18	1.740	18	2.260			
2. Reduced discount rate for both costs and outcomes	Costs and Outcomes = 3.5%		Costs and Outcomes = 1.5%		£352,765.73	17.00	£20,756.64
3. Assume same proportion for initial disease control for both treatment arms	ADV7103	SoC	ADV7103	SoC	£207,092.48	9.34	£22,163.09
	90.00%	43.00%	43.00%	43.00%			
	90.00%	43.00%	43.00%	43.00%			
4. Assume same discontinuation rate (non-responders) for both treatment arms	ADV7103	SoC	ADV7103	SoC	£124,104.27	5.94	£20,900.03
	0.00%	39.00%	39.00%	39.00%			
	3.30%	45.00%	45.00%	45.00%			
5. In ADV7103 arm, assume all discontinued patients receive no treatment	50% receive SoC treatment (ADV7103 arm)		0% receive SoC treatment (ADV7103 arm)		£205,564.27	9.41	£21,845.18
6. Assume same risk of transitory event in non-responder and discontinuation responder status	Non-responder	Disc.	Non-responder	Disc.	£219,185.03	6.87	£31,891.50
	9.39%	72.00%	9.39%	9.39%			
	12.91%	12.91%	12.91%	12.91%			
	10.00%	10.00%	10.00%	10.00%			
	0.17%	0.34%	0.17%	0.17%			
	40.00%	80.00%	40.00%	40.00%			
	8.09%	16.17%	8.09%	8.09%			
7. Assume lowest rate of efficacy (from all trial months) in treatment control and response for months 36 to 48 in the ADV7103 arm, and highest rate in SoC arm	Disease control ADV7103 = 80%, 80% Disease response ADV7103 = 67%, 67% Disease control SoC = 41%, 41% Disease response SoC = 10%, 10%		Disease control ADV7103 = 72%, 72% (18 to 24 months) Disease response ADV7103 = 28.6%, 28.6% (6 to 12 months) Disease control SoC = 53%, 59% (6 to 12 months) Disease response SoC = 10%, 10% (all months)		£185,962.83	7.31	£25,441.78

Table 108: Summary of scenario analyses – PAS price

Scenario	Base case value		Alternative inputs		ΔCosts (£)	ΔQALYs	ICER (£/QALY)
Base case					[redacted]	[redacted]	[redacted]
1. B22CS ADV7103 alternative doses	Age	Dose (B21C)	Age	Dose (B22C)	[redacted]	[redacted]	[redacted]
	3	6.110	3	4.806			
	11	3.800	11	3.413			
	17	2.790	17	2.606			
	18	1.740	18	2.260			
2. Reduced discount rate for both costs and outcomes	Costs and Outcomes = 3.5%		Costs and Outcomes = 1.5%		[redacted]	[redacted]	[redacted]
3. Assume same proportion for initial disease control for both treatment arms	ADV7103	SoC	ADV7103	SoC	[redacted]	[redacted]	[redacted]
	90.00%	43.00%	43.00%	43.00%			
	90.00%	43.00%	43.00%	43.00%			
4. Assume same discontinuation rate (non-responders) for both treatment arms	ADV7103	SoC	ADV7103	SoC	[redacted]	[redacted]	[redacted]
	0.00%	39.00%	39.00%	39.00%			
	3.30%	45.00%	45.00%	45.00%			
5. In ADV7103 arm, assume all discontinued patients receive no treatment	50% receive SoC treatment (ADV7103 arm)		0% receive SoC treatment (ADV7103 arm)		[redacted]	[redacted]	[redacted]
6. Assume same risk of transitory event in non-responder and discontinuation responder status	Non-responder	Disc.	Non-responder	Disc.	[redacted]	[redacted]	[redacted]
	9.39%	72.00%	9.39%	9.39%			
	12.91%	12.91%	12.91%	12.91%			
	10.00%	10.00%	10.00%	10.00%			
	0.17%	0.34%	0.17%	0.17%			
	40.00%	80.00%	40.00%	40.00%			
	8.09%	16.17%	8.09%	8.09%			
7. Assume lowest rate of efficacy (from all trial months) in treatment control and response for months 36 to 48 in the ADV7103 arm, and highest rate in SoC arm	Disease control ADV7103 = 80%, 80% Disease response ADV7103 = 67%, 67% Disease control SoC = 41%, 41% Disease response SoC = 10%, 10%		Disease control ADV7103 = 72%, 72% (18 to 24 months) Disease response ADV7103 = 28.6%, 28.6% (6 to 12 months) Disease control SoC = 53%, 59% (6 to 12 months) Disease response SoC = 10%, 10% (all months)		[redacted]	[redacted]	[redacted]

B.3.9 Subgroup analysis

Subgroup analysis was conducted to explore the effects when only specific age groups within the model are accounted for. To do this, the proportion of all age groups not of interest were set to 0% on the 'Settings' sheet of the model. The results of the subgroup analyses, presented as the total and incremental costs, QALYs and ICERs of ADV7103 compared with SoC are shown in Table 109 (list price) and Table 110 (PAS price). The base case ICER has been provided for reference.

Table 109: Subgroup analysis using list price

Technologies	Total Costs (£)	Total QALYs	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
Base case					
SoC	£164,593.34	8.43			
ADV7103	£370,697.65	17.87	£206,104.31	9.44	£21,827.49
Age group 1-3					
SoC	£190,828.64	8.17			
ADV7103	£391,755.90	20.59	£200,927.26	12.41	£16,184.42
Age group 4-11					
SoC	£179,840.78	9.22			
ADV7103	£405,304.50	20.67	£225,463.72	11.45	£19,684.30
Age group 12-17					
SoC	£158,089.57	10.77			
ADV7103	£377,299.70	20.72	£219,210.13	9.95	£22,029.92
Age group 18+					
SoC	£155,083.77	7.27			
ADV7103	£348,365.79	15.06	£193,282.08	7.79	£24,805.49

Table 110: Subgroup analysis using PAS price

Technologies	Total Costs (£)	Total QALYs	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
Base case					
SoC	£164,593.34	8.43			
ADV7103	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age group 1-3					
SoC	£190,828.64	8.17			
ADV7103	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age group 4-11					
SoC	£179,840.78	9.22			
ADV7103	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age group 12-17					
SoC	£158,089.57	10.77			
ADV7103	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Age group 18+					
SoC	£155,083.77	7.27			
ADV7103	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B.3.10 Validation

Validation of cost-effectiveness analysis

A cohort-based Markov model was used to illustrate patients' transition through different health states associated with dRTA and CKD. No previous cost-effectiveness studies for dRTA could be identified in literature. The model framework is considered appropriate when a repeated set of outcomes is possible through time, as it is the case in dRTA. The model input and assumptions, as well as the clinical pathway were validated by a Delphi panel (Oct 2020) involving nephrologists and urologists from Scotland and England (data on file). In addition further validation with a lead dRTA clinician was sort (November 2021).

Internal model validation was carried out by the company that produced the model, Syneos Health.

B.3.11 Interpretation and conclusions of economic evidence

Overall findings

This analysis assessed the cost-effectiveness of ADV7103 compared with SoC for patients with dRTA. The treatment effect of ADV7103 was modelled as the ability of patients to remain and return to a disease-controlled state (defined as sufficient alkali therapy and metabolic acidosis being absent) using patient level data from the B21CS study. Health state and adverse event utilities were derived from literature. Costs were identified from UK sources, including the National Cost Collection, the BNF, and the literature.

Treatment with ADV7103 is cost-effective compared with SoC at a WTP threshold of £30,000/QALY at list price with an ICER of £21,828, and at a WTP threshold of £20,000/QALY at PAS price with an ICER of [redacted]. A PSA was performed to explore the effect of the high levels of uncertainty associated with model inputs. The ICER in the probabilistic analysis remained cost effective at list price with an ICER of £21,788, and at PAS price with an ICER of [redacted]. The probabilities of cost-effectiveness at WTP threshold of £30,000/QALY were 85.5% at list price, and [redacted]% at PAS price.

Strengths and Limitations

The decision analytic model was based on a multicentre, open-label, non-inferiority sequential studies B21CS (and the extension of B22CS) performed to evaluate the efficacy, safety, and acceptability of ADV7103 relative to SoC on correcting metabolic acidosis in both paediatric and adult patients with an established dRTA, whether inherited or acquired. This makes the analysis relevant and inclusive of the affected dRTA patient population. Although patients in the B21CS study were recruited from France and Slovakia, results from the trial were validated by clinicians to ensure appropriateness and generalisability to UK settings.

Underlying efficacy within the model was informed using trial data from B21CS and B22CS. However, the B21CS study was a sequential study, designed to enable evaluation of the non-inferior efficacy on metabolic acidosis of ADV7103 compared with SoC. As such, no head-to-head data comparing

ADV7103 with SoC were available. Uncertainty in the relative efficacy of ADV7103 compared with SoC was tested in sensitivity and scenario analyses.

HRQoL and resource used data were not collected during the trials. Instead, the HRQoL and resource use inputs used in this analysis were derived from a targeted literature review and validated by a panel of specialised dRTA clinicians, adult and paediatric urologists and nephrologists. Using all available evidence at this time point, a range of scenario and sensitivity analyses have shown the model to be robust. It is recommended that future research focus on collecting real-world evidence on HRQoL or costs associated with ADV7103 treatment.

Conclusion

Despite the limitations identified above, scenario and subgroup analyses demonstrated the base case cost-effectiveness results (at PAS price) to be robust to variation in model inputs and assumptions. Although more costly, ADV7103 leads to larger benefits accrued in terms of life years gained per person (7.95) and QALYs gained per person (9.44).

In summary, the cost-effectiveness analysis shows ADV7103 to represent a cost-effective use of NHS resources compared with SoC treatment for people with dRTA where there is an evident unmet need.

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B.5 Appendices

- Appendix C: SmPC and EPAR
- Appendix D: Identification, selection and synthesis of clinical evidence (see sections 2.1, 2.4, 2.5 and 2.9)
- Appendix E: Subgroup analysis (see section 2.7)
- Appendix F: Adverse reactions (see section 2.10)
- Appendix G: Published cost-effectiveness studies (see section 3.1) (See Appendix D)
- Appendix H: Health-related quality of life studies (see section 3.4.3) (see Appendix D)
- Appendix I: Cost and healthcare resource identification, measurement, and valuation (see section 3.5)
- Appendix J: Clinical outcomes and disaggregated results from the model (see sections 3.7.1–3.7.2)
- Appendix K: Checklist of confidential information

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Slow-release potassium bicarbonate and potassium citrate for treating distal renal tubular acidosis [ID3787]

Clarification questions

December 2021

File name	Version	Contains confidential information	Date
ID3787 potassium bicarbonate clarification letter v2 from ERG 151221 FINAL v1	V1	Yes	14/01/2022

Section A: Clarification on effectiveness data

Clinical and statistical questions:

A1. ***Priority*: Clarify why 2 patients planned to be included in B22CS did not participate (page 55). It appears that the reason for one patient is stated at the bottom of page 55.**

Two patients, who had the possibility to be enrolled in B22CS Study after participating in B21CS Study, were not willing to continue in B22CS Study:

1. An adult patient (Subject # 006-001) with acquired dRTA (all other patients had inherited dRTA, the most severe form of dRTA), who preferred to pursue her previous usual treatment as it was not so constraining for her, and she was not motivated to follow the B22CS study procedures. The previous treatment was an official preparation of potassium citrate further dissolved in water by the patient.

2. A child (Subject # 005-005, 8 years old) who completed B21CS Study but did not continue in B22CS Study, without giving more information about that decision.

A2. *Priority*: CS page 50 states that the ITT set for B21CS included all 37 patients and that 32 patients completed the study with 2 of these excluded from the PP set due to major protocol deviations. Please reconcile these numbers for the ITT and PP sets with those shown in Table 33. Also please clarify the reason for different numbers in the SoC and ADV7103 ITT sets and whether there is possibility of bias in the ITT analysis from informative censoring.

The numbers of patients for the ITT set and the PP set are presented in Table 1.

Table 1: Number of subjects for ITT set and PP set according to the statistical analyses

Subject number	Enrolled / Completed	ITT set	PP set
Overall	37 / 32	37	30
Descriptive analysis			
Overall		35	30
SPI - SoC		34	29
SPIII – ADV7103		31	30
Non-inferiority and superiority analyses			
SPI - SoC		34	29
SPIII – ADV7103		31	29

There are 37 patients in the ITT set. A total of 7 patients were excluded from the PP set: 2 patients due to major protocol deviations (Patient # 001-006 due to treatment schedule not respected and examination not done, and Patient # 202-001 due to schedule timepoint not respected and missing data); and 5 patients due to early study discontinuation (Patients # 005-001, 005-003, 005-004, 005-006 and 015-002). Therefore, 30 patients had valid pre-dose plasma bicarbonate values in any of the two study periods (29 patients in SPI and 30 patients in SPIII) in the PP set.

The reason for different numbers in the SoC and ADV7103 ITT sets and the potential impact on the ITT analysis is explained here below.

Out of the 37 patients in the ITT set, 35 patients had valid pre-dose plasma bicarbonate values in any of the two study periods (34 patients in SPI and 31 patients in SPIII).

Due to the fixed sequence design of the study, there is a possibility of bias on the ITT analysis due to missing data in the superiority analysis using a mixed model, which the Sponsor acknowledged in Section B.2.5 of Document B (Company evidence submission). However, the magnitude of the effect observed is too great to have been an artifact of missing data, this was verified as superiority was also demonstrated in the following analyses that address the issue of the missing data in different ways:

- On the PP analysis set using a paired t-test (Page 74 of the report)
- Using LOCF imputation (Pages 75 and 76 of the report)
- Using WOC imputation (Pages 75 and 76 of the report)

Also, a tipping point analysis (Page 75 of the report) illustrated that a tipping point of 5.8 mmol/L would have been needed in the missing data as to not demonstrate superiority. The lack of likelihood of such a tipping point is discussed in Page 76 of the report.

A3. *Priority*: CS Table 63 and Table 65. Please reference the source of the initial health state proportions and ADV7103 proportions for disease control and disease recovery. Also in Table 64, please clarify the source as the table references don't seem to correspond to those in the CSR.

Table 63 –Source: Table 2.7.3-12 Demographics and key baseline characteristics – Study B21CS – EMA Module 2 Clinical Efficacy document

Table 63: Initial Health State

Age group	Without Nephrocalcinosis	Nephrocalcinosis	Nephrocalcinosis + Nephrolithiasis	Source/Justification
Children	6.66%	86.67%	6.67%	B21CS trial data
Adults	0.00%	85.71%	14.29%	B21CS trial data

Copy of Table 2.7.3-12 Demographics 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)

Source: Table 14.1.3.1, Table 14.1-3.3, Listing 16.2.4-1.1.2 – B21CS CSR

Abbreviations: BMI= body mass index, mths=months, N/A=not applicable, SD=standard deviation, yrs.=years, a: Age is calculated from date of screening and date of birth; b: Weight and height are taken from screening

Table 65: Disease control and Recovery across treatment arms

ADV7103							
Disease control (%)	0-6 months	6-12 months	12-18 months	18-24 months	24-36 months	36-48 months	Source
Children	84.21%	100.00%	92.00%	72.00%	88.89%	81.82%	*PLD up to 48 months*
Adults	84.21%	100.00%	92.00%	72.00%	88.89%	81.82%	
Disease recovery							
Children	63.64%	28.57%	40.00%	50.00%	66.67%	40.00%	*PLD up to 48 months*
Adults	63.64%	28.57%	40.00%	50.00%	66.67%	40.00%	
SoC							
Disease control (%)							
Children	40.23%	47.78%	43.96%	34.40%	42.47%	39.09%	*Assumes same relative efficacy of ADV7103 versus SoC across time*
Adults	40.23%	47.78%	43.96%	34.40%	42.47%	39.09%	
Disease recovery							
Children	10.00%	10.00%	10.00%	10.00%	10.00%	10.00%	*Assumes same relative efficacy of ADV7103 versus SoC across time*
Adults	10.00%	10.00%	10.00%	10.00%	10.00%	10.00%	

Source for Table 65 – Patient level data (48 months) for Sibnayal Disease Control and recovery. Assumed disease control and recovery/ relative efficacy for SoC based on ratio of efficacy from B21CS trial data. (PLD available on request)

Table 64: Initial Disease control

Age group	**ADV7103**	**Source/Justification**	**SoC**	**Source/Justification**
Children	90.00%	CSR table 2.7.3-21	43.00%	CSR table 2.7.3-21
Adults	90.00%	CSR table 2.7.3-21	43.00%	CSR table 2.7.3-21

Table 64 Source: Table 2.7.3-21 Bicarbonataemia non-responders Study B21CS (PP & ITT sets) (EMA Module 2 Clinical Efficacy)

Copy of Table 2.7.3-21: Bicarbonataemia non-responders - Study B21CS (PP & ITT sets)

Number (%) of non-responders with at least one value of bicarbonataemia (mmol/L) below the normal lower limit - on Day 2 t0, Day 3 t0, Day 4 t0					
	PP Set			**ITT Set**	
SoC	**ADV7103**	**n/N (%)**	**SoC**	**ADV7103**	**n/N (%)**
No	No	10/29 (34%)	No	No	10/30 (33%)
Yes	No	12/29 (41%)	Yes	No	13/30 (43%)
No	Yes	1/29 (3.4%)	No	Yes	1/30 (3.3%)
Yes	Yes	6/29 (21%)	Yes	Yes	6/30 (20%)
	p=0.003 [a]			p=0.002[a]	
Number (%) of non-responders with all values of bicarbonataemia (mmol/L) below the normal lower limit, on Day 2 t0, Day 3 t0, Day 4 t0					
	PP Set			**ITT Set**	
SoC	**ADV7103**	**n/N (%)**	**SoC**	**ADV7103**	**n/N (%)**
No	No	22/29 (76%)	No	No	23/30 (77%)
Yes	No	6/29 (21%)	Yes	No	6/30 (20%)
Yes	Yes	1/29 (3.4%)	Yes	Yes	1/30 (3.3%)
	p=0.031[a]			p=0.031[a]	
Number (%) of non-responders with the mean value of bicarbonataemia (mmol/L) below the normal lower limit, on Day 2 t0, Day 3 t0, Day 4 t0					
	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%)
Yes	Yes	3/29 (10%)	Yes	Yes	3/30 (10%)
	p<0.001[a]			p<0.001[a]	

Abbreviations: ITT=intent-to-treat, PP=per protocol, SoC=standard of care – No=responder, Yes=non-responder

Note: Post-dose samples are excluded from the analysis. n=number of patients per combination of treatment responses (No/No, No/Yes, Yes/No or Yes/Yes), N=total number of patients for whom data are available, %=proportion with N as the denominator for calculation of proportions. [a]: exact p-value obtained from a McNemar's test

A4. Priority: CS Table 64. Please explain the meaning of the assumption that relative efficacy is constant across time. The ratio of the proportions between treatments is not constant.

Correction made to model. SoC data is for the initial response at Day 5. The same ratio has then been applied at every time point. This was corrected in the updated model; to make it clearer the relative efficacy is now clearly displayed in 'Clinical efficacy' and the clinical parameters for SoC are calculated based on this relative efficacy.

A5. *Priority*: Clinical advice to the ERG suggests that all attempts would be made to ensure continuation of treatment in children 14 years of age and under. Provide further information on how the key opinion leader estimate that 39% of children discontinue SoC treatment each year if they are non-responders (Table 66) was elicited.

Advisory Board 22 October 2020 – Clinicians were asked questions until a consensus was reached around treatment compliance for children and adults. Estimations were also given via a Slido questionnaire (the same questions) asking for a percentage (free choice not banded). A compliance rate of 39% was established from these figures, with Clinicians noting this varied with age with younger children being more compliant (as care is more closely directed and enforced by parents / carers) to much less compliant as children entered teenage years and supervision over compliance / adherence to treatment wanes.

The advisory board was conducted as two-stage modified Delphi style research. Recruitment was targeted at expert nephrologists and urologists. 23 invitations were despatched. 11 nephrologists participated in stage 1 of this Delphi research. Individual telephone discussions were conducted with adult and paediatric nephrologists from England, Ireland, Scotland and Wales during September and October 2020. The duration of these calls was approximately 45 minutes

The panel on workshop on Thursday 22nd October 2020 was attended by the 11 nephrologist and 1 urologist. The objective of this meeting was to refine the findings from the individual discussions and seek consensus where this was lacking. Discussion was accompanied by voting software to gain further valuable insights from the panel. The report presents an anonymised and consolidated summary (included in reference pack).

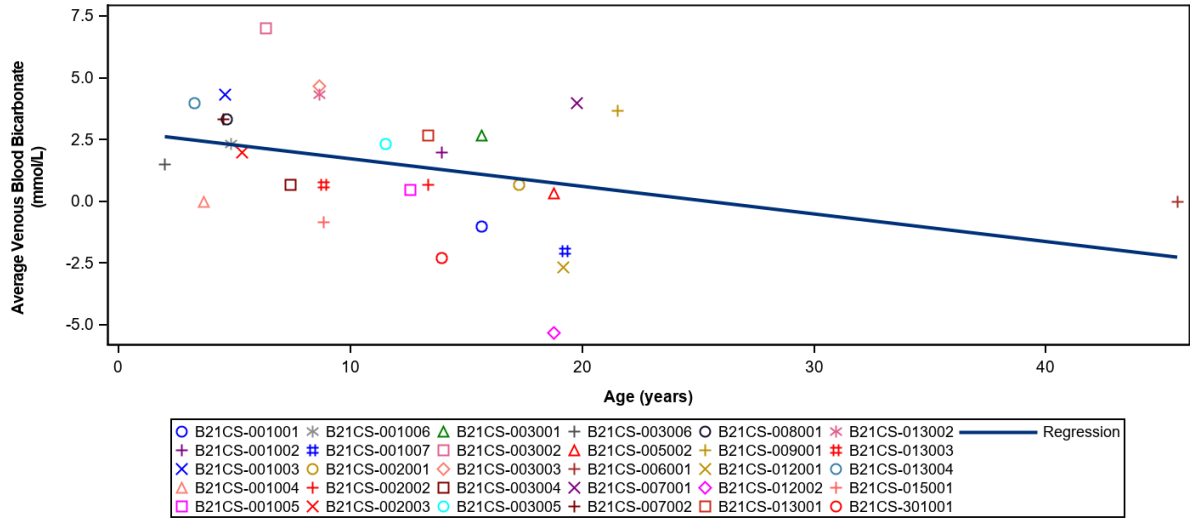
Patients in the non-controlled health state are assumed to discontinue treatment with a set probability (discontinuation rate). During the modified Delphi panel, key opinion leaders were asked about typical treatment compliance to SoC for children and adults with dRTA. As no data informing discontinuation rates in SoC for people with dRTA could be identified in literature, discontinuation rates have been assumed from compliance. If a patient is not compliant to therapy this was assumed to be an equivalent to discontinuation, i.e., the patients were no longer receiving treatment that delivers metabolic control.

A6. *Priority:* For key results, such as Table 37, provide analyses where only patients who are included in both of the PP sets are used to generate results. Provide plots of

the differences between outcome measures with age on the x-axis so that possible trends can be evaluated.

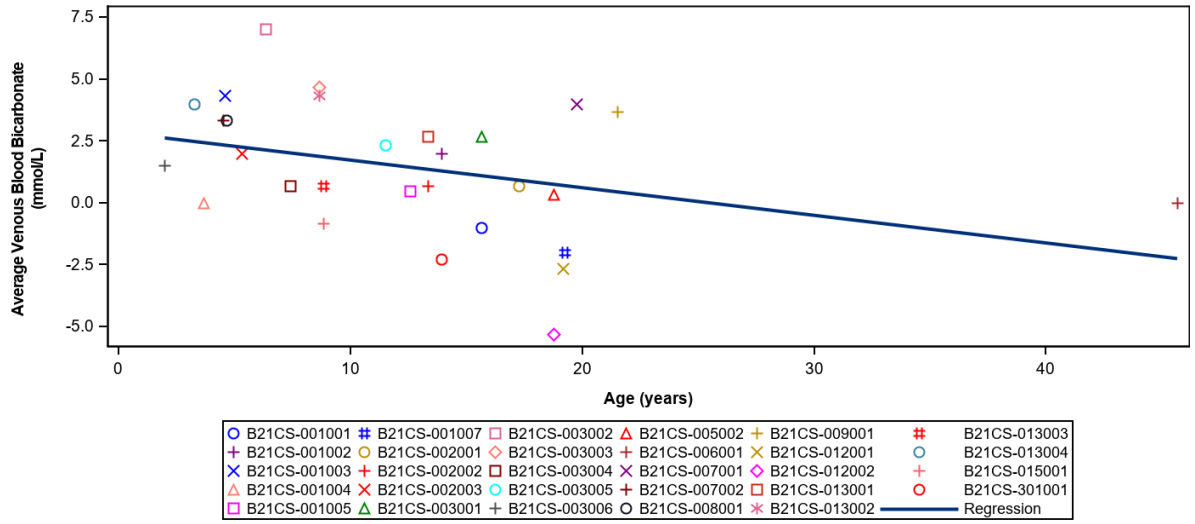
Analysis where only patients who are included in both the ITT set and the PP set are used to generate results are presented in Figure 1 and in Figure 2, respectively.

Figure 1: Scatterplot of average of plasma bicarbonate levels (mmol/L) difference (ADV7103 – SoC) versus age – ITT set



Source: B21CS – Figure 14.2-15.1

Figure 2: Scatterplot of average of plasma bicarbonate levels (mmol/L) difference (ADV7103 – SoC) versus age – PP set



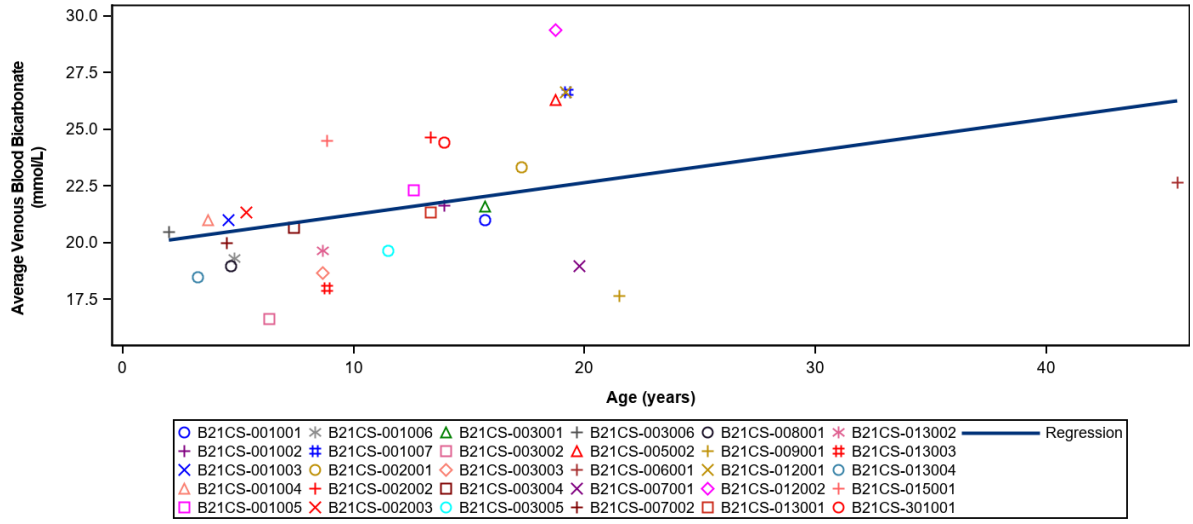
Source: B21CS – Figure 14.2-15.4

The ITT set basically includes one extra patient (Subject # 001-006) as the difference is plotted.

In these plots, the trend looks negative. This is because adults were more likely to have a plasma bicarbonate level > 21 mmol/L. Therefore, the plots of raw values for SPI with SoC

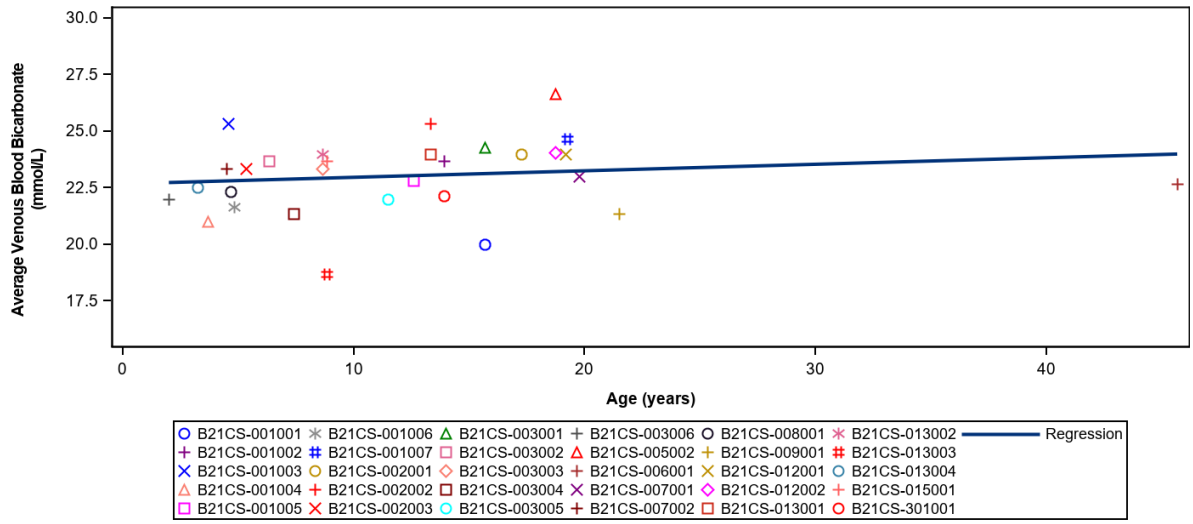
and SPIII with ADV7103 are also provided for the ITT set, as presented in Figure 3 and in Figure 4, respectively.

Figure 3: Scatterplot of average of plasma bicarbonate levels (mmol/L) for SoC versus age – ITT set



Source: B21CS – Figure 14.2-15.6

Figure 4: Scatterplot of average of plasma bicarbonate levels (mmol/L) for ADV7103 versus age – ITT set



Source: B21CS – Figure 14.2-15.5

In terms of the difference between ADV7103 and SoC, the value in fact appears to slightly decrease as age increases (Figure 1 and Figure 2). This however, is not driven due to ADV7103 being unable to control plasma bicarbonate level above the desired limit, but due to some older patients having quite high average plasma bicarbonate values with SoC (Figure 3) and the ADV7103 dose was calibrated to a lower normal value (Figure 4).

A7. *Priority:* Clarify what evidence exists for supporting the assumption that the efficacy of ADV7103 would be equivalent in adults and children. Table 37 indicates, albeit from a small sample size, that the mean blood bicarbonate level was greater for SoC for those patients 18 years or older yet was higher for ADV7103 in all remaining patients.

ADV7103 is effective at normalising bicarbonate levels across all age ranges.

The assumption that the efficacy of ADV7103 would be equivalent in adults and children is explained by:

- As shown in Figure 3 in the response to Question A6, 3 adults (Subjects # 001-007, 012-001 and 012-002) have quite high plasma bicarbonate levels (between 27 and 29 mmol/L) with SoC, whilst the ADV7103 dose was calibrated to a lower normal value (between 20 and 22 mmol/L according to the laboratory).
- Two adult patients had abnormally low plasma bicarbonate level with SoC (Subjects # 007-001 and 009-001), this level increased of at least 3.5 mmol/L with ADV7103, to reach/approach normal value, and no patients responders with SoC became non-responders with ADV7103.
- The paediatric population is usually considered as a more severe subgroup than the adult population due to the high level of physiological acid metabolism related to growth.

Therefore, the assumption that the efficacy is equivalent in adults and children is justified because mean plasma bicarbonate were in the normal range over time in both adult and children cohorts in the B22CS study. By M48, the mean±SD (mmol/L) plasma bicarbonate level was 23.07±3.44 in the adult group, 23.54±3.35 in the adolescent group, 22.08±5.45 in the child group, 22.00 in the infant group and 22.61±4.23 overall, when blood tests were done before study drug intake. In general, ADV7103 allowed very good control of the metabolic acidosis, which is the main characteristic of dRTA and the main goal for the treatment of this condition, with the majority of patients showing normal values of bicarbonataemia over time up to 48 months.

A8. *Priority:* Clarify what evidence exists to support the hypothesis that the effect of ADV7103 does not wane over time.

There is no curative treatment available for dRTA. Treatment is thus symptomatic via the normalisation of blood pH (i.e. bicarbonataemia) using alkaline therapy. Control of homeostasis improves prognosis of the disease, reducing the risk of nephrocalcinosis, renal stone development, bone complications, and enabling normal growth in children if the

treatment is implemented at an early stage. Continuous treatment is necessary to provide a sustained clinical improvement, using alkaline therapy, 1 to 8 milliequivalents (mEq)/kg/day depending on the age and needs of the patients, usually with higher doses in children than in adults [1,2]. Results from B22CS showed a continuous and significant clinical improvement after 48 months of treatment with ADV7103. It is an unlikely clinical plausibility of applying waning effect for the therapy. Waning is not logical for the correction of metabolic acidosis. The effect of Sibnayal and standard of care (Alkali therapy) does not wane over time. If patients are fully compliant it should maintain blood acid levels and prevent metabolic acidosis. Results from the trials show no waning over time.

Long-lasting therapy with sodium bicarbonate is extensively used for management of metabolic acidosis associated with chronic kidney disease (CKD), as current guidelines suggest sodium bicarbonate supplementation to maintain serum bicarbonate ≥ 22 mmol/L (mM) (level of evidence 2B) [3].

A9. ***Priority:*** **Table 32 states that *"a mixed-effect ANOVA was provided on the ITT. This type of analysis handles missing values if data can be considered as missing at random."* Please provide further details of the statistical approach taken and the variables that were adjusted for in the ANOVA model. Please explain how missing data were handled in the ANOVA when the data were considered missing at random (in contrast to the further sensitivity analyses provided where the imputation methods are explained).**

The mixed effects ANOVA model only included as a treatment factor and a subject level random effect, no other variables were used for adjustment in the ANOVA model. It is the sponsors' opinion that the Missing At Random (MAR) assumption, due to the confounding of treatment and period, may have overestimated the treatment effect in the original analysis. An example of missing data where the MAR assumption would have been optimistic and overestimated the effect is missing data due to lack of efficacy. However, due to the design of the study it is impossible to decompose the two confounded variables, and the only way to address potential biases introduced by the MAR assumption is using an imputation method as described in response to Question A2 (see also responses to Questions Z7, Z13 and Z15 in the previous set).

A10. Clarify that none of the identified studies of comparator treatments (8+ studies of alkali therapy, CS Appendix D.5.2) were considered suitable to provide evidence for an indirect comparison with ADV7103 data from B21CS or B22CS.

The company believe that none of the studies identified in the SLR were suitable for an IDC with ADV7103. The majority of studies identified were discussion papers with insufficient clinical data. The remaining clinical studies were deemed inappropriate given difference in the aims of the studies (e.g., impact on bone density, growth or renal failure) and the outcomes measured (the ADV7103 trials measured blood bicarbonate levels as a primary outcome).

A11. Clarify why ethnicity was not deemed relevant to treatment effect (B21CS protocol amended not to collect ethnicity data).

The company removed ethnic origin from the demographic data because it was sensitive data not specifically required for the study.

A12. Clarify the average number of boxes used per year by children to complement Table 5 (page 15).

Dosing is based on age and weight. When initiating alkalising therapy, the target starting daily dose indicated below for each age group should be used and incrementally titrated to obtain the optimal dose that provides adequate metabolic acidosis control based on plasma bicarbonate levels. - Adults: initiation at 1 mEq/kg/day, with a maximal incremental increase/decrease of 0.5 mEq/kg/day to optimal dose - Adolescents from 12 years: initiation at 1 mEq/kg/day, with a maximal incremental increase/decrease of 1.0 mEq/kg/day to optimal dose - Children from 4 to 11 year inclusive: initiation at 2 mEq/kg/day, with a maximal incremental increase/decrease of 1.5 mEq/kg/day to optimal dose - Children from 1 to 3 years inclusive: initiation at 4 mEq/kg/day, with a maximal incremental increase/decrease of 1.5 mEq/kg/day to optimal dose 3 When switching from another alkalising therapy to Sibnayal, treatment should be initiated at the target dose used with the previous therapy (in mEq/kg/day) and titrated where necessary as described above. The maximum dose, regardless of the age group, is either 10 mEq/kg/day or a total daily dose of 336 mEq, whichever is lower. The total daily dose should be administered in two intakes. For each individual patient, the nearest dose to the target dose should be fixed by combining whole sachets of the two available strengths [4].

The estimations below of average costs for an average adult / adolescent / child / infant are based on the mean weights used in the economic model and M24 average dosing in the

B22CS trial (by M24, this represented a dose of 2.260±1.299 mEq/kg/day in the adult group, 2.606±1.728 mEq/kg/day in the adolescent group, 3.413±1.297 mEq/kg/day in the child group and 4.806±2.002 mEq/kg/day in the infant group). The split between 8mEq and 24mEq strength is arbitrarily assigned and does not impact cost.

Table 2: Average adult patient cost per year

Adult	**8 mEq**	**24 mEq**
Boxes for average adult patient per year	7	29
Sachets per year	408	1,740
mEq per year	3,264	41,760
Total mEq per year		45,024

Average cost for an average adult per year £11,256 (45,025*0.25).

Table 3: Average adolescent patient cost per year

Adolescent	**8 mEq**	**24 mEq**
Boxes for average Adolescent patient per year	14	35
Sachets per year	848	2,083
mEq per year	6,784	50,002
Total mEq per year		56,786

Average cost for an average adolescent per year £14,196.50 (56,786 *0.25).

Table 4: Average child patient cost per year

Child	**8 mEq**	**24 mEq**
Boxes for average Child patient per year	6	26
Sachets per year	375	1,535
mEq per year	3,000	36,864
Total mEq per year		39,864

Average cost for an average child per year £9,966 (39,864 *0.25).

Table 5: Average infant patient cost per year

Infant	**8 mEq**	**24 mEq**
Boxes for average Infant patient per year	5	14
Sachets per year	302	833
mEq per year	2,419	20,000
Total mEq per year		22,419

Average cost for an average infant per year £5,604.75 (22,419 *0.25).

A13. In Table 22, please add the SOC dose for each patient.

Table 22 from the original submission, with two additional columns Subject # and SoC treatment and doses during the 4 years before study entry (when data are available), is presented below.

Table 6: Treatment schedule and dosage, by patient

Subject #	B21CS – B22CS Subject age	SoC treatment duration	Lines of SoC before study entry	SoC treatment duration at the last therapeutic dose	SoC treatment and doses during years before study entry
Adults					
001-007	19 years old	4 years	2 different doses	8.5 months	• Sodium bicarbonate 1.5 g t.i.d. • Sodium bicarbonate 1.5 g q.i.d.
005-002	18 years old	4 years	1	48 months	Potassium citrate 20 mmol/L t.i.d.
	46 years old				
	19 years old				
009-001	21 years old	3 years	6 products and/or doses	4.5 months	• Potassium citrate 6 g qd, sodium bicarbonate 8 g qd • Potassium citrate 5 g t.i.d., potassium bicarbonate 1 g t.i.d. • Potassium citrate 15 g qd, potassium bicarbonate 3 g qd • Potassium bicarbonate 5 g qd • Potassium citrate 6 g t.i.d. • Potassium citrate 24 g qd
012-001	19 years old	4.7 years	3 different doses	14.5 months	• Potassium citrate 150 mEq qd • Potassium citrate 120 mEq qd • Potassium citrate 100 mEq qd
012-002	18 years old	>2 years	2 different doses	25.5 months	• Potassium citrate 180 mEq qd • Potassium citrate 150 mEq qd
Adolescents					
001-001	15 years old	4 years	3 products and/or doses	23.5 months	• Potassium citrate 1 g 5/day • Potassium bicarbonate 1 g 5/day • Potassium citrate 1.5 g q.i.d., potassium bicarbonate 1 g q.i.d.
001-002	14 years old	4 years	4 products and/or doses	10.5 months	• Sodium bicarbonate 5 g qd • Potassium bicarbonate 5 g qd. • Sodium bicarbonate 2 g qd, potassium bicarbonate 4 g qd • Potassium bicarbonate 2 g q.i.d.
	12 years old				
002-001	17 years old	4 years	6 different doses	7 months	• Potassium citrate 19 mL t.i.d. • Potassium citrate 28 mL t.i.d. • Potassium citrate 23 mL t.i.d. • Potassium citrate 5 g t.i.d. • Potassium citrate 25 mL t.i.d. • Potassium citrate 27 mL t.i.d.
002-002	13 years old	4 years	6 different doses	1 month	• Potassium citrate 13 mL q.i.d. • Potassium citrate 17 mL t.i.d. • Potassium citrate 20 mL t.i.d. • Potassium citrate 22 mL t.i.d. • Potassium citrate 25 mL t.i.d.

					• Potassium citrate 28 mL t.i.d.
003-001	15 years old	3.8 years	4 products and/or doses	0.5 month	• Citrate salts 1 sachet qd, sodium bicarbonate 2 g qd then sodium bicarbonate 750 mg t.i.d. • Potassium citrate 1 g t.i.d., sodium bicarbonate 1 g q.i.d. • Potassium citrate 1 g q.i.d., sodium bicarbonate 750 mg t.i.d.
013-001	13 years old	4 years	3 different doses	4 months	• Sodium bicarbonate 2 g t.i.d. • Sodium bicarbonate 1.5 g t.i.d. • Sodium bicarbonate 2 g t.i.d.
	14 years old				
Children					
001-003	4 years old	4 years	3 different doses	13.5 months	• Sodium bicarbonate 750 mg t.i.d., potassium citrate 500 mg t.i.d. • Sodium bicarbonate 750 mg b.i.d., potassium citrate 750 mg b.i.d. • Sodium bicarbonate 500 mg t.i.d., potassium citrate 1 g t.i.d.
001-006	4 years old	4 years	4 products and/or doses	22 months	• Sodium bicarbonate 60 mL q.i.d. • Sodium bicarbonate 500 mg q.i.d. • Sodium bicarbonate 1 g q.i.d. • Potassium bicarbonate 1.25 g q.i.d.
002-003	5 years old	3.7 years	5 different doses	1 month	• Potassium citrate 3 mL q.i.d. • Potassium citrate 3.5 mL q.i.d. • Potassium citrate 4.6 mL t.i.d. • Potassium citrate 7 mL t.i.d. • Potassium citrate 9 mL t.i.d.
003-002	6 years old	4 years	5 products and/or doses	14.8 months	• Sodium bicarbonate 500 mg 10/day • Sodium bicarbonate 500 mg 7/day • Sodium bicarbonate 1 g q.i.d., citrate salts 1 sachet qd • Sodium bicarbonate 1 g t.i.d., potassium citrate 500 mg b.i.d. then potassium citrate 500 mg t.i.d.
003-003	8 years old	8 months	1	8 months	• Sodium bicarbonate 1 g q.i.d., potassium citrate 500 mg 5/day
003-004	7 years old	4 years	2 products and/or doses	37 months	• Sodium bicarbonate 30 mL q.i.d. • Sodium bicarbonate 2 g q.i.d., potassium citrate 1 g t.i.d.
003-005	11 years old	1.2 years	2 products and/or doses	2 months	• Sodium bicarbonate 1 g t.i.d. • Potassium citrate 1 g t.i.d • Sodium bicarbonate 1 g 5/day • Sodium bicarbonate 1 g q.i.d.
	8 years old				
007-002	4 years old	1.2 years	3 different doses	7 months	• Sodium bicarbonate 1 g b.i.d. • Sodium bicarbonate 1.5 g b.i.d. • Sodium bicarbonate 2 g b.i.d.
008-001	4 years old	4 years	6 products and/or doses	7.8 months	• Sodium bicarbonate 500 mg b.i.d. • Sodium bicarbonate 500 mg t.i.d. • Potassium citrate 500 mg b.i.d. • Sodium bicarbonate 1 g b.i.d. • Sodium bicarbonate 1.5 g b.i.d. • Potassium citrate 750 mg b.i.d.
013-002	8 years old	4.3 years	1	51 months	Sodium bicarbonate 12 mEq t.i.d., potassium bicarbonate 10 mEq t.i.d.
013-003	8 years old	3.7 years	1	44 months	Sodium bicarbonate 8 mEq t.i.d., potassium bicarbonate 3 mEq t.i.d.

015-001	8 years old	4 years	1	48 months	Sodium bicarbonate 1 g q.i.d., potassium citrate 6 g qd.
	5 years old				
Infants/Toddlers					
	3 years old				
003-006	2 years old	2 years	4 products and/or doses	17 months	• Sodium bicarbonate 40 mL qd., potassium citrate 8 mL qd • Sodium bicarbonate 30 mL q.i.d. • Potassium citrate 10 mL t.i.d • Sodium bicarbonate 50 mL q.i.d. • Potassium citrate 5 mL t.i.d , sodium bicarbonate 20 mL q.i.d.
013-004	3 years old		1?	37 months?	Sodium bicarbonate 45 mEq t.i.d.

Source: B21CS CSR, B22CS Listing 16.2.4.3.2.7. Abbreviations: n = number; SD = standard deviation; SoC = standard of care; b.i.d = twice (two times) a day; t.i.d. = three times a day; q.i.d. =four times a day; gd = once a day

A14. Clarify number of patients in B21CS providing palatability data, and GI tolerability data.

For standard of care, palatability data was collected from 35 patients, and for those receiving ADV7103 the data was collected from 31. For GI tolerability, this was 35 patients and 32 patients, respectively.

A15. Clarify the definition of hypokalaemia used in the report and the model.

B22CS trial utilised the normal range of plasma potassium usual median normal values as from 3.5 to 5.1 mmol/L Below 3.5 mmol/L was deemed to indicate hypokalaemia.

A16. Clarify whether the infection with vomiting referred to on page 47 was considered related to ADV7103 treatment.

Subject # 202-001: this patient, who was hospitalised during the study procedures, had an intrahospital infection (enterocolitis) with fever, nausea and vomiting. These events occurred during the ADV7103 titration period and were not related to the study product (B21CS – Listing 16.2.7-1.1)

A17. Clarify why Page 50 states the ITT set “included all 37 patients” but outcome analyses labelled ITT did not include all 37 patients, and number in ITT set was not consistent across outcomes.

See the response to Question A2.

A18. Provide the reasons for rejection for the last paper listed in Table 31.

CJASN and JASN refused the manuscript at the editorial level before peer-review (high impact journals are not able to publish all the manuscripts they receive).

Refusal by Pediatric Nephrology was based on the comments of the three reviewers that were involved in its peer-review. A first reviewer found it very interesting and had only some minor comments. Another reviewer found it was valuable and had some major comments, particularly regarding the statistical methods and suggested simplification of the supplemental tables. However, the third reviewer found the manuscript of limited interest, as positive BMD and growth changes were limited in magnitude, and for BMD, they were only positive at the spine level. He also indicated that the heterogeneity of the cohort was a limitation when addressing growth and bone status.

The manuscript was subsequently sent to Nefrologia and is currently at the state of revision. Reviewers' comments and questions have been addressed and the revised manuscript has been submitted December 20th, 2021.

A19. Clarify whether one (or more) patient who was not a responder on SoC was not treated with ADV7103? On page 82 it is stated that 14/17 non-responders became responders when switching from SoC to ADV7103, yet Table 39 indicates that 18 (12+6) patients had abnormal bicarbonataemia in the PP set, and 19 (13+6) in the ITT set.

The difference between the ITT set and the PP set becomes from Subject 001-006 who was excluded from the PP set. However, the patient was actually a responder with ADV7103 even though she was a non-responder with SoC. Therefore, this patient was treated in SPIII with ADV7103 but the treatment schedule was not respected and examination not done (see the response to Question A2).

Table 39 includes only paired data. There were actually 22 non-responder patients (*i.e.* patients with abnormally low plasma bicarbonate level) with SoC, but 3 of them did not have valid records for the ADV7103 period (namely Subjects # 005-001, 005-003 and 015-002). Considering this could be a source of bias, the analysis has been performed imputing these 3 patients as remaining non-responders with ADV7103, as presented in Table 7. The difference remains statistically significant, with a greater probability of a responder occurring with ADV7103

Table 7: Number/proportion of patients with abnormally low plasma bicarbonate value – ITT set

Parameter	**ADV7103**	**SoC**	**n / N**	**(proportion)**	**p-value [a]**
Plasma bicarbonate value below the lower normal limit (mmol/L)	No	No	10 / 33	(30%)	0.002
	No	Yes	13 / 33	(39%)	
	Yes	No	1 / 33	(3%)	
	Yes	Yes	9 / 33	(27%)	

Source: B21CS – Table 14.2-3.11

Abbreviations: ITT=intent-to-treat, n=number pf patients per combination of treatment response 'No/No, No/Yes, Yes/No, Yes/Yes', N=total number of patients for whom data are provided or imputed, No=responder (*i.e.* patients with normal plasma bicarbonate value), SoC=standard of care, Yes=non-responder (*i.e.* patients with abnormally low plasma bicarbonate value)
Notes: Non-responders in SoC and without data in ADV7103 are imputed as non-responders in ADV7103, Post-dose samples are excluded from the analysis
[a]exact p-value obtained from a McNemar's test

A20. In Table 56, clarify what the asterisk is denoting.

The asterisk denotes:

* Nephrocalcinosis corrected as not observed by the Investigator for Patient 001-004 at Month 24. Therefore 1 (33.3%) of the infants did not have nephrocalcinosis while 2 (66.7%) of the infants had nephrocalcinosis. Overall, 2 (6.9%) did not have nephrocalcinosis, while 27 (93.1%) had nephrocalcinosis.

A21. Clarify the apparent discrepancy between the statement on p131 that '*None of the severe TEAEs was considered related to treatment*' and in Table 75 where it is said that '*one possibly related … to the treatment*'.

The statement on p131 (page 124 on revised version) is relating to severe TEAEs reported in the B22CS trial, whereas the statement in Table 75 relates to the B21CS trial.

A22. Clarify how serious AE, and severe AE were defined.

B22CS "The Investigator was required to systematically assess the severity of AEs according to the following definitions:

- Mild: The AE required minimal or no treatment. The AE did not interfere with the patient's daily activities,
- Moderate: The AE resulted in a low level of inconvenience or concern with the therapeutic measures. The AE caused some interference with functioning or reduction with the usual level of activity of the patient,
- Severe: The AE required systemic drug therapy or other treatment. The AE caused a significant impairment of functioning, interrupted a patient's usual daily activity and was usually incapacitating. Changes in the severity of an AE were to be documented to allow an assessment of the duration of the event at each level of intensity to be performed. An AE characterised as intermittent required documentation of the onset and duration of each episode."

Serious Adverse Events

An SAE was defined as an AE that, at any dose, met one of the following conditions: • Death during the period of protocol defined surveillance, i.e. the AE caused or contributed to the death. In case of fatality, the cause of death was considered as the AE and the death was its outcome.

- Life threatening event (defined as a patient at immediate risk of death at the time of the event), i.e. the AE placed the patient at immediate risk of death (the definition did not apply to an AE that hypothetically could have caused death if it was more severe),

- An event requiring inpatient hospitalisation or prolongation of existing hospitalisation during the period of protocol defined surveillance, i.e. the AE required at least 24 hours inpatient hospitalisation or prolonged a hospitalisation beyond the expected length of stay,

- Resulted in congenital anomaly or birth defect, i.e. an adverse outcome in a child or foetus of a patient exposed to the treatment(s) before conception or during pregnancy,

- Resulted in a persistent or significant disability/incapacity, i.e. the AE resulted in a substantial disruption of the patient's ability to conduct normal activities,

- Any other important medical condition, i.e. the AE may not have immediately resulted in death, been life threatening, or required hospitalisation, but was clearly of major clinical significance. Based upon appropriate medical judgment, the event may have jeopardised the patient or may have required medical or surgical intervention to prevent one of the serious outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasia or convulsions that did not result in inpatient hospitalisation, or the development of drug dependency or drug abuse. All deaths and immediately life-threatening events, regardless of relationship to study drug, were to be communicated to the sponsor within 24 hours of site awareness. Serious AEs other than death and immediately life-threatening events that met expedited reporting criteria were to be communicated to the sponsor within 72 hours of the Investigator becoming aware of the event, regardless of relationship to treatment.

A23. Long term outcomes, page 21 states "*It has been reported that CKD prevalence in dRTA is 41-71% at 20- and 40-years follow-up. In general population CKD prevalence reported is 5-17% at 20 and 40 years, respectively*." Please clarify if these are intended as ranges or point estimates at the respective ages of 20 and 40 years. It is also not always clear in this section where the data are derived from, e.g. "*Rickets are present in a large proportion of children with RTA. The proportion of dRTA children with rickets was 25% (7/28).*" Please clarify the source of all statements.

The CKD prevalence quote is from Gómez-Conde et al 2021 - Molecular aspects and long-term outcome of patients with primary distal renal tubular acidosis. The figures quoted are point estimates (not ranges) of kidney decline to CKD 3, at 20 years this being 41% and 40 years this being 71%.

"Rickets are present in a large proportion of children with RTA. The proportion of dRTA children with rickets was 25% (7/28)." – is from Caldas.A. Primary distal tubular acidosis in childhood: clinical study and long-term follow-up of 28 patients. J Pediatr. 1992:233-241.

All other statements in this section are fully referenced.

A24. CS page 25 states "*Very recently, it has been reported that UK dRTA patient life expectancy is estimated in 72 years*". Please clarify whether this is a mean or median summary. Please provide both mean with standard deviation and median with interquartile range.

As per Bianic et al 2021 Epidemiology of Distal Renal Tubular Acidosis: A Study Using Linked UK Primary Care and Hospital Data, of diagnosed patients in the database (n = 216), 55 were recorded as deceased prior to 2017. The mean age of death was 72 years (SD = 13.4 years). There were insufficient data to draw any firm conclusions regarding evidence of excess mortality in this renal condition. Raw data is not available to calculate median with interquartile range. [5]

A25. Table 14 states "*We do not recommend the use of GH in children with dRTA, unless there is persistent growth retardation despite adequate metabolic control*". Clarify whether the abbreviation GH stands for growth hormones.

Yes this abbreviation stands for growth hormones, this has been updated in the CS.

A26. Figure 9. Please clarify the abbreviation BGA.

BGA stands for Blood gas analysis.

A27. CS page 41. Please give median and interquartile range for ages of patients in study B03CS.

The median was 27.0 years, with an interquartile range of 19-53 years.

A29. CS Table 18 page 49. Please discuss whether exclusion criteria 11 and 12 could have introduced bias into the study.

B21CS - Exclusion criterion 11: "*Patient who was at risk of non-compliance of the study procedure in the judgement of the investigator*"

The study was designed as a non-inferiority study first, so the intention was always a valid PP set. Therefore, if the patients at risk of non-compliance of study procedures can be included in the study, that would have meant that these patients would be enrolled but dropped from the primary analysis. Regarding ITT analysis, including these patients would have been firstly a source of variability but not bias (as non-compliance could have occurred in either period). However, due to the reduced number of daily intakes with ADV7103, these patients would have been likely to be less compliant with SoC (repeated daily intakes) than with ADV7103 (2 daily intakes), so likely to cause bias in favour of ADV7103 in that respect. Importantly, there is no subgroup of dRTA patients omitted due to the exclusion criterion 11, that would have caused bias.

B21CS - Exclusion criterion 12: "*Patient who presented any other condition, which in the opinion of the investigator, would preclude participation in the study*"

No exclusion related to the exclusion criterion 12 occurred during the study.

In general, the children and young adults with the inherited form of dRTA usually do not have other special conditions. Adults with the acquired form of dRTA may have other unusual condition due to the age and/or the autoimmune disease, which should have been evaluated/considered prior to enrolment.

A28. CS page 48. Please clarify the problems with clinical study protocol compliance for included patients in trial B21CS.

Two patients presented major protocol deviations (Subject # 001-006 due to treatment schedule not respected and examination not done, and Subject # 202-001 due to schedule timepoint not respected and missing data).

A30. CS page 55. Of the 32 patients completing B21CS, one declined to continue into B22CS. Please clarify the reasons for the one other patient who did not continue.

See response to Question A1.

A31. CS page 74 states that *"As the lower bound of the 95% CI is 0.67 mmol/L, the results suggested also a potentially clinically relevant difference between ADV7103 and SoC".* Please state and justify what is assumed to be a minimum threshold for clinical significance.

Due to the fact that the patients enrolled in B21CS Study had received a working SoC treatment (i.e. a therapeutic dose or the maximal well-tolerated dose), a clinically meaningful increase would be any increase that would increase any plasma bicarbonate levels below the limit of normal to within normal range. Therefore, a uniform threshold cannot be defined for all patients. However, out of the 20 patients with an average plasma bicarbonate value below the limit of normal range during SoC treatment, an increase of 0.67 mmol/L (the lower bound of the 90% CI) would increase plasma bicarbonate level to within the normal range for 7 of them. This means that 35% of the patients would still have had a superior benefit by being treated with ADV7103 by reaching the normal range.

A32. CS Table 26. There appears to be a mistake in presenting the inherited versus acquired dRTA characteristics.

Correct – these should be as per Table 8 below;

Table 8: Inherited versus acquired dRTA characteristics in B21CS trial

Parameter	**Adult [≥18Y] (N=6)**	**Adolescent [12-18Y] (N=8)**	**Child 4-12Y] (N=13)**	**Infant [0.5-4Y] (N=3)**	**Overall (N=30)**
Form of dRTA					
Acquired - n (%)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)
Inherited - n (%)	6 (85.7)	10 (100.0)	14 (93.3)	5 (100.0)	35 (94.6)
Not specified - n (%)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (2.7)

Source B21CS – Table 14.1-3.3

A33. CS Table 32. Please justify the chosen non-inferiority margin for study B21CS. Please state the reasons for not adjusting the test significance level nor the sample size calculation for multiple comparisons and any implications for the interpretation of results.

The non-inferiority margin for Study B21CS is justified as follows:

The non-inferiority margin was selected in accordance with the EMA Guideline on the choice of the non-inferiority margin (EMA 2005) considering a statistical margin (delta) suitable for indirect comparison to placebo, a discussion of the clinical relevance of that margin to ensure that ADV7103 is not substantially inferior to SoC.[6]

Rationale for a switch trial

The dRTA is an orphan disease for which no reference therapy is currently approved in Europe. Clinical practice involves controlled diet and the administration of alkalising therapy. Placebo controlled trials are considered as being unethical by CHMP in that disease condition as the patient's effective standard alkalising therapy would need to be withdrawn for the duration of the study.

Literature review summary

As no therapy is approved in the condition, very few clinical trials have been conducted in dRTA. To our knowledge, only one trial (Domrongkitchaiporn et al 2002) was found to present efficacy results prior to and following treatment intervention. In that study, mean ± SD bicarbonate levels (in mmol/L) in serum was significantly increased when comparing baseline (16.5 ± 3.0) to post-alkalising therapy (24.6 ± 2.8) in 10 patients with distal renal tubular acidosis. Post-treatment values were similar to bicarbonate levels (25 ± 1.5) collected in a control group of 28 healthy subjects. Furthermore, all dRTA patients could maintain their bicarbonate levels above the lower normal limit of 20 mmol/L throughout the study. [7]

Although only one trial is available, dating back in 2002, results seem to be consistent with the current clinical practice, showing that bicarbonate levels return to normal after alkalising therapy and remain stable over time, as long as treatment is maintained. The lower limit of significance in that trial (20 mmol/L) is also consistent with current practice for bicarbonate normal ranges in serum. [7]

Margin (Delta) for indirect comparison to placebo

The variance for the mean difference in bicarbonate levels between SoC (R) and non-treated (P) conditions is not reported in Domrongkitchaiporn et al. [7] But we can estimate it using standard formula as:

Var (R-P) = var (R) + var (T) - 2 Cov(R,P)

As data is not available, we shall assume that R and P are uncorrelated in order to obtain a conservative estimate of Var (R-P) = $3.0^2+2.8^2 = 16.84$.

Based on this value, the mean difference ± standard error (SE) in bicarbonate levels between SoC (R) and non-treated (P) conditions is approximately 8.1± 1.3 mmol/L. The 95% confidence interval is close [5.5, 10.7]. So, there is a high probability (≥ 97.5%) that the mean difference (R-P) will be at least 5.5 mmol/L.

In the planned study of 24 patients, assuming a similar variability as in the historical trial, the SE of the mean difference between ADV7103 (T) vs. SoC (R) is planned to 0.8.

Combining both the historical and planned trial results, it is possible to estimate the SE for the indirect comparison of ADV7103 (T) to no-treatment (P) as $\sqrt{1.3^2 + 0.8^2} = 1.54$. The half width of the 95% CI for that difference T-P is estimated to be 3.0. Therefore, the mean difference T-P needs to be at least equal to 3.0 in order to achieve statistical significance in the indirect comparison of T to P.

When combining the lower bound for the historical difference R-P = 5.5 with the lower bound for the indirect difference T-P=3.0, one can determine the minimum non inferiority margin for T-R as:

Delta(T-R) = LCI(T-P) - LCI(R-P) = 3.0 - 5.5 = -2.5 mmol/L.

This non-inferiority margin is derived by applying statistical reasoning following the EMA guidance.

Clinical judgement of the non-inferiority margin

According to a survey of key opinion leaders by the sponsor, the proposed non-inferiority margin of -2.5 mmol/L is adequate to insure that ADV7103 is not substantially inferior to SoC in the treatment of dRTA.

That margin is also justified by the following clinical judgement:

The margin (2.5) is within the standard variability for bicarbonate (SD = 2.9) in dRTA patients.Compared to the mean benefit of SoC (+8.1 mmol/L), a reduction by -2.5 mmol/L would still preserve 67% of the overall benefit. Benefit is still at least 55% in the worst case scenario when SoC benefit is only +5.5 mmol/L. As a comparison, the draft FDA guidance on non-inferiority clinical trial considers margins preserving at least 50% of the clinical

benefit as being generally acceptable. This provides statistical and clinical justification for the selection of a non-inferiority margin equal to -2.5 mmol/L in the B21CS trial. [8]

The reasons for not adjusting the test significance level nor the sample size calculation for multiple comparisons and any implications for the interpretation of results are provided here below.

This study was designed with the intention of demonstrating non-inferiority of ADV7103 compared to SoC on the primary endpoint. After demonstrating non-inferiority as per the EMA's points to consider on switching between superiority and non-inferiority (EMA 2020) superiority was also tested. [9]

There was no co-primary endpoint or interim analysis so there is no likelihood to have inflated the Type 1 error for the primary analysis.

All other inferential analyses were presented in a descriptive manner to support the primary endpoint, and not to make further claims about the compound. As these analyses were not presented to make claims, no control of the Family Wise Error Rate (FWER) was considered as necessary.

As such the sponsor considers no implication of the interpretation of results, acknowledging that claims can only be made on the Primary Endpoint.

A34. CS Table 37. Please clarify if the SD values reported are correct. For instance, mean (SD) of 24.1 (4.39) does not seem compatible with a range of 18-29.

It is confirmed that the SD values presented are correct. For instance, the individual plasma bicarbonate values that yielded the mean (SD) results of 24.1 (4.39) mmol/L are for the 7 adult patients: 17.7, 19.0, 22.7, 26.3, 26.7, 26.7 and 29.4 mmol/L.

Section B: Clarification on cost-effectiveness data

B1. *Priority*: Please provide an updated executable model that incorporates the functionality to explore the changes made within the clarification process.

See updated model that accompanies this response. The new functions that were implemented are as user-friendly as possible: the implementation of age-specific utilities and multipliers, as well as the discontinuation timepoints for Sibnayal patients can be explored by the user. See Appendix 1 for a summary of model changes.

B2. *Priority:* Please provide an updated base case (deterministic and probabilistic) that incorporates all changes that are made following the clarification process. Omit pennies from these numbers. Provide supplementary analyses as you see fit.

See Appendix 2.

B3. *Priority:* Clarify whether the price of ADV7103 has been approved. Table 4, page 15 suggests that this has not been approved by the Department of Health.

The price has been approved and has been updated in the CS.

B4. *Priority:* Clarify the definition of responder used within the model. Clarify which data in the report are used to categorise patients into responders and non-responders.

Responders are defined as disease-controlled patients with sufficient alkali therapy and metabolic acidosis is absent. From the B22CS patient level data, this was estimated as the probability of achieving normal bicarbonataemia levels as per the trial. Abnormality status (low, normal, high) was derived according to normal range applied according to the patient's age and sex (if appropriate) e.g. normal between 22-29 mmol/L

Non-responders are defined as disease-uncontrolled patients with insufficient alkali therapy and metabolic acidosis is present. From the B22CS patient level data, this was estimated as the probability of not achieving normal range bicarbonataemia levels as per the trial (either below or above normal range).

B5. *Priority:* Table 66 suggests that the level of discontinuation was sourced from 'KOL opinion'. Tables 67 and 68 also rely on clinical opinion. These will be associated with significant uncertainty. Please provide further information on obtaining KOL opinion such as: how many KOLs were used, was there a formal elicitation process undertaken.

Although a reliance on KOL opinion in these instances could be associated with uncertainty, due to the lack of published data in this condition, reliance on KOL opinion was needed to verify modelling assumptions being made to ensure they reflected clinical practice in the closest way possible.

A standard methodology for conducting this research was employed to minimise bias. There were no conflicts of interest declared by participants. None were employees of Advicenne.

Recruitment was targeted at expert nephrologists and urologists. 23 invitations were despatched. 11 nephrologists participated in stage 1 of this Delphi research. Individual

telephone discussions were conducted with adult and paediatric nephrologists from England, Ireland, Scotland and Wales during September and October 2020. The duration of these calls was approximately 45 minutes

The panel workshop on Thursday 22nd October 2020 was attended by the 11 nephrologist and 1 urologist. The objective of this meeting was to refine the findings from the individual discussions and seek consensus where this was lacking. Discussion was accompanied by voting software to gain further valuable insights from the panel. Results from the panel were presented in an anonymised and consolidated report.

In addition, a further one to one interview was conducted in November 2021 with a KOL (Dr Stephen Walsh) (also previously part of the advisory panel) to verify sourced values and model changes conducted after the previous advisory board.

Reports from these meetings have been provided as part of the reference pack.

B6. *Priority*: Clarify whether the additional costs associated with the three people who withdrew from ADV7103 treatment in SPII/SPIII as shown in Table 25 have been included in the economic model. Consider adding additional costs to the treatment arm to incorporate the costs of people who do not continue treatment.

Treatment discontinuation is considered in the model. People defined as non-responders can transition to the discontinued treatment health states based on an annual discontinuation rate. In the base case, using data from the B22C study (Table 4), this was estimated to be 3.3% (adults) and 0% (children) for the ADV7103 arm.

No specific discontinuation cost is applied to patients who discontinue treatment. For the ADV7103 arm, a proportion of patients who discontinue ADV7103 will receive SoC (as either a responder or non-responder), and the remaining are assumed to be discontinued without treatment (disease-uncontrolled and untreated). For the SoC arm, all patients who discontinue SoC are assumed to be discontinued without treatment (disease-uncontrolled and untreated). All patients who discontinue and do not receive treatment can progress to end of stage renal disease (ESRD) which requires dialysis at home or in hospital. Kidney transplant is only possible for patients with ESRD.

B7. *Priority:* In Table 56 and 57 there are different numbers of respondents at each time period. Provide analyses assuming different imputation measures, including a scenario where missing data is associated with the worst outcome.

Tables 56 and 57 are provided with the missing data (Table 56b and Table 57b) and with the worst-case imputation of the missing data (Tables 56c and Table 57c).

Tables 56 and 57 do not include the missing data.

Table 56: B22CS the long-term effects of ADV7103 on nephrocalcinosis

Analysis Visit	Nephrocalcinosis	Adults >=18Y (N=6)	Adolescents [12-18Y] (N=8)	Children [4-12Y] (N=13)	Infants [0.5-4Y] (N=3)	Overall (N=30)
Baseline	n	6	8	13	2	29
	No	1 (16.7)	2 (25.0)	0	1 (50.0)	4 (13.8)
	Yes	5 (83.3)	6 (75.0)	13 (100.0)	1 (50.0)	25 (86.2)
Month 24	n	5	8	13	3	29
	No	0	1 (12.5)	0	0*	1 (3.4)*
	Yes	5 (100.0)	7 (87.5)	13 (100.0)	3 (100.0)*	28 (96.6)*
Month 36	n	5	7	12	2	26
	No	0	1 (14.3)	0	1 (50.0)	2 (7.7)
	Yes	5 (100.0)	6 (85.7)	12 (100.0)	1 (50.0)	24 (92.3)
Month 48	n	4	7	8	3	22
	No	0	0	1 (12.5)	1 (33.3)	2 (9.1)
	Yes	4 (100.0)	7 (100.0)	7 (87.5)	2 (66.7)	20 (90.9)

Source: B22CS CSR. Abbreviations: n = number; y = years.

Table 57: Number (Percentage) of Patients Presenting Nephrolithiasis, by Visit, Age Group and Overall

Analysis Visit	Nephrolithiasis	Adults >=18Y (N=6)	Adolescents [12-18Y] (N=8)	Children [4-12Y] (N=13)	Infants [0.5-4Y] (N=3)	Overall (N=30)
Baseline	n	6	8	13	2	29
	No	4 (66.7)	7 (87.5)	11 (84.6)	1	23 (79.3)
	Yes	2 (33.3)	1 (12.5)	2 (15.4)	1	6 (20.7)
Month 24	n	5	8	13	3	29
	No	3 (60.0)	7 (87.5)	12 (92.3)	2 (66.7)	24 (82.8)
	Yes	2 (40.0)	1 (12.5)	1 (7.7)	1 (33.3)	5 (17.2)
Month 36	n	5	7	12	2	26
	No	5 (100.0)	4 (57.1)	9 (75.0)	1	19 (73.1)
	Yes	0	3 (42.9)	3 (25.0)	1	7 (26.9)
Month 48	n	4	7	8	3	22
	No	4 (100.0)	5 (71.4)	5 (62.5)	1 (33.3)	15 (68.2)
	Yes	0	2 (28.6)	3 (37.5)	2 (66.7)	7 (31.8)

Source: B22CS CSR. Abbreviations: N, n = number of patients; Y = years.*

Tables 56b and 57b include the missing data, without imputation of the missing data.

Table 56b: B22CS the long-term effects of ADV7103 on nephrocalcinosis

Analysis Visit	Nephrocalcinosis	Adults >=18Y (N=6)	Adolescents [12-18Y] (N=8)	Children [4-12Y] (N=13)	Infants [0.5-4Y] (N=3)	Overall (N=30)
Baseline	n	6	8	13	3	30
	No	1 (16.7)	2 (25.0)	0	1 (33.3)	4 (13.3)
	Yes	5 (83.3)	6 (75.0)	13 (100.0)	1 (33.3)	25 (83.3)
	Missing	0	0	0	1 (33.3)	1 (3.3)
Month 24	n	5	8	13	3	29
	No	0	1 (12.5)	0	0*	1 (3.4)*
	Yes	5 (100.0)	7 (87.5)	13 (100.0)	3 (100.0)*	28 (96.6)*
	Missing	0	0	0	0	0
Month 36	n	5	7	12	3	27
	No	0	1 (14.3)	0	1 (33.3)	2 (7.4)
	Yes	5 (100.0)	6 (85.7)	12 (100.0)	1 (33.3)	24 (88.9)
	Missing	0	0	0	1 (33.3)	1 (3.7)
Month 48	n	5	7	12	3	27
	No	0	0	1 (8.3)	1 (33.3)	2 (7.4)
	Yes	4 (80.0)	7 (100.0)	7 (58.3)	2 (66.7)	20 (74.1)
	Missing	1 (20.0)	0	4 (33.3)	0	5 (18.5)

Source: B22CS CSR. Abbreviations: n = number; y = years.

Table 57b: Number (Percentage) of Patients Presenting Nephrolithiasis, by Visit, Age Group and Overall

Analysis Visit	Nephrolithiasis	Adults >=18Y (N=6)	Adolescents [12-18Y] (N=8)	Children [4-12Y] (N=13)	Infants [0.5-4Y] (N=3)	Overall (N=30)
Baseline	n	6	8	13	3	30
	No	4 (66.7)	7 (87.5)	11 (84.6)	1 (33.3)	23 (76.7)
	Yes	2 (33.3)	1 (12.5)	2 (15.4)	1 (33.3)	6 (20.0)
	Missing	0	0	0	1 (33.3)	1 (3.3)
Month 24	n	5	8	13	3	29
	No	3 (60.0)	7 (87.5)	12 (92.3)	2 (66.7)	24 (82.8)
	Yes	2 (40.0)	1 (12.5)	1 (7.7)	1 (33.3)	5 (17.2)
	Missing	0	0	0	0	0
Month 36	n	5	7	12	3	27
	No	5 (100.0)	4 (57.1)	9 (75.0)	1 (33.3)	19 (70.4)
	Yes	0	3 (42.9)	3 (25.0)	1 (33.3)	7 (25.9)
	Missing	0	0	0	1 (33.3)	1 (3.7)
Month 48	n	5	7	12	3	27
	No	4 (80.0)	5 (71.4)	5 (41.7)	1 (33.3)	15 (55.6)
	Yes	0	2 (28.6)	3 (25.0)	2 (66.7)	7 (25.9)
	Missing	1 (20.0)	0	4 (33.3)	0	5 (18.5)

Tables 56c and 57c include the worst-case imputation of the missing data.

Table 56c: B22CS the long-term effects of ADV7103 on nephrocalcinosis

Analysis Visit	Nephrocalcinosis	Adults >=18Y (N=6)	Adolescents [12-18Y] (N=8)	Children [4-12Y] (N=13)	Infants [0.5-4Y] (N=3)	Overall (N=30)
Baseline	n	6	8	13	3	30
	No	1 (16.7)	2 (25.0)	0	1 (33.3)	4 (13.3)
	Yes	5 (83.3)	6 (75.0)	13 (100.0)	2 (66.7)	26 (86.7)
Month 24	n	5	8	13	3	29
	No	0	1 (12.5)	0	0*	1 (3.4)*
	Yes	5 (100.0)	7 (87.5)	13 (100.0)	3 (100.0)*	28 (96.6)*
Month 36	n	5	7	12	3	27
	No	0	1 (14.3)	0	1 (33.3)	2 (7.4)
	Yes	5 (100.0)	6 (85.7)	12 (100.0)	2 (66.7)	25 (92.6)
Month 48	n	5	7	12	3	22
	No	0	0	1 (8.3)	1 (33.3)	2 (7.4)
	Yes	5 (100.0)	7 (100.0)	11 (91.7)	2 (66.7)	25 (92.6)

B22CS CSR. Abbreviations: n = number; y = years.

Table 57c: Number (Percentage) of Patients Presenting Nephrolithiasis, by Visit, Age Group and Overall

Analysis Visit	Nephrolithiasis	Adults >=18Y (N=6)	Adolescents [12-18Y] (N=8)	Children [4-12Y] (N=13)	Infants [0.5-4Y] (N=3)	Overall (N=30)
Baseline	n	6	8	13	3	30
	No	4 (66.7)	7 (87.5)	11 (84.6)	1 (33.3)	23 (76.7)
	Yes	2 (33.3)	1 (12.5)	2 (15.4)	1 (66.7)	7 (23.3)
Month 24	n	5	8	13	3	29
	No	3 (60.0)	7 (87.5)	12 (92.3)	2 (66.7)	24 (82.8)
	Yes	2 (40.0)	1 (12.5)	1 (7.7)	1 (33.3)	5 (17.2)
Month 36	n	5	7	12	3	27
	No	5 (100.0)	4 (57.1)	9 (75.0)	1 (33.3)	19 (70.4)
	Yes	0	3 (42.9)	3 (25.0)	1 (66.7)	8 (29.6)
Month 48	n	5	7	12	3	27
	No	4 (80.0)	5 (71.4)	5 (41.7)	1 (33.3)	15 (55.6)
	Yes	1 (20.0)	2 (28.6)	70 (58.3)	2 (66.7)	12 (44.4)

Source: B22CS CSR. Abbreviations: N, n = number of patients; Y = years.*

Source B22CS CSR. Abbreviations: N, n = number of patients; Y = years.*

Considering the number of missing data per visit, more particularly for the age group of children at Month 48, the results with imputation have to be analysed with caution. Nevertheless, overall, the number of patients with nephrocalcinosis or nephrolithiasis is stable over time.

B8. *Priority:* Clarify the evidence to support the assumption that responders remaining on treatment cannot progress beyond CKD 2.

The assumption that responders remaining on treatment cannot progress beyond CKD2 is based on control of metabolic acidosis preventing further decline of kidney function due to dRTA (not in relation to other causes).

As per Lopez Garcia et al 2019:

"A third (34.7%) of the children (aged 2–18 years) had an impaired eGFR (<90mL/min/1.73m2), mostly CKD Stage 2 (Figure 3A). Mean (SD) eGFR at last follow-up in adults (N=83) was 75mL/min/1.73m2 (623) and was broadly similar across the genetic groups: ATP6V1B1 81 (627), ATP6V0A4 79 (626), SLC4A1 66 (620) and Unknown 75 (620) (P=0.2). No patient with end-stage renal disease was noted, yet of the 83 adult patients (≥18 years), eGFR was<90mL/min/1.73m2 in 68 (82%) as shown in Figure 3B. In adults, the overall rate of eGFR decline was 0.8mL/min/1.73m2/year (Figure 3C). The prevalence of CKD Stage ≥2 was significantly higher (50/61=82%) in dRTA patients aged 20–60 years compared with the NHANES III population (2729/10 444=26%) (Figure 3D). »
"As a marker for the long-term effect on kidney function, we compared eGFR in adults with or without adequate metabolic control: mean (6SD) eGFR was significantly higher (P=0.023) in those with adequate metabolic control at 79
(±19) compared with those without at 67 (±22) mL/min/ 1.73m2 (Figure 4E)."

B9. *Priority:* Clarify the evidence to support the assumption that non-responders remaining on treatment cannot progress beyond CKD 4.

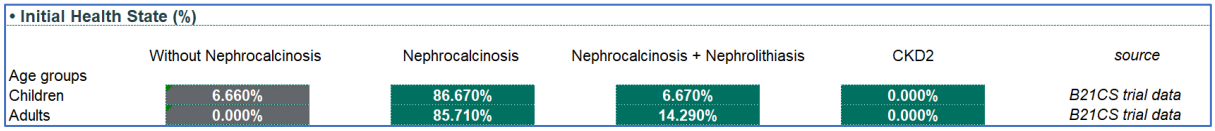
The assumption that non-responders remaining on treatment cannot progress beyond CKD4 is based on the stopping rule that patients who progress beyond 3b stop treatment (and move to the Discontinuation category). Patients under Sibnayal have to stop treatment when eGFR levels equal, or fall below, 44 ml/min/1.73m2; therefore the patients in the non-controlled group reaching the stages CKD3b-4 (defined as a fixed proportion among the health state CKD3-4) will discontinue treatment and patients on ESRD will automatically stop treatment.

B10. *Priority:* Figure 19 suggests that disease-related deaths can only occur in those who discontinue treatment. Clarify whether this can happen for patients in CKD 3-4 for non-responders.

Disease-related death occurs in patients from stage CKD3-4 (regardless of the treatment and response status).

B11. *Priority:* Provide a version of the model where all patients in each arm start the model in the same health states. Currently, this is not the case. Add in an additional cycle (of appropriate length) to model the movement of patients from equivalent health states to the differential level of response that the submitted model starts with.

The model was structured based on the response and treatment status, and includes 3 components: responders, non-responders and discontinued patients. The initial response was assessed at day 5, therefore no initial cycle was included for such a short period of time, considering a cycle length of 6 months. The initial split of patients can be found in the sheet 'clinical efficacy':



• Initial Health State (%)

Age groups	Without Nephrocalcinosis	Nephrocalcinosis	Nephrocalcinosis + Nephrolithiasis	CKD2	source
Children	6.660%	86.670%	6.670%	0.000%	*B21CS trial data*
Adults	0.000%	85.710%	14.290%	0.000%	*B21CS trial data*

The model starts when the initial response has been assessed and distribute the patients according to their initial health state and response rate. A way to assess if patients are correctly split is to set up the same response rate for Sibnayal and SoC and check row 95 of Markovcal_patients (age 1-4). Please note the trace starting in row 6 has the half-cycle correction applied, therefore if the user wants to test the same split of patients between Sibnayal and SoC he needs to apply same initial response rate and same efficacy at time '0 to 6 months' (for both disease control and disease recovery).

B12. *Priority:* For Table 69 and Table 71, clarify the process of identifying data sources to populate the model, and the selection criteria used to choose the paper to provide values in the company's base case.

Due to the paucity of dRTA specific publications given the rarity of the disease and the varied comorbidities that accompany the condition, data sources to populate the model came from a variety of sources (as identified in the model). These include Clinical Trial data from B21Cs and B22CS CSRs and Patient level data from B22CS for Clinical efficacy values; dRTA specific publications e.g. Palazzo et al, Zhang et al, Lopez-Garcia et al for some transition probabilities (identified via the SLR) and other values from a non-targeted

search of the literature e.g. Surgue et al; Collins et al for values where non dRTA specific values did not exist in the published literature. Non targeted values were informally evaluated from the papers found, to select conservative values for the model inputs.

B13. *Priority:* For all distributions used in the model provide the absolute values used rather than means and standard deviation. Thus, for example, provide the alpha and Beta parameters for Beta distributions.

Mean, Standard deviation, Alpha and Beta values are all included in the PSA and are calculated based on the mean and SE. The SE is calculated based on the variations entered in the DSA. The variation of the efficacy parameters is based on the 95% confidence intervals.

B14. *Priority:* Age-adjust all utilities. It is implausible that patients without NC and responding to treatment would have a utility of 0.86 at 80 years of age.

The model has been adjusted to incorporate age adjusted utilities. The model has been amended and now incorporates age-specific baseline utilities. The effect of the health states are accounted using multipliers. The patients 'without NC' have no decrement of utilities, the level of utility only varies with age. The new set of inputs can be found in the 'quality of life' sheet. The 'MarkovCalc_QoL' sheet was amended accordingly, separating the patients starting in age 1, 2 , 3 and 4, and applying the corresponding baseline utility according to their age overtime. Then the model applies the multipliers based on the health states (from column CQ) as well as the decrement of utility associated with events (from column EE).

B15. *Priority:* Clarify how the uncertainty associated with the utility for the w/NC was calculated, Consider using utility from Ara and Brazier, without uncertainty, and applying utility multipliers (with uncertainty) for each health state. If appropriate consider maintaining ranking of utilities (an option for this is presented in Ren *et al*. A new approach for sampling ordered parameters in probabilistic sensitivity analysis. Pharmacoeconomics 2018; 36 (3), 341-347)

The recommendation has been followed. The utilities set from Ara and Brazier (patients without condition), applying multipliers for each health state has been used. The multipliers were derived based on the mean age of the cohorts from each source used to estimated the health state utilities. The calculations can be found in the 'quality of life' sheet.

B16. *Priority:* It appears that the Dirichlet distributions are not implemented correctly. An example of this can be observed in cell C13 on the clinical efficacy worksheet whilst stepping through the PSA macro as this cell becomes negative, which cannot

happen if the Dirichlet distribution is correctly applied. Correct the Dirichlet distribution and where similar errors have occurred.

This has been appropriately adjusted in the model. The Dirichlet is now used only for the baseline characteristics and was corrected. Now the random values that are generated are always equal to 1 (as shown in cells Y17:Y23 of 'PSA' sheet). All the parameters on patient progression are now applied a Beta distribution.

B17. *Priority:* Clarify why assumed standard errors are used for Dirichlet distributions - the count data provides the uncertainty.

The Dirichlet is now using the count data, as shown in cells K17:K23 of PSA sheet.

B18. *Priority:* For binary outcomes such as disease control outcomes, clarify why a Dirichlet distribution (or a Gamma distribution) is used rather than a Beta distribution.

This has been appropriately adjusted. This has been changed for a Beta distribution.

B19. *Priority:* Clarify how SOLVER can be used within a Dirichlet distribution as implied in Table 77.

The Dirichlet was changed for a Beta distribution. Please note the solver is not run during the sensitivity analyses. The solutions from the solver are considered as the BC inputs for the risk of progression of N and N+N to CK2. Those values are then tested in SA.
The solver is running each time the user move from the 'Transition probabilities' sheet or close and save the model; if changes have been done to the TPs, new solutions will be found by the solver. However, varying TPs in the DSA or PSA will not activate the solver; once the solver found solution for the BC, there are considered as fixed values, varied in sensitivity analyses as any other input of the model.

B20. *Priority:* Clarify why the costs of ADV7103 are varied (with an arbitrary standard error) in the PSA.

This has been appropriately adjusted. This was removed from the PSA

B21. *Priority:* There is an apparent error within the model. Cells AB88, AC89, AD90, AE91, AF92, AB144, AC 145, AD146, AE147, AF148, AB200, AC201, AD202, AE203, AF204, FAB256, AC257, AD258, AE259, AF260, AB312, AC313, AD314, AE315, AF316, AB368, AC369, AD370, AE371, AF372 of Table TP worksheet have the value of 1,

resulting in patients being unable to leave this health state apart from death based on background mortality rates. Please amend the model.

There is no error. Once the patients discontinue Sibnayal, 50% will move to SoC and 50% will stop completely treatment (based on what value is set up in 'Clinical efficacy'row 70). The patients who move to SoC are then applied TP from the SoC matrice.

The diagonals of 100% are not used in the model; when we look at the Markov traces in 'MarkovCalc_Patients age1' for example, the formula in cells CV95:DO95 are using the TP table 211 (the index is indicated in column CU); table 211 corresponds to the TPs for SoC.

B22. *Priority:* Clarify the process used to identify mortality rates associated with stage 3-4 CKD and stage 5 CKD (ESRD) used in the model and the selection of the most appropriate source. The company uses mortality rates of 13.8% & 17.7% for stage 3-4 CKD & stage 5 CKD (ESRD) respectively. The ERG has identified (from a non-systematic literature review) a recent report published (Gibertoni D, Reno C, Rucci P, Fantini MP, Buscaroli A, Mosconi G, et al. (2021) COVID-19 incidence and mortality in non-dialysis chronic kidney disease patients. PLoS ONE 16(7): e0254525. <https://doi.org/10.1371/journal. pone.0254525>) which gives crude mortality rates of 2.33%, 4.51%, 7.32% and 10.65% for stage 3A CKD, stage 3B CKD, stage 4 CKD and stage 5 CKD (ESRD) respectively which are lower than those used in the model. Ideally, targeted literature reviews should be undertaken to populate any key parameters within the model.

The values sourced for mortality rates of 13.8% (3-4 CKD) and 17.7% (ESRD) were from a non-systematic literature search. The ERG sourced values will be used as basecase in the re-worked model. Model mortality value for CKD3-4 will take average of suggested mortality rates (excluding ESRD) with bounds tested in DSA and PSA.

B23. *Priority:* Many of the benefits of ADV7103 are due to the longevity of successful treatment. Appendix J indicates that the median time being a responder on treatment is in excess of 50 years for ADV7103 whereas this is less than 1 year for SoC. For treatment, independent of response, the median duration is approximately 60 years for ADV7103 and 3 years for SoC. Clarify the evidence supporting the estimated

duration of both ADV7103 and SoC treatment. Provide exploratory analyses to clarify the impact of assuming that patients discontinue ADV7103 at 5, 10 and 20 years.

A discontinuation function for Sibnayal has been implemented to explore the impact of patients discontinuing ADV7103 at 5, 10 and 20 years ; the drop-down can be found in 'treatment efficacy' sheet. Two specific matrices (1 for children and 1 for adults) were added in the 'Table TP' sheet in cells AT320: BX367: this specific set of TP is applied in Markovcal_patients (1-4), rows 102, 107, 117 (cells are in orange), depending on the timepoint selected (5, 10 or 20). They replace the TP sets used at those timepoints when no discontinuation is applied. Changes were also done in the markov traces in columns CL:CF for patients who are on SoC after they discontinued Sibnayal, to account for this update.

B24. *Priority:* Perform exploratory analyses where the annual discontinuation rates for those on SoC (Table 66) are much lower. For example, 5% for children and 20% for adults.

See Appendix 2.

B25. *Priority:* Clarify why patients have worse utility in the years after transplant than in the year of the transplant. This seems implausible. Please review the evidence, and amend the model if appropriate.

This has been appropriately adjusted. Laupacis 1996 is applied for both year of /and post-transplant values for consistency.[10]

B26. Priority: It is stated that the "ratio of efficacy between ADV7103 and SoC at each cycle is the same as the initial levels of efficacy observed after the first 5 days of treatment." However, in Table 65 for adults the efficacy between 18 and 24 months is lower than for 24-36 months. Please amend the report and model as appropriate.

This was corrected in the updated version; to avoid any mistake, the relative efficacy is now clearly visible in the 'treatment efficacy' sheet and used to assess the SoC estimates.

B27. *Priority:* Please clarify (p141) what was the threshold used for compliance to proxy discontinuation. Clarify why those patients who are semi-compliant (and assumed to discontinue) would derive no benefit?

KOL's were asked what percentage of adult and child patients were fully compliant with SoC treatment. Those not compliant were assumed to have discontinued treatment. Full compliance in children was estimated to be 61%, noting that compliance will be closer to

100% in younger children, falling to 20%-30% in teenagers. Full compliance in adults was estimated to be 55%.

The modelling structure does not account for semi-compliant / semi-discontinuation patients.

B28. ***Priority:* Clarify whether it is plausible that patients with NC+NL have a lower utility than patients with CKD2 if CKD2 is seen to be a worse state in the model. Please review the evidence, and amend the model if appropriate.**

NC + NL utility is sourced from Polotti et al 2020 (0.83) and the CKD2 utility is sourced from Jesky et al 2016 (0.85) [11,12]. This small difference in utility is justified and clinician verified due to the impact of nephrolithiasis (pain and recurrent stone removal) verses CKD2.

B29. P104 Clarify how outcome measures listed in Table 65 were assessed. Provide structured questionnaires if these exist.

The scales used, VAS and FHS, these are commonly used and widely accepted to evaluate the taste or the acceptability of a product, or the pain and discomfort in adults and children, respectively. [13,14]

Acceptability

In B21CS Study, product acceptability was assessed through 3 different endpoints: palatability, ease of administration and ease of swallowing, and during V2 and V3.

Palatability was worth assessing since it is an issue hindering good compliance in patients with dRTA, and it was expected that ADV7103 specific pharmaceutical formulation (prolonged-release granules which are coated to mask the bitterness of the active ingredients) could represent an improvement as compared to existing products used in the clinical practice, and in particular in children.

Assessment was performed using a 100mm Visual Analogue Scale (VAS) or a 5- point facial hedonic scale (FHS) (Figure 2.7.3-3 Facial Hedonic Scale for palatability evaluation). 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. Palatability was assessed as follows:

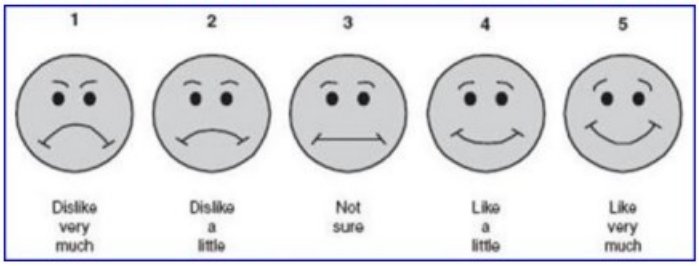
− Adults (subset 1) and adolescents (subset 2) had to answer the question ‘How much did you like the taste of the medication?’ using VAS for which a score of ‘0’ meant ‘I dislike very much’ and a score of ‘100’ meant ‘I like very much’.

− The VAS was also used for infants (subset 4), and the same parent at each of the Visit, based on infant's behaviour or possible words had to answer the question: 'How much did you think your child like the taste of the medication?'

− Children (subset 3) had to use the FHS with the help of their parents where necessary, to select the appropriate face to indicate their preference when answering the question: 'How much did you like the taste of the medication?'

Figure 2.7.3-3 Facial Hedonic Scale for palatability evaluation

Figure 2.7.3-3 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 2.7.3-6).

Table 2.7.3-6 Linkages between VAS and Hedonic Face Scale

Table 2.7.3-6 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

➢ Ease of administration and ease of swallowing were assessed in order to evaluate the acceptability of the ADV7103 new formulation as multi-particulate granules, which is not a formulation commonly used with such a quantity of granules (e.g. several hundreds of granules per intake), compared to SOC usually provided as liquid, power, or monolithic formulations.

Ease of administration and ease of swallowing were assessed either by (subsets 1 and 2) patients or (subsets 3 and 4) parents/caregivers using a VAS where a score of '0' meant 'very difficult' and a score of 100 'very easy', to answer the following questions:

− ‘How do you find the administration of the medication?’ – for subsets 1, 2, 3 and 4 − ‘How do you find the swallowing of the medication?’ – for subsets 1 and 2

− ‘How do you think that your child swallows the medication?’

– for subsets 3 and 4. In Study B22CS, ADV7103 was assessed at Month 24 using 6 100mm

-VAS questioning the patient about particularly the efficacy, the safety (gastro-intestinal tolerability), the formulation, the number of daily dose intakes and the taste.

Treatment compliance

In Study B21CS, compliance was assessed during V2 and V3, based on study drug retrieval and data recorded by patients in the diary book, and subsequently reviewed and included in the CRF by the investigator. A patient was defined compliant if for each study period at least 80% and no more than 125% of all planned treatments were to be taken during the considered period, i.e. SPI, SPII and SPIII.

In Study B22CS, compliance was assessed throughout the study based on the number of unused treatment units, questioning of the patient and/or his/her family, and on the review of his/her laboratory results. The compliance was evaluated at each study visit by the investigator as follows: compliance of 90% or more, between 75% and less than 90%, between 50% and less than 75%, and less than 50%.

Quality of Life

In Study B22CS, the improvement of the patient’s quality of life (QoL) was evaluated using a 100 mm VAS with a score of ‘0’ meaning ‘Not at all improvement of the quality of life’ and a score of ‘100’ meaning ‘Extremely great improvement of the quality of life’. The scale was filled-in at Visit 3 (Month 6) and Visit 6 (Month 24) of Study B22CS by the patient (subsets 1, 2 and 3 where possible) while answering the question: ‘Do you find that ADV7103 improves your quality of life compared to the alkalising medication that you used before the study?’.

At Visit 3 (M6) and Visit 6 (M24) when the patient (potentially subset 3, and subset 4) was not able to complete the VAS, their parents completed the scale while answering the question: ‘Do you find that ADV7103 improves the quality of life of your child compared to the alkalising medication that you used before the study?’.

Similarly, the improvement of parents' QoL was evaluated using a VAS completed at Visit 6 (M24) when answering the question: 'How the change of treatment of your child has improved your daily life?'; in this situation, a score of '0' meant 'No at all improvement of the quality of life' and a score of '100' meant 'Extremely great improvement of the quality of life'. Visit 6 results are not included in this submission

B30. If possible, add to Table 66 the QoL of patients at Month 0 and at initiation of Phase I

There was no evaluation of the quality of life (QoL) at initiation of study period I of B21CS Study, as this evaluation was not initially planned.

There was no evaluation of the QoL at Month 0 in B22CS study, timepoint that represents also the end of B21CS study, characterised by many unusual constraints for the patients (repeated investigator' visits and phone calls, repeated blood drawings, in-patient periods). Therefore, the evaluation of the QoL at that time would not have been a reflection of the patient's real life.

B31. In Table 74, please provide further details of the Serious TEAE observed and the severe TEAE in SPII.

In B21CS study, a serious TEAE, which necessitated a hospitalisation, was reported in 1 (2.9%) adolescent patient (Subject 301-001) during study period II (i.e., titration phase of ADV7103). It was an acute gastroenteritis (classified as 'Infections and Infections' in the system organ class), moderate in severity, considered as unrelated to the treatment, and resolved within 24 hours without corrective treatment. Treatment with ADV7103 was interrupted since vomiting was associated to the gastroenteritis and alkali agents were provided by intravenous route for 36 hours, Then, ADV7103 was reintroduced without dose change.

B32. Clarify what data exist regarding the age of patients with dRTA. Clarify why a 50:50 split would be considered conservative.

The main source of data summarising the age of patients with dRTA is the CPRD data (published in Bianic F.et al 2021 and further analysis also provided in the reference pack as data on file). Clinical Practice Research Datalink (CPRD) is an ongoing primary care database of anonymised medical records from general practitioners. Using data extrapolated from the CPRD, in confirmed diagnosed cases, 22.1% were defined as inherited dRTA. These would be assumed to be <18 years in the model, meaning 77.9% were acquired and assumed in the model to be over 18 years. This split was deemed too high by Clinicians

(advisory Board 2020) and not reflective of the treated population which would be more heavily paediatric weighted.

The B21CS study aimed to have at least 4 patients in each subset (infant, child, adolescent, adult) and included those with either genetic or inherited dRTA. For the license, which is inclusive of children it is important to have sufficient paediatric data. There is also high unmet need within the paediatric cohort due to heightened issues with palatability and compliance, especially with respect to night-time dosing associated with standard of care. If the model were to reflect this trial split (75/25 Paediatric/Adult), this would have weighted the results in the opposite direction to the CPRD data. In the absence of any other age related dRTA data, a 50:50 split in the population was selected.

As shown in the subgroup analysis (Table 87), the ICER for ADV7103 improves considerably for younger age groups. As such, selecting a 50:50 split (where the proportion of adult patients may be higher than real-world clinical estimates) was deemed conservative.

B33. Clarify the methods used to identify and select values used in the model, for example related to patient weight.

Patient weight values were calculated from a search of the literature for average weight values. So et al and Tinning and Ackworth were used for paediatric values and Warpole for average adult weight.

Table 58: Patients' composition at model entry

Age groups	Composition (%)	Mean age	Mean weight (kg)	Source (weight)
1-3	8.8	2.00	12.78	So et al [15]
4-11	23.5	8.00	32.00	Tinning and Acworth 2007 [16]
12-18	17.6	15.00	59.70	Linear interpolation between weight at fifteen from Tinning and Acworth [16] and weight at 18 years
>18	50.0	25.00	70.80	Walpole et al, 2012 [17]

Detail on the calculations used, has been provided on page 134 of the company evidence submission.

B34. Clarify why patients are not assumed to increase in weight above the age of 18 years.

The standard method of using mean average weight for adults has been used to avoid additional complexity being added to the model. The company believe this has been

acceptable on other HTA submissions. Variation to average adult weight is reflected in sensitivity analysis.

B35. Clarify whether it is possible for patients with CKD 3-4 to become a responder, both in reality and in the model.

In reality, there is small chance of becoming responders with CKD3-4. In the model, a simplified structure was adopted so that patients could not go back to the responder group once progressed to CKD3-4. The model structure was judged appropriate by KOL opinion.

B36. Clarify the evidence to support the assumption that moving from a non-responder status to a responder status is independent of nephrocalcinosis and nephrolithiasis status.

The assumption that moving from a non-responder status to a responder status is independent of nephrocalcinosis and nephrolithiasis is made because whether a patient's treatment status happens regardless of their health state. The only interdependence relates to that a responder would therefore have better metabolic control and thus prevent progression of / or reverse their risk of nephrocalcinosis / nephrolithiasis.

Due to the limited patient numbers in the trial a sub group analysis of the non-responder to responder group is not possible. The assumption is made on clinical judgement.

B37. Provide a sensitivity analysis where data in the model have been continuity corrected (by adding half a unit to the numerator and a full unit to the denominator) where there are less than five observations in an outcome measure, for example, the proportion of patients who become responders or remain non-responders.

The continuity correction was calculated for all efficacy outcomes from patient level data (disease control and recovery up to 48 months). The user has now the possibility to apply or not the continuity correction in 'clinical efficacy' sheet. The base case uses the values corrected but the impact on ICERs is very minor (see Appendix 2).

B38. Clarify potential reasons for the dose of ADV7103 observed in B21CS being higher for patients aged 17 years and under than in B22CS, whilst the dose for ADV7103 was higher for patients aged 18 years and older in B22CS compared with B21CS.

Table 61 and Table 62 page 139 of the Document B present the mean daily dose of ADV7103 in mEq/kg/day, as summarised in Table 9, which presents also the mean daily dose of ADV7103 in mEq/day, the standard deviations, and the minimal and maximal doses.

Table 9: Descriptive summary of the ADV7103 daily doses in mEq/kg/day and in mEq/day, per subset of age and study

Subset of age Mean (SD) age at enrolment	ADV7103 daily dose - mEq/kg/day		ADV7103 daily dose - mEq/day	
	B21CS Mean (SD) Min – Max	**B22CS M24** Mean (SD) Min – Max	**B21CS** Mean (SD) Min – Max	**B22CS M24** Mean (SD) Min – Max
6 months – 3 years old 2.6 (1.05)	6.11 (2.26) 4.0 – 8.5	4.81 (2.00) 3.1 – 7.0	90.00 (25.52) 61.2 – 109.8	96.0 (27.7) 64.0 – 112.0
4 – 11 years old 7.3 (2.40)	3.80 (1.15) 1.9 – 6.0	3.41 (1.30) 1.9 – 5.8	96.46 (59.96) 30.5 – 272.0	109.5 (7.5) 32.0 – 336.0
12-17 years old 14.0 (1.69)	2.79 (1.74) 0.9 – 6.0	2.53 (1.88) 1.1 – 5.8	124.25 (79.19) 53.0 – 291.0	130.0 (73.8) 64.0 – 288.0
≥ 18 years old 23.3 (9.92)	1.74 (1.05) 0.8 – 4.0	2.26 (1.30) 1.5 – 4.6	108.39 (44.33) 78.3 – 204.0	128.0 (55.4) 96.0 – 224.0

Source: B21CS – Table 14.1-3.1, B21CS - Table 14.3-2.2, B22CS – Table 14.1.5.3

The ADV7103 dose can be variable in a subset of age, as shown with the standard deviation, the minimal and maximal doses, in Table 9.

While growth is continuous during childhood, the weight curves show two rapid increases of weight during infancy then adolescence.

Due to the high level of body metabolic activity in the youngest children, the amount of alkalising agents (in mEq/kg/day) to be administered is higher for them than for the older children or adults, then decrease with time. As indicated in the Summary of Product Characteristics of Sibnayal, the dosing scheme is:

- Adults: initiation at 1 mEq/kg/day, with a maximal incremental increase/decrease of 0.5 mEq/kg/day to optimal dose
- Adolescents from 12 years: initiation at 1 mEq/kg/day, with a maximal incremental increase/decrease of 1.0 mEq/kg/day to optimal dose
- Children from 4 to 11 year inclusive: initiation at 2 mEq/kg/day, with a maximal incremental increase/decrease of 1.5 mEq/kg/day to optimal dose
- Children from 1 to 3 years inclusive: initiation at 4 mEq/kg/day, with a maximal incremental increase/decrease of 1.5 mEq/kg/day to optimal dose

Considering all these elements, even if the ADV7103 daily dose in mEq/day has been increased over time to be adjusted to the bodyweight, as it is the case for the 3 paediatric subsets of age, the ADV7103 daily dose in mEq/kg/day can decrease with peak of growth

and time, as particularly occurred for the subset of age 6 months-3 years old. In addition, doses in mEq/kg/day decrease over time.

The increase of the ADV7103 daily dose in mEq/kg/day in the subset of adults (N=5 at Month 24) is mainly driven by Subject 005-002 who last 17.8 kg within 24 months (from 87.0 kg at Month 1 to 69.2 kg at Month 24), while the daily dose was not changed.

In addition, the ADV7103 daily dose in mEq/day in the subset of adults was increased for 2 patients as plasma bicarbonate level was abnormally low at some time-points, Subject 009-001 from 192 to 224 mEq/day with a decreased weight of 1.2 kg, Subject 012-002 from 80 to 112 mEq with an increased weight of 2.3 kg.

B39. Clarify whether consideration of age impacted on the values chosen for Table 66 of the CS. For example, for mortality following fracture the reference appears to be for adults aged over 60 years, which is unlikely to be applicable, both through age and likely distribution of fracture site. Using an age-standardised mortality rate for the most common fracture type is likely to be a more accurate approach.

No appropriate source for an age-standardised mortality rate for the most common fracture type (rib and long bone) that would not result in double counting (identified studies looked at all-cause mortality) could be identified. Furthermore, age-standardised mortality rates are not included in the model as disease specific risk of death may not vary based on age.

B40. Clarify why the disutility of a hip fracture was used for all fractures. Clarify what fracture sites are the most common in patients with dRTA. If required, adjust the costs associated with fracture too.

The most common fracture sites in dRTA are long bone and rib fractures (validated by clinician). Hip fracture was used as a proxy value as disutilities for long bone / rib fractures could not be sourced at time of submission. Following a review of the literature, a new method of estimating disutility associated with fracture has now been applied in the model. The model now uses a multiplier for utility loss, as reported by WHO Scientific group - Assessment of osteoporosis at the primary health care level (2007). [18]

B41. Clarify whether there is potential for double-counting in the health disutility values provided in Table 68 of the CS. For instance, the 0.352 disutility associated with bone deformities appears to assume that the full disutility associated with severe rickets can be

attributed to a bone deformity. Clarify the site and severity of bone deformities due to dRTA, and how similar this is to severe rickets.

There is potential for double counting in the health disutility values provided in Table 68. See response to B43 for how this has been adjusted in the model.

B42. Clarify why the 0.180 disutility associated with acute renal failure was assumed to be applicable to all patients with acquired dRTA, regardless of disease control. It is noted that this population comprised 46% with cardiovascular disease, 47% with hypotension, ischaemia or massive bleeding, 25% sepsis and 81% needed intensive care treatment, and that there was a mortality of 41% at 28 days and thus this value may be overestimated.

This has been adjusted in the model and can now be tested appropriately in scenario analysis. A selection box has been added to allow the user to remove the disutility in disease controlled patients (always applied to disease uncontrolled patients). The model includes now the option to apply the 0.18 disutility only to non-responders and discontinued patients in 'quality of life' sheet.

B43. Clarify how the 8.09% of bone deformities per year used in the model, attributed to Jha *et al.* was estimated. Clarify whether the values reported in studies by Kiran, Bajpai, Ramya and Zhang contributed to the estimated rate of bone deformities.

The estimates from the values reported in studies by Kiran, Bajpai, Ramya and Zhang for the estimated rate of bone deformities were not used in the model.

The 8.09% reported in the model is incorrect. The model has been adjusted, using the probability of having Osteomalacia and Rickets from the Jha et al. paper as follows:

- Osteomalacia rate = 5/52 = 9.6% - applied only to adults
- Rickets rate = 26/44 = 59.1% - applied only to children

General model change:

- Bone deformities has been renamed in the model to Rickets

Management costs sheet:

- 'Osteomalacia-fracture' cell has been renamed to 'Fracture'

- 'Bone deformities' cell has been renamed to 'Osteomalacia/Rickets' – no change to the relevant cost per year as both Osteomalacia and Rickets are treated with Vitamin D (as per current reference Zipitis et al.)

Quality of life sheet:

Same as management costs

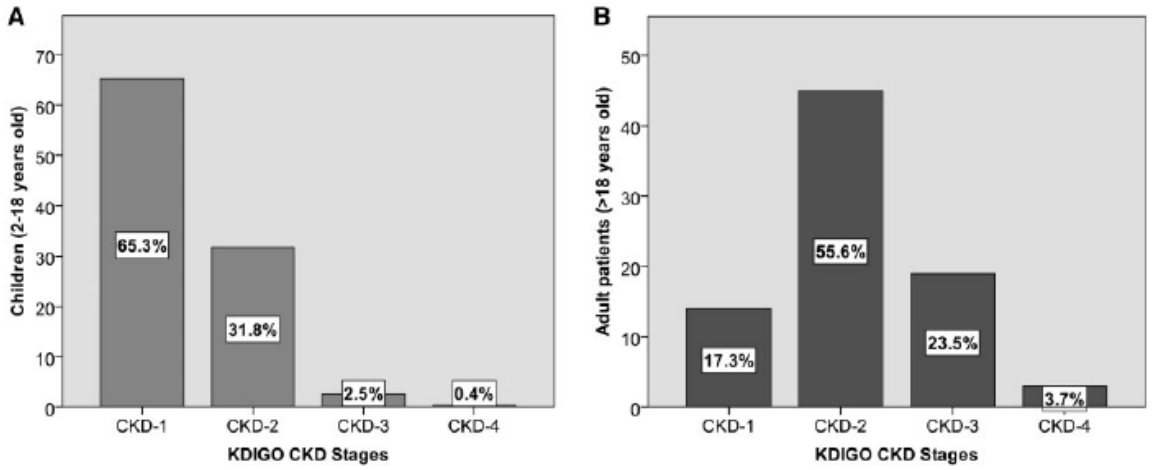
- ‘Osteomalacia-fracture’ cell has been renamed to ‘Fracture’ – no change to the disutility other than applying the new fracture age related disutility multiplier

- ‘Bone deformities’ cell has been renamed to ‘Osteomalacia/Rickets’ – no change to the disutility value of 0.352 (the Yanes paper looked at both adults and children)

B44. Clarify how the values of 31.8% for the assumed prevalence of CKD Stage 2 and 2.9% for CKD 3-4 were derived from the Lopez-Garcia *et al.* paper. Check that the 31.8% is in the Lopez-Garcia paper.

Lopez-Garcia:

Figure 5: Renal function and CKD. (A) Prevalence of CKD stages in the paediatric age group. (B)Prevalence of CKD stages in the adult age group.



Values of 31.8% for the assumed prevalence of CKD Stage 2 and 2.9% for CKD 3-4 (2.5% + 0.4%) are sourced from figure A from the supplementary tables from the Lopez Garcia paper

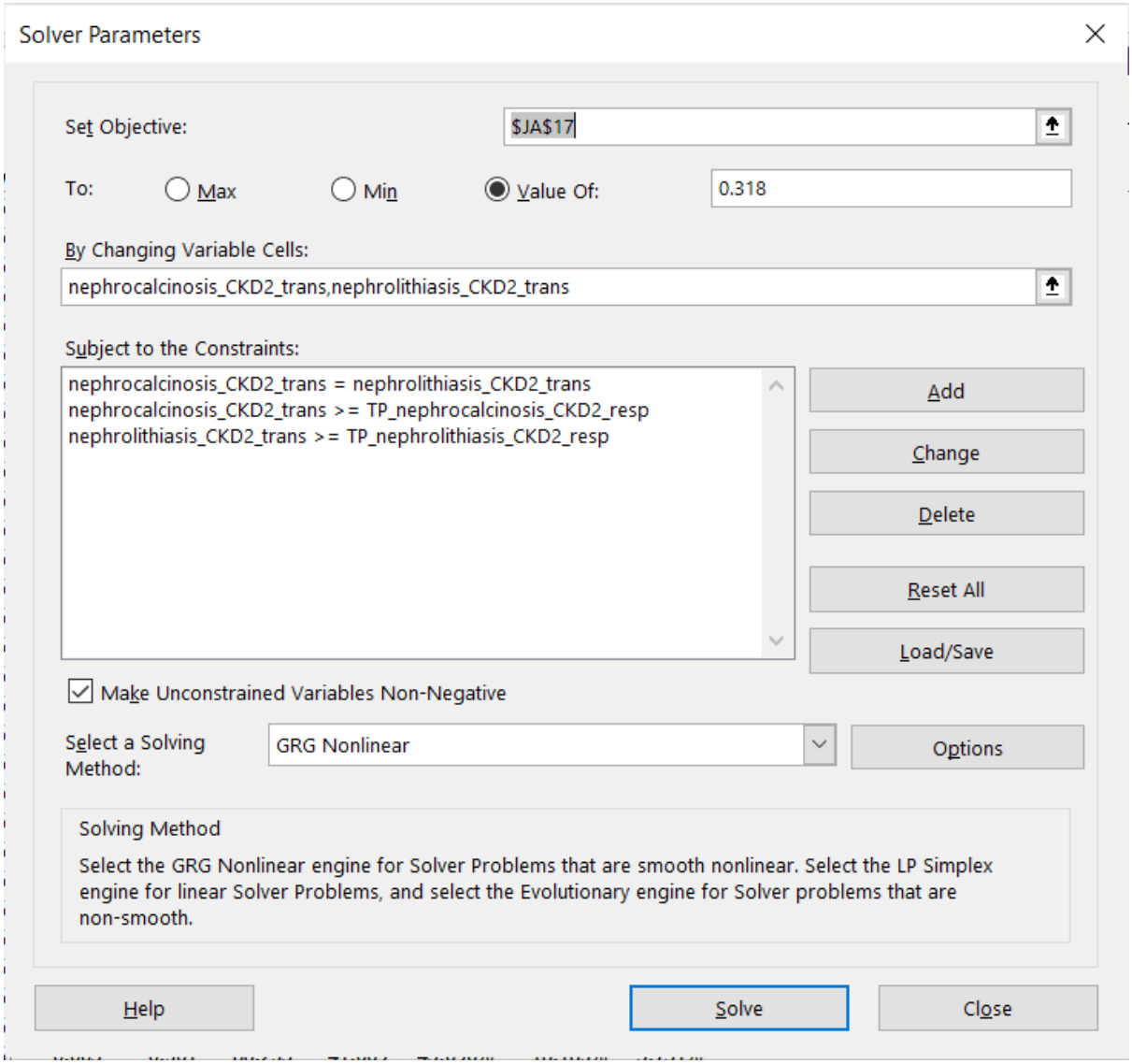
Paediatric values have been used as the solver function operates from age 11 years.

B45. Provide full documentation related to the SOLVER calculation used to estimate the risk of progression from NC and NC+ NL to CKD2. Clarify, and justify, the assumed age of the cohort used to derive the transition probability.

SOLVER is used to estimate the risk of progression from Nephrocalcinosis and Nephrolithiasis to CKD2 for non-responders that results in the prevalence of CKD2 patients observed in Lopez-Garcia (31.80%) in a hypothetical cohort of patients treated with average

SoC after a simulated period of time that would correspond with the mean age of the cohort presented in the study (11 years old). The solver parameters are represented in the screenshot below.

The cell J17 of the sheet ‘‘MarkovCalc_Patients age1’ is the proportion of CKD2 observed in the cohort 1 under SoC when they reach 11 years old. This target cell is assumed to be equal to 31.80%. The solver is providing solutions for the TPs from NC and NC+ NL to CKD2 (called the variable cells) to fulfil the objective of the 31.80%. Three constraints were added in the solver: the risk of progression of non-responders have to be superior or equal to the risk of responders, and the risk of progression from NC and NC+NL should be equal.



B46. For patients who have discontinued treatment, clarify why the transition from w/NC to NC has been set to 100% per year, when the clinical opinion suggested 100% at 2 years. Provide a scenario analysis where 90% a year is used.

This has been appropriately adjusted. The base case has been change to 90%.

B47. Clarify whether it is plausible that patients with NC+NL who are responding have a higher probability of progressing to CKD2 than patients who are not responding.

Two new constraints have been added to the solver: the risk of progression of non-responders have to be superior or equal to the risk of responders. Please see answer to question B45.

B48. Clarify whether the values for 'Health Disutility' reported in Table 71 are actually QALY losses. If these are disutilities then add in a column for the expected duration of each event. Review and clarify whether the model has calculated QALY losses appropriately.

The ERG are correct and the health disutility's reported in Table 71 are QALY losses. This is a reporting error and is correctly applied in the model.

B49. Clarify why the utility loss associated with Acquired dRTA was assumed equivalent to the loss of patients with acute renal failure.

Acquired utility loss was sourced from Ahlstrom et al 2005. HRQoL of adult patients incurs fixed decrement associated to underlying condition because they are assumed to have acquired dRTA. Acquired forms of the disease are usually associated with autoimmune diseases, such as Sjögren's syndrome, systemic lupus erythematosus or autoimmune chronic liver disease.

Wong et al 2017[19] describe the loss of utility of chronic liver disease as a decrement of 0.09 from the healthy population, whereas Lendrem et al describe the disutility for Sjogrens syndrome at as much as 0.24. Both conditions for which Acquired dRTA is associated. [20]

The Ahlstrom et al 2005 value of 0.180 for acute renal failure sitting between these values. The lower (0.09) and upper (0.24) utility values have been tested in scenario analyses (see Appendix 2)[21]

B50. Clarify why the threshold for becoming an adult is assumed uncertain in the PSA.

This has been appropriately adjusted and removed from the PSA.

B51. Clarify why clinical opinion was used to generate an estimate of 9.39% per year for hypokalaemia (Table 68) when other sources are available (for instance, Palazzo *et al* which reports 33 of 82 patients as being hypokalemic)

It was felt that the cross-sectional study from Palazzo did not reflect hypokalaemia as an annual event rate. The more conservative 9.39% was KOL opinion and was used rather than 40.2% from Palazzo. [22] Additional scenario analysis has been provided to reflect the uncertainty in this value.

B52. Clarify the value used in the model, and how this was derived, to estimate the proportion of patients in the CKD 3-4 state that are assumed to have eGFR levels equal or below 44 ml/min/1.73m^2.

The estimate of the proportion of patients in the CKD3-4 state that are assumed to have a eGFR levels equal or below 44 ml/min/1.73 m^2 is stated as 20% will move from stage 3a to stage 3b. This was validated with KOL opinion.

B53. Provide details relating to the input parameters which produce outlier points in Figure 20. For example, what combinations of PSA produce: 3 or less incremental QALYs, 13 or more incremental QALYs, incremental costs above £300,000 and incremental costs below £100,000.

This is no longer relevant in updated model.

B54. Provide a scenario analysis where alternative doses (as in Table 85 Scenario 1) are used for patients aged 18 years and over and provide an ICER for this age group.

This has been provided in the updated scenario analysis (See Appendix 2).

B55. Clarify why the initial ratio of patients in health states without nephrocalcinosis, nephrocalcinosis and nephrocalcinosis + nephrolithiasis differs for age group 4 compared with age groups 1, 2 and 3.

The initial ratio of patients in health states without N, N and N+N is different for adults and children as displayed in the ‘clinical efficacy’ sheet.

B56. If dose wastage can occur, clarify why the mean weight was used rather than an appropriate distribution (see Hatswell AJ, Porter J, Lee D, Hertel N, Latimer NR. The Cost of Costing Treatments Incorrectly: Errors in the Application of Drug Prices in Economic Evaluation Due to Failing to Account for the Distribution of Patient Weight. Value in Health

2016 19 1055-1058). If appropriate, provide a qualitative estimation on how using a distribution would impact on the results.

Given the administration method (granules) of ADV7103 and SoC treatment, the impact of weight on dose wastage is assumed to be minimal.

B57. Clarify whether the total cost of aftercare following kidney transplantation considers only the cost of immuno-suppression. Recent literature suggests that the cost of immuno-suppression is only one half the total cost of aftercare following transplantation. See von Zur-Mühlen, B., Wintzell, V., et al. 2018. Healthcare resource use, cost, and sick leave following kidney transplantation in Sweden: A population-based, 5-year, retrospective study of outcomes: COIN. Annals of transplantation, 23, p.852

Transplant first year costs used was £14,631.12 from 2019/2020 National Cost Collection. Cost of aftercare following kidney transplantation was sourced from NHS Blood and Transplant fact sheet 7 (2009) with a cost per year of £5,913.50 (at 2020 prices).
The company do not believe that transplant costs from outside of the UK are an appropriate alternative. The cost for subsequent years is also in line with NICE guidance GID-TA10808 - Dapagliflozin for treating chronic kidney disease.

B58. Clarify the reasons for choosing the source to populate weight within the model. An alternative source provides data for males and females lower which result in lower estimates (https://www.disabled-world.com/calculators-charts/height-weight-teens.php)

Walpole et al (2012) was selected as a British weight source for adult weight estimations. Paediatric weight references for England/Britain were more difficult to locate therefore So et al (US) and Tinning and Acworth (Australasia) were deemed next most generalisable sources. [16,17]

Table 10: Patients' composition at model entry

Age groups	Composition (%)	Mean age	Mean weight (kg)	Source (weight)
1-3	8.8	2.00	12.78	So et al [15]
4-11	23.5	8.00	32.00	Tinning and Acworth 2007 [16]
12-18	17.6	15.00	59.70	Linear interpolation between weight at fifteen from Tinning and Acworth [16] and weight at 18 years
>18	50.0	25.00	70.80	Walpole et al, 2012 [17]

B59. Clarify why modified Shohl's solution appears as a one-product option and also as a two-product option in Table 60.

This should read Modified Shohl's solution with Sodium Bicarbonate (2 products). Corrected in CS.

B60. Clarify whether responders are assumed to have zero probability of sustaining any of the transitory events listed in Table 68 (on page 144 [we note there are two Table 68s)

Yes correct – responders are assumed to have zero probability of sustaining any of the transitory events. Table number issue corrected.

B61. Clarify whether there has been an error relating to the cost of a visit to a doctor to manage disease. The company states that this is taken from the 2019/20 National Cost Collection using currency code WF02A in Nephrology with a cost of £361.54. The ERG identified a cost of £180.77 for consultant-led meetings and £202.64 for non-consultant-led meetings.

The £361.54 reported in Table 74 is the sub-total cost which is calculated using the reported resource use (2) multiplied by the unit cost of a doctor visit (£180.77).

Section C: Textual clarification and additional points

C1. Check Table numbering (for example, there are two of the following tables: Table 16s, 18s, 19s, 20s, 21s, 68s, 74s)

Updated in CS.

C2. Define abbreviation "AA set" (page 50)

Acceptability analysis set.

C3. CS page 79. The CS states that "As shown in Figure 16 the return to urine pH baseline values is reached within 24 hours after the last administration of ADV7103 regardless of the dose." Please confirm if this interpretation should reference Figure 18.

This is correct, this has been updated in the submission.

Appendix 1

Model Change Summary

Within the model, changes are indicated with an orange cell colour. Below is a summary of structural (Table 11) and input changes (

Table 12).

Table 11: Structural changes to the model

Q.	Description of change	Where it is applied	Justification
A4	Change made to relative efficacy ratios (Clinical efficacy tab)	Clinical efficacy (cells K20:K21 and rows 43 and 44); PSA row 32	In response to QA4
B14	Age Adjusted utilities – recommendation followed. The utilities set from Ara and Brazier has been used (patients without condition), applying multipliers for each health state. The multipliers were derived based on the mean age of the cohorts from each source used to estimate the health state utilities.	Quality of life (D7:D19) and MarkovCalc_QoL (columns J to M)	In response to B14
B16	Dirichlet distributions	PSA (rows 17 to 23)	In response to B16
B17	The Dirichlet now uses the count data	PSA (rows 17 to 23)	In response to B17
B18	Beta distribution	PSA (column I)	In response to B18
B19	SOLVER	Clinical Efficacy (G14:G16) and MarkovCalc_Patients age1 (JA17)	In response to B19
B20	Costs of ADV7103 are varied (with an arbitrary standard error) in the PSA. – removed	PSA	In response to B20
B23	Discontinuation function for Sibnayal has been implemented to explore the impact of patients discontinuing ADV7103 at 5, 10 and 20 years ; the drop-down can be found in 'treatment efficacy' sheet. Two specific matrices (1 for children and 1 for adults) were added in the 'Table TP' sheet in cells AT320: BX367: this specific set of TP is applied in Markovcal_patients (1-4), rows 102, 107, 117 (cells are in orange), depending on the timepoint selected (5, 10 or 20). They replace the TP sets	Clinical efficacy (cell C62); Table TP (AT320: BX367); Markovcal_patients (1-4), rows 102, 107, 117	In response to B23

Q.	Description of change	Where it is applied	Justification
	used at those timepoints when no discontinuation is applied. Changes were also done in the markov traces in columns CL:CF for patients who are on SoC after they discontinued Sibnayal.		
B37	Continuity corrected (by adding half a unit to the numerator and a full unit to the denominator) for all efficacy outcomes from patient level data	Clinical Efficacy (rows 25 to 37)	In response to B37
B41	Bone deformity – split out into rickets (children only) and Osteomalacia (adults only)	MarkovCalc_QoL (cells EJ3:EK3) and MarkovCalc_costs (cells DS3:DT3)	In response to B41
B42	Acquired dRTA disutility – tick box Can now be applied to 'All model patients' or 'Non-responders and discontinued patients only'.	Quality of life (C62)	In response to B42
B45	SOLVER - Three constraints were added in the solver: the risk of progression of non-responders have to be superior or equal to the risk of responders, and the risk of progression from NC and NC+NL should be equal	Solver module (add constraint)	In response to B45
B50	Threshold for becoming an adult in the PSA removed	PSA	In response to B50
n/a	DSA range for efficacy parameters	DSA (I31:J110)	Use calculated 95% confidence intervals from PLD counts

Table 12: Input changes to the model

Q.	Description of change	Where it is applied	Justification
B22	Mortality rates associated with stage 3-4 CKD and stage 5 CKD (ESRD) used in the model. Model mortality value for CKD3-4 will take average of suggested mortality rates (excluding ESRD) with bounds tested in DSA and PSA	Transition probabilities rows 50 and 52 DSA row 176	In response to B22
B25	Utility in the years after transplant set equal to utility in first year of transplant taken from Laupacis et al., 1996.	Quality of life Row 36	In response to B25
B40	Disutility of fracture – updated – now applied as a multiplier	Quality of life Row 44	In response to B40
B42 & B49	Uncertainty of the loss of QoL in Acquired dRTA	DSA I217:J217	In response to B42 & B49
B43	Bone deformities values have been updated (split into Osteomalacia and Rickets) – as described in answer to QB43 above.	Transition probabilities Rows 41 and 43 Management costs Row 50 Quality of life Row 49	In response to B43 – correction, and a more accurate calculation of probabilities avoiding double counting
B46	Transition from w/NC to NC - For patients who have discontinued treatment, transition from w/NC to NC changed to 90%	Transition probabilities Row 8	In response to B46
N/A	Disease Control and Disease recovery figures for 24 to 36 months and 36 to 48 months have been updated to reflect 48 month data (previously assumed steady state from 24 months onwards)	Clinical efficacy Rows 29:30 Rows 36:37	To better reflect actual trial patient level data for accuracy, updated with 48-month PLD DSA range for efficacy parameters
	Risk of progression to CKD2 for discontinued patients	Transition probabilities (cell J14:J16)	Adjusted in order for the solver to find a solution respecting the new constraints
	Utility value for ESRD amended to 0.505	Quality of life (cell D34)	Corrected based on the original source

Appendix 2

Updated Base case results presented in response to question B2:

B2. Priority: Please provide an updated base case (deterministic and probabilistic) that incorporates all changes that are made following the clarification process. Omit pennies from these numbers. Provide supplementary analyses as you see fit.

1. Summary of base-case analysis inputs

Values that have been updated following NICE clarification questions (in line with Appendix 1) are indicated with orange text.

Table 13: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: standard error (distribution)	Reference to section in submission
Population composition	8.8% (1-3 years old age group) 23.5% (4-11 years old) 17.6% (12-17 years old) 50% (>18 years old)		B.3.2 Economic Analysis – patient population
Mean Age	2 years old (1-3 years old) 8 years old (4-11 years old) 15 years old (12-17 years old) 25 years old (>18 years old)		B.3.2 Economic Analysis – patient population
Mean Weight	12.78 (2 years old) 32 (8 years old) 59.70 (15 years old) 70.80 (25 years old)	Normal SE 7.2% *applied only to adult weight (kg)	B.3.2 Economic Analysis – patient population
Adult age threshold (years)	18		B.3.2 Economic Analysis – patient population
Failure to thrive age limit (years)	15	Normal SE 1.5%	B.3.2 Economic Analysis – patient population
Discount rate for costs and outcomes	3.5%		B.3.5 Cost and healthcare resource use identification,

			measurement and valuation
Initial Health State (%)			
w/NC Children Adults NC Children Adults NC+NL Children Adults CKD2 Children Adults	 6.66% 0.00% 86.67% 85.71% 6.67% 14.29% 0.00% 0.00%	Dirichlet **Alpha and Beta from PLD**	B.3.3 Clinical parameters and variables
Disease Control - Initial Efficacy (%)			
ADV7103 Children Adults SoC Children Adults	 90% 90% 43% 43%	**Beta** **SE 5.29%** **SE 5.29%** **Unvaried (value based on relative efficacy)**	B.3.3 Clinical parameters and variables
Relative efficacy (%)			
SoC **Children** **Adults**	 **47.78%** **47.78%**	**Beta** **SE 4.88%** **SE 4.88%**	**New input**
Disease Control 0 to 6 month (%)			
ADV7103 Children Adults SoC Children Adults	 84.21% 84.21% **40.23%** **40.23%**	**Beta** **SE 8.43%** **SE 8.43%** **Unvaried (value based on relative efficacy)**	B.3.3 Clinical parameters and variables ***Updated values since original submission**
Disease Recovery 0 to 6 month (%)			
ADV7103 Children	 63.64%	**Beta** **SE 12.68%**	B.3.3 Clinical parameters and variables

Adults SoC Children Adults	63.64% 10.00% 10.00%	**SE 12.68%** **SE 1.02%** **SE 1.02%**	
Disease Control 6 to 12 month (%)			
ADV7103 Children Adults SoC Children Adults	 100% 100% **47.78%** **47.78%**	**Beta** **SE 4.45%** **SE 4.45%** **Unvaried (value based on relative efficacy)**	B.3.3 Clinical parameters and variables ***Updated values since original submission**
Disease Recovery 6 to 12 month (%)			
ADV7103 Children Adults SoC Children Adults	 **28.57%** **28.57%** 10.00% 10.00%	**Beta** **SE 14.48%** **SE 14.48%** **SE 1.02%** **SE 1.02%**	B.3.3 Clinical parameters and variables
Disease Control 12 to 18 month (%)			
ADV7103 Children Adults SoC Children Adults	 92.00% 92.00% **43.96%** **43.96%**	**Beta** **SE 6.14%** **SE 6.14%** **Unvaried (value based on relative efficacy)**	B.3.3 Clinical parameters and variables ***Updated values since original submission**
Disease Recovery 12 to 18 month (%)			
ADV7103 Children Adults SoC Children Adults	 40.00% 40.00% 10.00% 10.00%	**Beta** **SE 16.68%** **SE 16.68%** **SE 1.02%** **SE 1.02%**	B.3.3 Clinical parameters and variables
Disease Control 18 to 24 month (%)			
ADV7103 Children Adults	 72.00% 72.00%	**Beta** **SE 8.56%** **SE 8.56%**	B.3.3 Clinical parameters and variables

SoC Children Adults	 **34.40%** **34.40%**	 **Unvaried (value based on relative efficacy)**	***Updated values since original submission**
Disease Recovery 18 to 24 month (%)			
ADV7103 Children Adults SoC Children Adults	 50.00% 50.00% 10.00% 10.00%	**Beta** **SE 17.86%** **SE 17.86%** **SE 1.02%** **SE 1.02%**	B.3.3 Clinical parameters and variables
Disease Control 24 to 36 month (%)			
ADV7103 Children Adults SoC Children Adults	 **88.89%** **88.89%** **42.47%** **42.47%**	**Beta** **SE 7.95%** **SE 7.95%** **Unvaried (value based on relative efficacy)**	B.3.3 Clinical parameters and variables ***Updated values since original submission**
Disease Recovery 24 to 36 month (%)			
ADV7103 Children Adults SoC Children Adults	 **66.67%** **66.67%** 10.00% 10.00%	**Beta** **SE 13.51%** **SE 13.51%** **SE 1.02%** **SE 1.02%**	B.3.3 Clinical parameters and variables ***Updated values since original submission**
Disease Control 36 to 48 month (%			
ADV7103 Children Adults SoC Children Adults	 **81.82%** **81.82%** **39.09%** **39.09%**	**Beta** **SE 8.14%** **SE 8.14%** **Unvaried (value based on relative efficacy)**	B.3.3 Clinical parameters and variables ***Updated values since original submission**
Disease Recovery 36 to 48 month (%)			
ADV7103 Children Adults	 **40.00%** **40.00%**	**Beta** **SE 16.68%** **SE 16.68%**	B.3.3 Clinical parameters and variables

SoC Children Adults						*Updated values since original submission
		10.00% 10.00%			SE 1.02% SE 1.02%	
Treatment Discontinuation for non-responders (1 year probability)						
ADV7103 Children Adults SoC Children Adults		0.00% 3.30% 39.00% 45.00%			Beta SE 1.01% SE 0.34% SE 3.98% SE 4.59%	B.3.3 Clinical parameters and variables
ADV7103: Treatment Discontinuation (% at 5, 10 or 20 years)						
ADV7103		**Not applied in basecase**				**New input**
Treatment after discontinuation						
ADV7103 Average SoC No treatment SoC Average SoC No treatment		50.00% 50.00% 0.00% 100.00%			Beta SE 5.10% SE 5.10% N/A	B.3.3 Clinical parameters and variables
Discontinuation of CKD3b or CKD4 (% amongst CKD3-4)						
ADV7103 SoC		20.00% 20.00%			Beta SE 2.04% SE 2.04%	
GI (events/dose [mEq]) rate						
ADV7103 SoC		0.0000021 0.0000028			Beta SE 0.0000002% SE 0.0000014%	B.3.3 Clinical parameters and variables
Health State transitions 1 year probability						
From	**To**	**Responders**	**Non-responders**	**Discontinuation**	**Measurement of uncertainty and distribution: standard error (distribution)**	**Reference to section in submission**
w/NC NC NC+NL NC NC+NL CKD2 CKD3-4 ESRD	NC NC+NL NC CKD2 CKD2 CKD3-4 ESRD Transplant	12.56% 4.66% 20.00% 3.82% 3.82% n/a n/a n/a	25.13% 9.23% 20.00% 4.27% (SOLVER) 4.27% (SOLVER) 3.00% 3.00% n/a	90.00% 40.00% 20.00% 7.69% 7.69% 7.80% 7.80% 5.50%	Beta SE+-20%	B.3.3 Clinical parameters and variables

Transitory events 1-year probability	Non-Responders	Discontinuation	Measurement of uncertainty and distribution: standard error (distribution)	Reference to section in submission
Hypokalaemia Failure to thrive Failure to thrive recovery Fracture **Osteomalacia (adults only)** **Rickets (children only)**	9.39% 12.91% 10.00% 0.17% **9.62%** **59.09%**	72.00% 12.91% 10.00% 0.34% **19.23%** **80.00%**	**Beta** **SE+-20%**	B.3.3 Clinical parameters and variables
Disease and Event related Mortality 1-year probability			**Measurement of uncertainty and distribution: standard error (distribution)**	**Reference to section in submission**
CKD3-4 ESRD Transplant Hypokalaemia No CKD CKD ESRD Fracture	**4.72%** **10.65%** 5.30% 0.67% 2.28% 5.82% 3.54%		**Beta** **SE+-20%**	B.3.3 Clinical parameters and variables
Treatment costs (unit cost/mEq)	**Cost**		**Measurement of uncertainty and distribution: standard error (distribution)**	**Reference to section in submission**
ADV7103 Acquisition Average SoC Acquisition	 £0.2500 £0.1628		***not varied in PSA** **Gamma** **SE+-20%**	B.3.5 Cost and healthcare resource use identification, measurement and valuation
Management costs (per year)				
Health states Responders Non-responders Nephrolithiasis Nephrocalcinosis CKD2 CKD3-4 ESRD Transplant (first year) Transplant (subsequent years) Transitory event **Fracture** Failure to thrive **Osteomalacia/Rickets** GI event	 £513.53 £1,048.32 £6,240.93 £1,211.41 £1,211.41 £4,241.65 £32,360.40 £14,631.12 £5,913.50 £2,125.56 £2,089.39 £3,182.68 £148.12		Gamma SE+-20%	B.3.5 Cost and healthcare resource use identification, measurement and valuation

Hypokalaemia	£1,329.93		
HRQoL (per year)	Health state utility multipliers	**Measurement of uncertainty and distribution: standard error (distribution)**	**Reference to section in submission**
w/NC NC+NL NC CKD2 CKD3-4 ESRD Transplant first year Transplant subsequent years	**General population age-adjusted** **0.880** **0.907** **0.907** **0.822** **0.541** **0.736** **0.736**	Beta SE+-20%	B.3.5 Measurement and valuation of health effects
HRQoL	QALY decrement		
Transitory Events **Fracture** Failure to thrive **Osteomalacia/Rickets** GI event Hypokalaemia Loss of QoL in Acquired dRTA	 **0.023 (multiplier)** 0.130 0.352 0.001 0.050 0.180	Gamma SE+-20% **Beta (acquired dRTA only)** **SE 0.038%**	B.3.5 Measurement and valuation of health effects
Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease, GI, gastrointestinal			

2. Base-case deterministic results

Table 14: Base case deterministic results per person – list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
SoC	£164,218	18.18	10.62				
ADV7103	£357,605	24.52	19.42	£193,387	6.34	8.80	£21,969
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 15: Base case deterministic results per person – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
SoC	£164,218	18.18	10.62				
ADV7103	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 16: Base case disaggregated costs per person – list and PAS price

Per person costs	ADV7103	SoC	Incremental
Total cost			
List price	£357,605	£164,218	£193,387
PAS price	[redacted]	£164,218	[redacted]
Total Treatment costs			
List price	£274,643	£20,173	£254,470
PAS price	[redacted]	£20,173	[redacted]
Total Management costs	£82,962	£144,045	-£61,083
w/NC, NC, NC+NL costs	£47,083	£51,875	-£4,792
CKD costs	£19,469	£22,578	-£3,110
ESRD costs	£4,421	£22,999	-£18,578
Transplant costs	£971	£5,793	-£4,822
Musculoskeletal costs	£8,319	£25,593	-£17,274
Other costs (GI/hypokalaemia)	£2,699	£15,206	-£12,508

3. Sensitivity analysis

Probabilistic sensitivity analysis (1,000 iterations)

A probabilistic sensitivity analysis (PSA) was performed to explore the effect of uncertainty associated with all model inputs. PSA results for 1,000 iterations are presented in Table 17 (list price) and Table 18 (PAS price). The mean incremental costs and QALYs of ADV7103 compared with SoC were calculated to estimate the probabilistic ICER.

Table 17: Base case probabilistic results per person – list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
SoC							
ADV7103				£190,251		8.75	£21,744
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 18: Base case probabilistic results per person – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
SoC							
ADV7103				[redacted]		[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

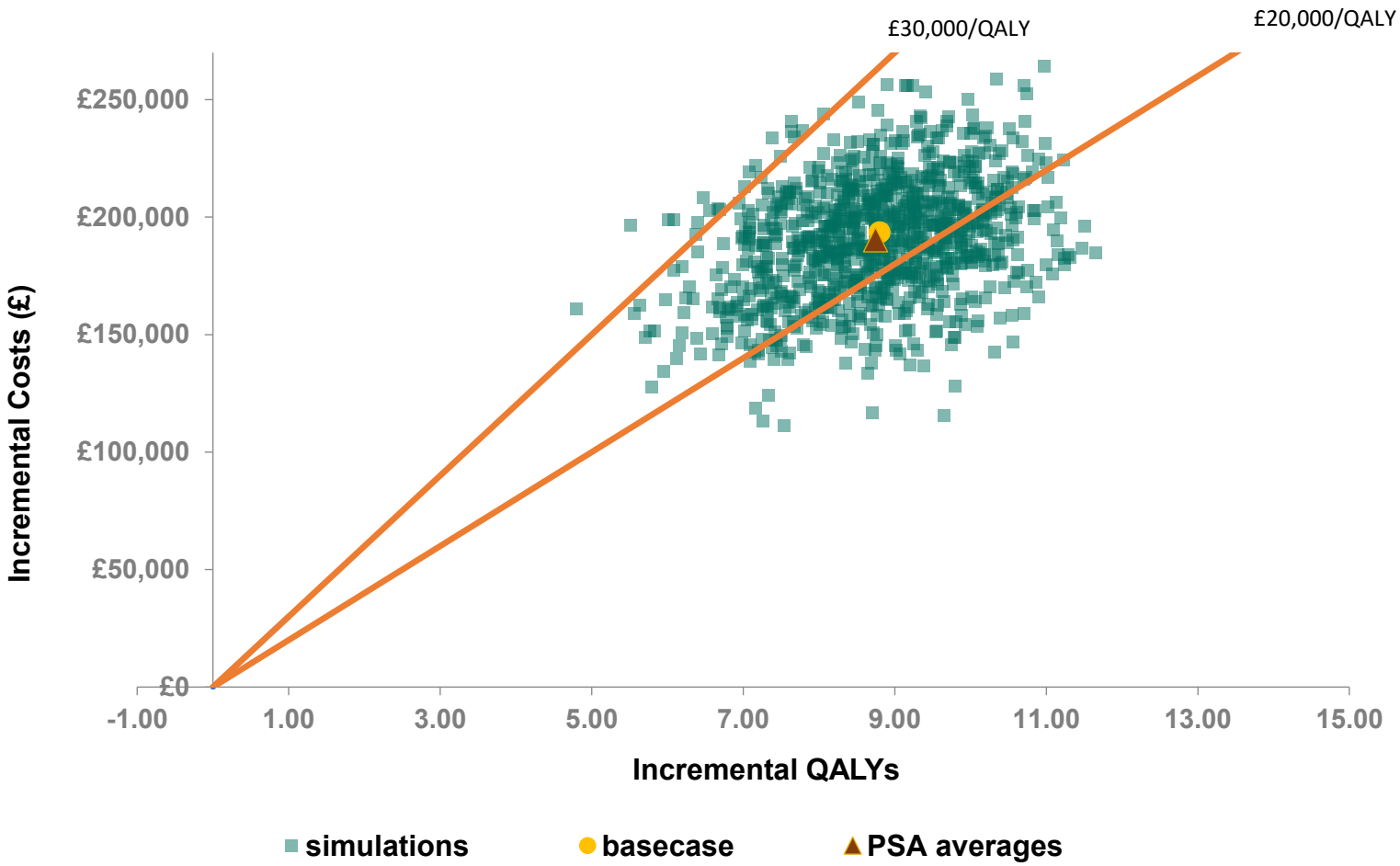


Figure 6: Cost-effectiveness plane from PSA - list price

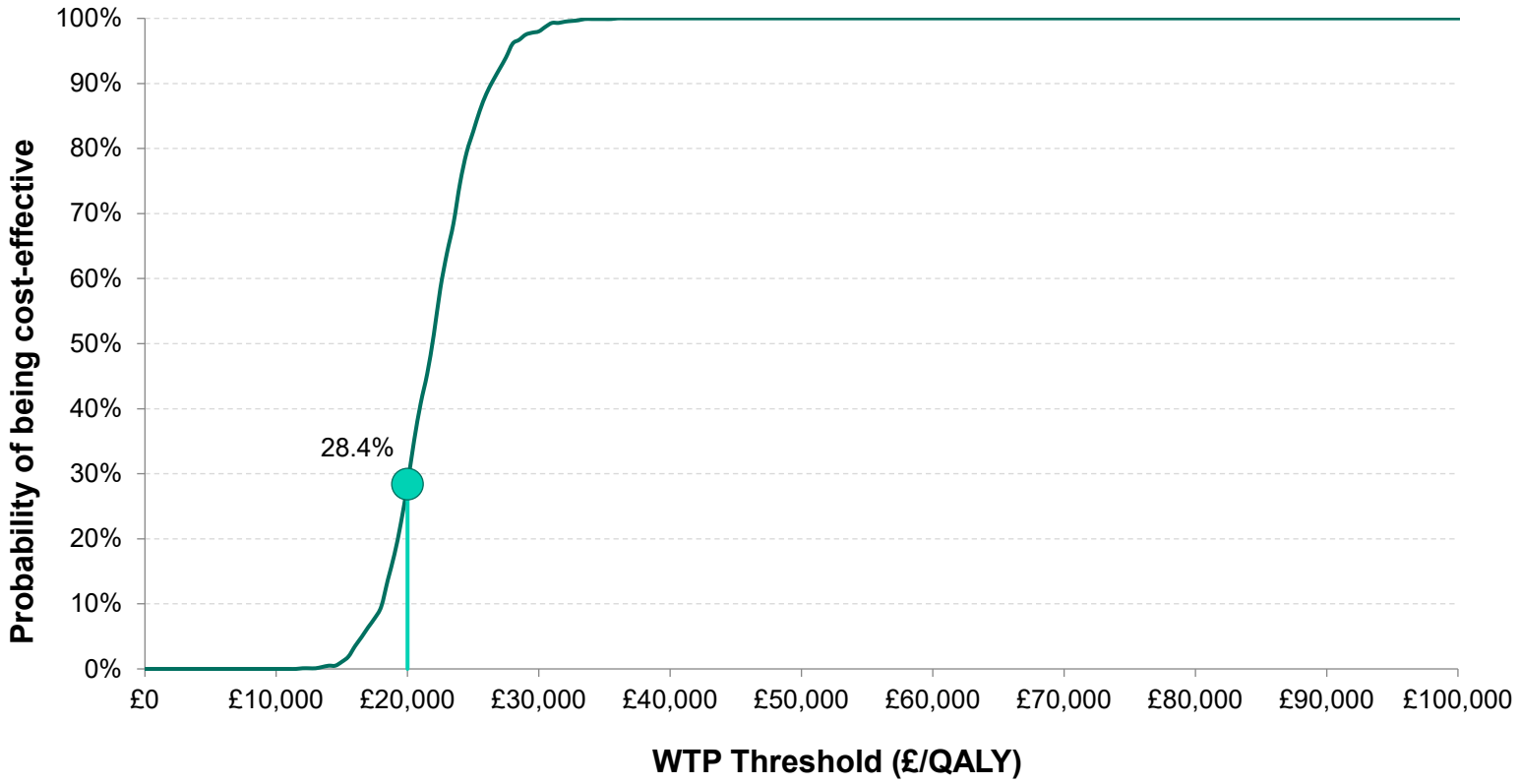


Figure 7: Cost-effectiveness acceptability curve from PSA (£20,000/QALY) - list price

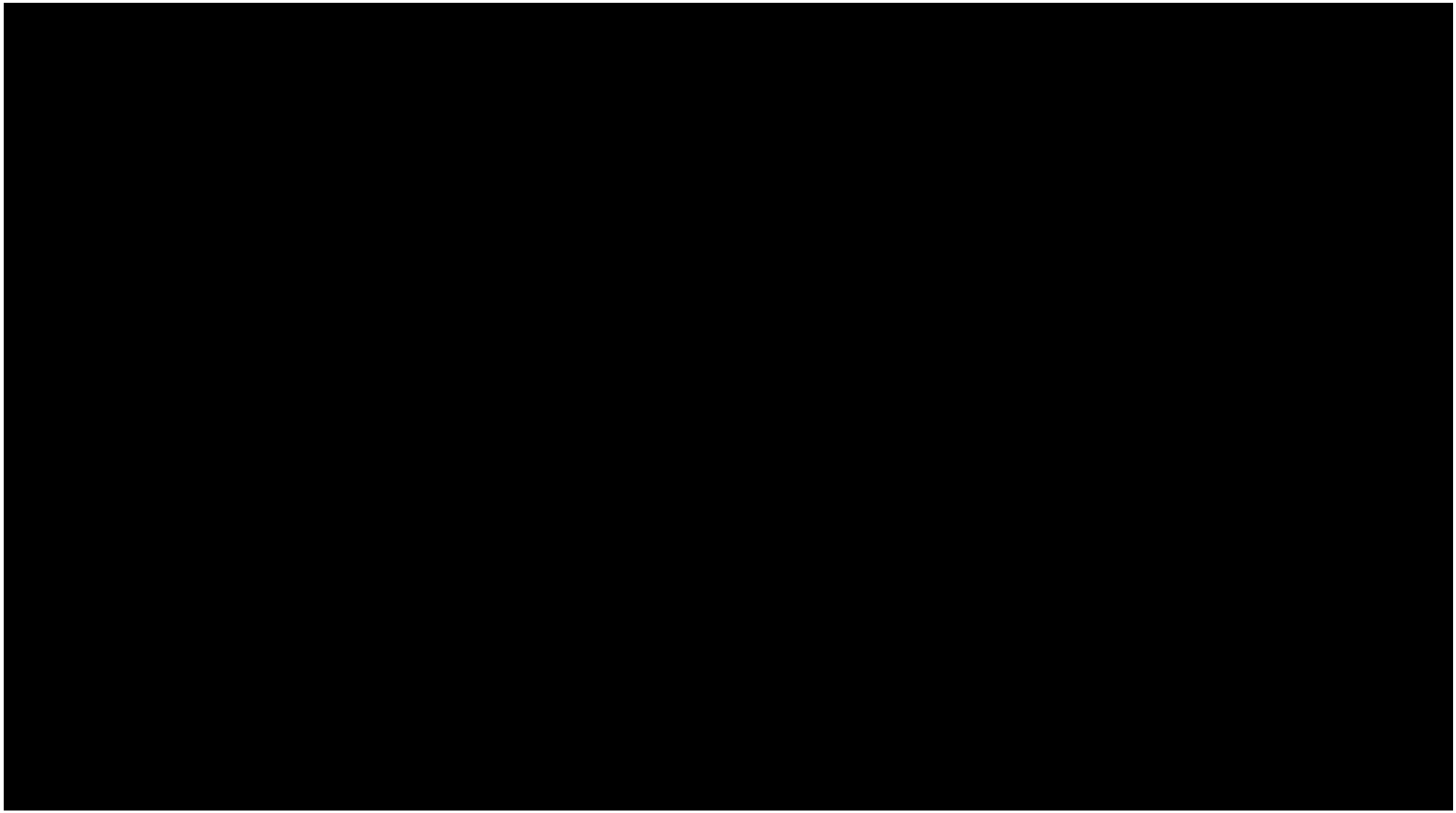


Figure 8: Cost-effectiveness plane from PSA (1,000 simulations) – PAS price

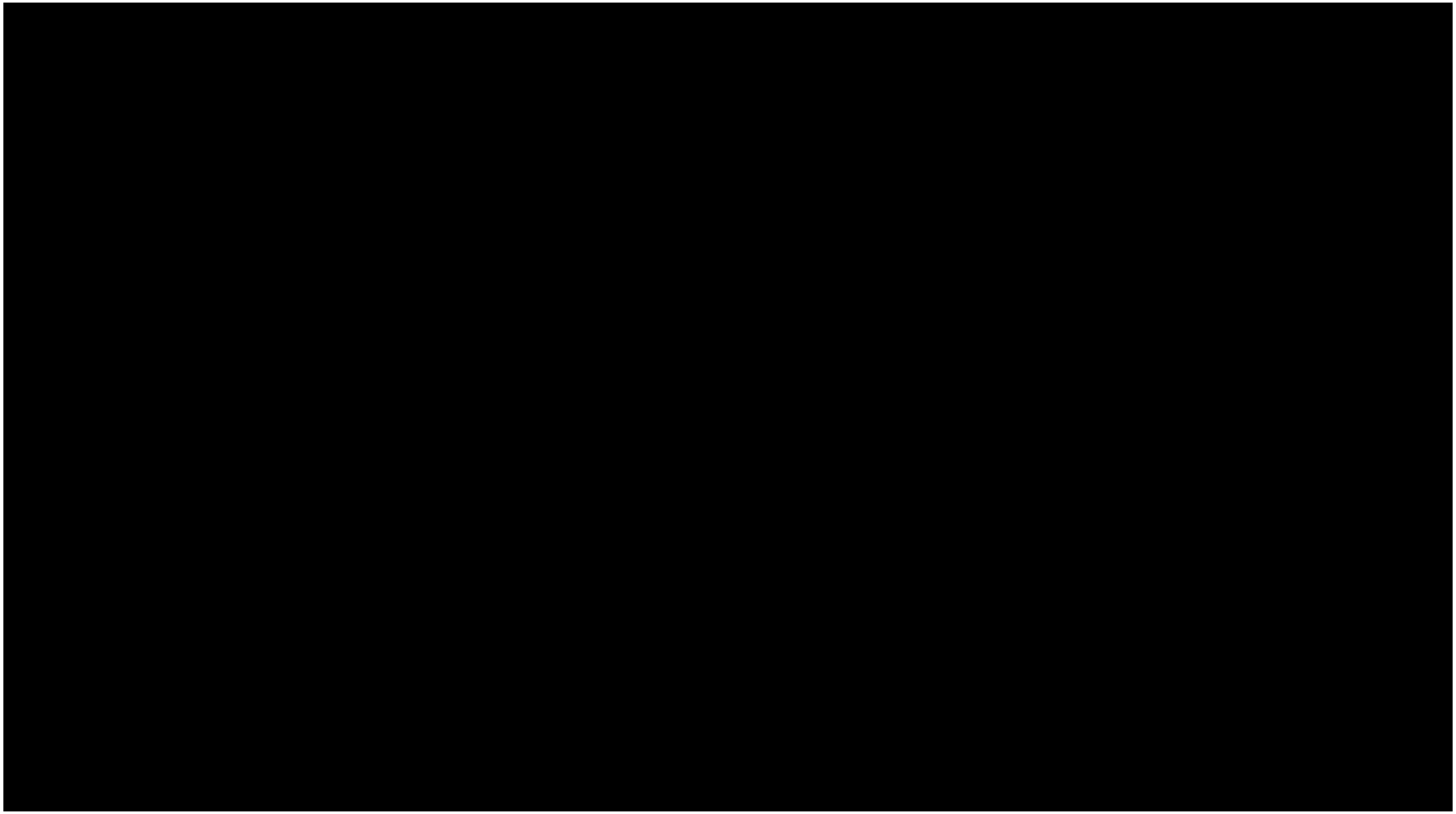


Figure 9: Cost-effectiveness acceptability curve from PSA (£20,000/QALY) – PAS price

Deterministic sensitivity analysis

Deterministic sensitivity analyses (DSA) were performed to explore the effect of uncertainty associated with varying individual model inputs. Inputs with an impact on the ICER >£1,000/QALY gained are presented in descending order as a tornado plot in Figure 10 (list price) and Figure 11 (PAS price).

- All efficacy related inputs were varied using upper and lower bound limits estimated from trial data.
- The lower bounds for the model time horizon were 40 years. A lifetime horizon (75 years) was adopted as basecase.
- The upper and lower bounds for the discount rate were 1.5% and 5%.
- The upper and lower bounds for the QALY decrement applied to patients with acquired dRTA were taken from literature (see answer to question B49).
- Mortality rates for CKD3-4 were varied using values for CKD3a (lower) and CKD4 (upper) from Gibertoni et al., 2021 (ERG suggested source)
- All other inputs were varied by 20%.

Please note, an error in the explanation of the DSA results was identified in the company's original submission. This has been amended for the updated results presented here.

<u>Explanation for DSA impact resulting in cross of £20,000/QALY or £30,000/QALY threshold</u>

1. A reduction in the discount rate of costs results in an increase of the ICER by £13,828/QALY at list price, and by £9,098/QALY at PAS price. An increase in the discount rate of costs results in a decrease of the ICER by £5,478/QALY at list price, and by £3,475/QALY at PAS price.

Following the increase in life years and longer duration spent without CKD, and in earlier stages of CKD for patients treated with ADV7103, by lowering the discount rate of costs, the incremental cost of treating patients with ADV7103 compared with SoC increases. At list price, the incremental increase in treatment costs for ADV7103 is £135,279 per patient compared with an incremental increase in treatment costs for SoC of £963 per patient.

By increasing the discount rate of costs, the opposite effect is observed. At list price, the incremental reduction in treatment costs for ADV7103 is £57,528 per patient compared with an incremental reduction in treatment costs for SoC of £650 per patient.

Only a reduction in the discount rate of costs results in an increase of the ICER beyond the £20,000/QALY threshold at PAS price.

2. An increase in the discount rate of outcomes results in an increase of the ICER by £8,865/QALY at list price, and by £4,983/QALY at PAS price. A reduction in the discount rate of outcomes results in a decrease of the ICER by £9,420/QALY at list price, and by [redacted]/QALY at PAS price.

Following an increase in the discount rate of outcomes, the value of an increase in life years and longer duration spent without CKD, and in earlier stages of CKD for patients treated with ADV7103 is reduced. The relative reduction in life years gained per person is 5.47 (22%) and QALYs gained per person is 4.24 (22%) for ADV7103 compared with a relative reduction in life years gained per person of 3.03 (17%) and QALYs gained per person of 1.71 (16%) for SoC.

By reducing the discount rate of outcomes, the opposite effect is observed. The relative increase in life years gained per person is 13.13 (54%) and QALYs gained per person is 10.10 (52%) for ADV7103 compared with a relative increase in life years gained per person of 6.23 (34%) and QALYs gained per person of 3.49 (33%) for SoC.

3. An increase in the average weight of adults (kg) results in an increase of the ICER by £4,742/QALY at list price, and by [redacted]//QALY at PAS price.

The intervention and comparator's costs are based on milliequivalent (mEq) as dosage is adjusted based on patient's weight. As ADV7103 has a higher unit cost per mEq than SoC, and as there is an increase in life years associated with treatment with ADV7103, as the average patient weight increases, so too does the incremental cost of treatment with ADV7103 compared with SoC. At list price, the incremental increase in treatment costs for ADV7103 is £44,485 per patient compared with an incremental increase in treatment costs for SoC of £2,772 per patient.

By decreasing the average weight of adults (kg), the opposite effect is observed. At list price, the incremental reduction in treatment costs for ADV7103 is £44,476 per patient compared with an incremental reduction in treatment costs for SoC of £2,772 per patient.

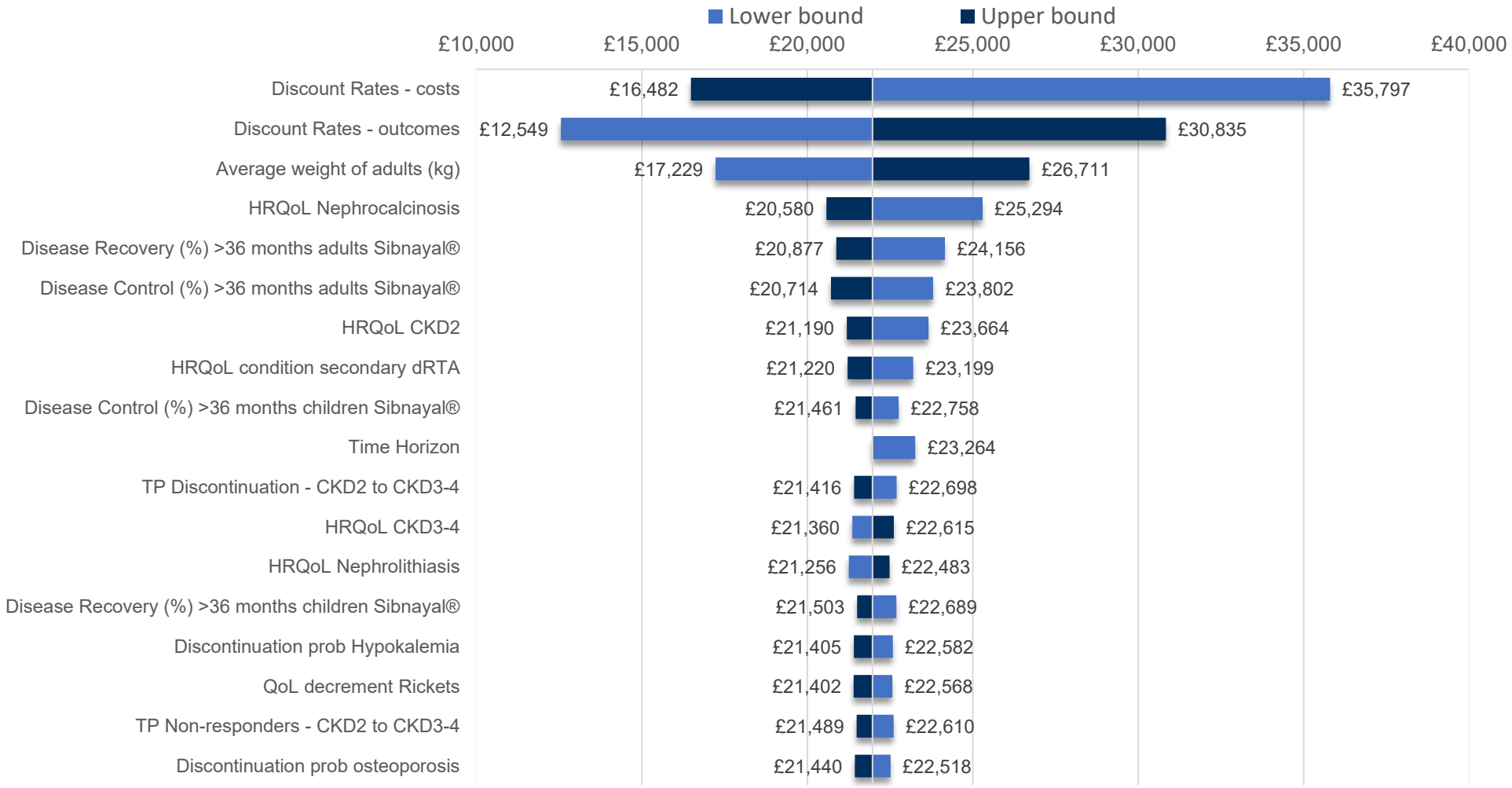


Figure 10: Tornado plot of DSA (change in ICER >£1,000/QALY) – list price

Figure 11: Tornado plot of DSA (change in ICER >£1,000/QALY) – PAS price

Scenario analysis

A range of scenario analyses were conducted to test the robustness of the model to alternative model inputs and assumptions. The details of the undertaken scenario analyses and the results of the scenario analyses, presented as the incremental costs, QALYs and ICERs of ADV7103 compared with SoC are shown in Table 19(list price) and Table 20(PAS price). The base case ICER has been presented for reference. All results for previous scenarios have been updated and six new scenarios have also been added in response to the clarification questions – these have been indicated in **orange text**.

At PAS price, the results show that the cost-effectiveness analysis is robust and ADV7103 consistently remained cost-effective with an ICER below £20,000/QALY.

Table 19: Summary of scenario analyses – list price

Scenario	**Base case value**		**Alternative inputs**		**ΔCosts (£)**	**ΔQALYs**	**ICER (£/QALY)**
Base case					£193,387	8.80	£21,969
1. B22CS ADV7103 alternative doses	Age	Dose (B21C)	Age	Dose (B22C)	£259,030	8.80	£29,429
	3	6.110	3	4.806			
	11	3.800	11	3.413			
	17	2.790	17	2.606			
	18	1.740	18	2.260			
2. Reduced discount rate for both costs and outcomes	Costs and Outcomes = 3.5%		Costs and Outcomes = 1.5%		£315,106	15.41	£20,448
3. Assume same proportion for initial disease control for both treatment arms ***relative efficacy changed to 100%**	ADV7103	SoC	ADV7103	SoC	£187,005	7.48	£24,986
	90.00%	43.00%	43.00%	43.00%			
	90.00%	43.00%	43.00%	43.00%			
4. Assume same discontinuation rate (non-responders) for both treatment arms	ADV7103	SoC	ADV7103	SoC	£90,199	4.85	£18,591
	0.00%	39.00%	39.00%	39.00%			
	3.30%	45.00%	45.00%	45.00%			

5. In ADV7103 arm, assume all discontinued patients receive no treatment	50% receive SoC treatment (ADV7103 arm)		0% receive SoC treatment (ADV7103 arm)		£192,347	8.74	£22,000
6. Assume same risk of transitory event in non-responder and discontinuation responder status	Non-responder	Disc.	Non-responder	Disc.	£190,626	6.73	£29,321
	9.39%	72.00%	9.39%	9.39%			
	12.91%	12.91%	12.91%	12.91%			
	10.00%	10.00%	10.00%	10.00%			
	0.17%	0.34%	0.17%	0.17%			
	9.62%	19.23%	9.62%	9.62%			
	59.09%	80.00%	59.09%	59.09%			
7. Assume lowest rate of efficacy (from all trial months) in treatment control and response for months 36 to 48 in the ADV7103 arm, and highest rate in SoC arm	**No longer relevant – 48-month data from trial used**						
Additional scenarios from clarification questions - (relevant question)							
8. Continuity correction for efficacy (B37)	Correction drop down selection on efficacy sheet. Applies to all efficacy values under the following subheadings: Disease Control Sibnayal, Disease Recovery Sibnayal, and Disease Control Average SoC				£194,025	8.76	£22,158
9. Assume that patients discontinue ADV7103 at 5, 10, and 20 years (B23)	Not applicable to original model		Discontinuation at: 5 years 10 years 20 years		£27,804 £62,433 £115,976	1.85 3.58 5.77	£15,028 £17,451 £20,083
10. Reduce treatment discontinuation rates for non-responders for SoC only (B24)	Children: 39.00% Adult: 45.00%		Children: 5.00% Adult: 20.00%		£167,018	7.54	£22,149
11. Use value from Palazzo et al. for annual event rate of hypokalaemia (B51)	9.39%		40.24%		£189,421	8.43	£22,477
12. Adjustment to scenario 1. - B22CS ADV7103 alternative doses in adult population only (B54)	Demographic split Age group 1-3 = 8.8% Age group 4-11 = 23.5% Age group 12-17 = 17.6% Age group 18+ = 50.0% *See Scen 1. for B21C dose values		Demographic split Age group 1-3 = 0% Age group 4-11 = 0% Age group 12-17 = 0% Age group 18+ = 100.0% *See Scen 1. for B22C dose values		£264,752	8.37	£31,632
13. Vary utility loss associated with Acquired dRTA patients (B49)	0.180		Lower = 0.09 Upper = 0.24		£193,387 £193,387	8.34 9.11	£23,199 £21,220

Table 20: Summary of scenario analyses – PAS price

Scenario	Base case value		Alternative inputs		ΔCosts (£)	ΔQALYs	ICER (£/QALY)
Base case					[redacted]	[redacted]	[redacted]
1. B22CS ADV7103 alternative doses	Age	Dose (B21C)	Age	Dose (B22C)	[redacted]	[redacted]	[redacted]
	3	6.110	3	4.806			
	11	3.800	11	3.413			
	17	2.790	17	2.606			
	18	1.740	18	2.260			
2. Reduced discount rate for both costs and outcomes	Costs and Outcomes = 3.5%		Costs and Outcomes = 1.5%		[redacted]	[redacted]	[redacted]
3. Assume same proportion for initial disease control for both treatment arms ***relative efficacy changed to 100%**	ADV7103	SoC	ADV7103	SoC	[redacted]	[redacted]	[redacted]
	90.00%	43.00%	43.00%	43.00%			
	90.00%	43.00%	43.00%	43.00%			
4. Assume same discontinuation rate (non-responders) for both treatment arms	ADV7103	SoC	ADV7103	SoC	[redacted]	[redacted]	[redacted]
	0.00%	39.00%	39.00%	39.00%			
	3.30%	45.00%	45.00%	45.00%			
5. In ADV7103 arm, assume all discontinued patients receive no treatment	50% receive SoC treatment (ADV7103 arm)		0% receive SoC treatment (ADV7103 arm)		[redacted]	[redacted]	[redacted]
6. Assume same risk of transitory event in non-responder and discontinuation responder status	Non-responder	Disc.	Non-responder	Disc.	[redacted]	[redacted]	[redacted]
	9.39%	72.00%	9.39%	9.39%			
	12.91%	12.91%	12.91%	12.91%			
	10.00%	10.00%	10.00%	10.00%			
	0.17%	0.34%	0.17%	0.17%			
	9.62%	19.23%	9.62%	9.62%			
	59.09%	80.00%	59.09%	59.09%			
7. Assume lowest rate of efficacy (from all trial months) in treatment control and response for months 36 to 48 in the ADV7103 arm, and highest rate in SoC arm	**No longer relevant – 48-month data from trial used**						
Additional scenarios from clarification questions - (relevant question)							

8. Continuity correction for efficacy (B37)	Correction drop down selection on efficacy sheet. Applies to all efficacy values under the following subheadings: Disease Control Sibnayal, Disease Recovery Sibnayal, and Disease Control Average SoC		[redacted]	[redacted]	[redacted]
9. Assume that patients discontinue ADV7103 at 5, 10, and 20 years (B23)	Not applicable to original model	Discontinuation at: 5 years 10 years 20 years	[redacted]	[redacted]	[redacted]
10. Reduce treatment discontinuation rates for non-responders for SoC only (B24)	Children: 39.00% Adult: 45.00%	Children: 5.00% Adult: 20.00%	[redacted]	[redacted]	[redacted]
11. Use value from Palazzo et al. for annual event rate of hypokalaemia (B51)	9.39%	40.24%	[redacted]	[redacted]	[redacted]
12. Adjustment to scenario 1. - B22CS ADV7103 alternative doses in adult population only (B54)	Demographic split Age group 1-3 = 8.8% Age group 4-11 = 23.5% Age group 12-17 = 17.6% Age group 18+ = 50.0% *See Scen 1. for B21C dose values	Demographic split Age group 1-3 = 0% Age group 4-11 = 0% Age group 12-17 = 0% Age group 18+ = 100.0% *See Scen 1. for B22C dose values	[redacted]	[redacted]	[redacted]
13. Vary utility loss associated with Acquired dRTA patients (B49)	0.180	Lower = 0.09 Upper = 0.24	[redacted]	[redacted]	[redacted]

4. Subgroup analysis

Subgroup analysis for specific age groups was conducted in the updated model following clarification. To do this, the proportion of all age groups not of interest were set to 0% on the 'Settings' sheet of the model. The results of the subgroup analyses, presented as the total and incremental costs, QALYs and ICERs of ADV7103 compared with SoC are shown in Table 21(list price) and Table 22(PAS price). The base case ICER has been provided for reference.

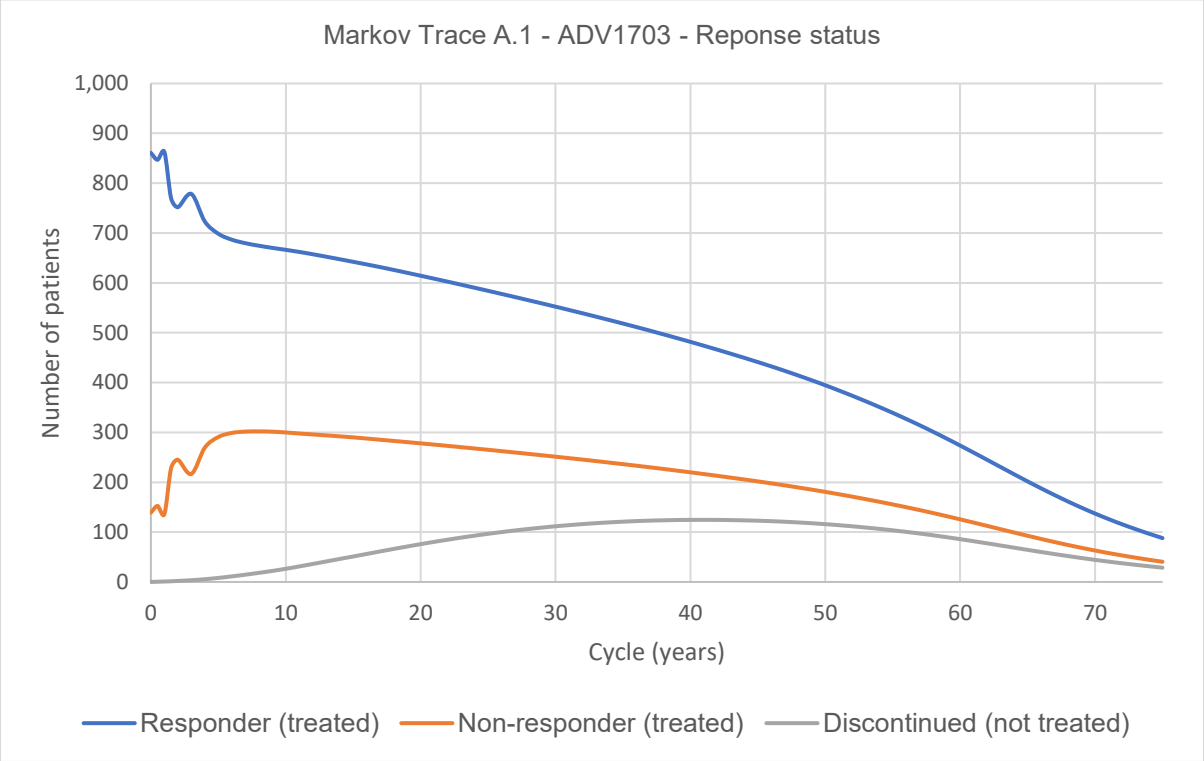
Table 21: Subgroup analysis - list price

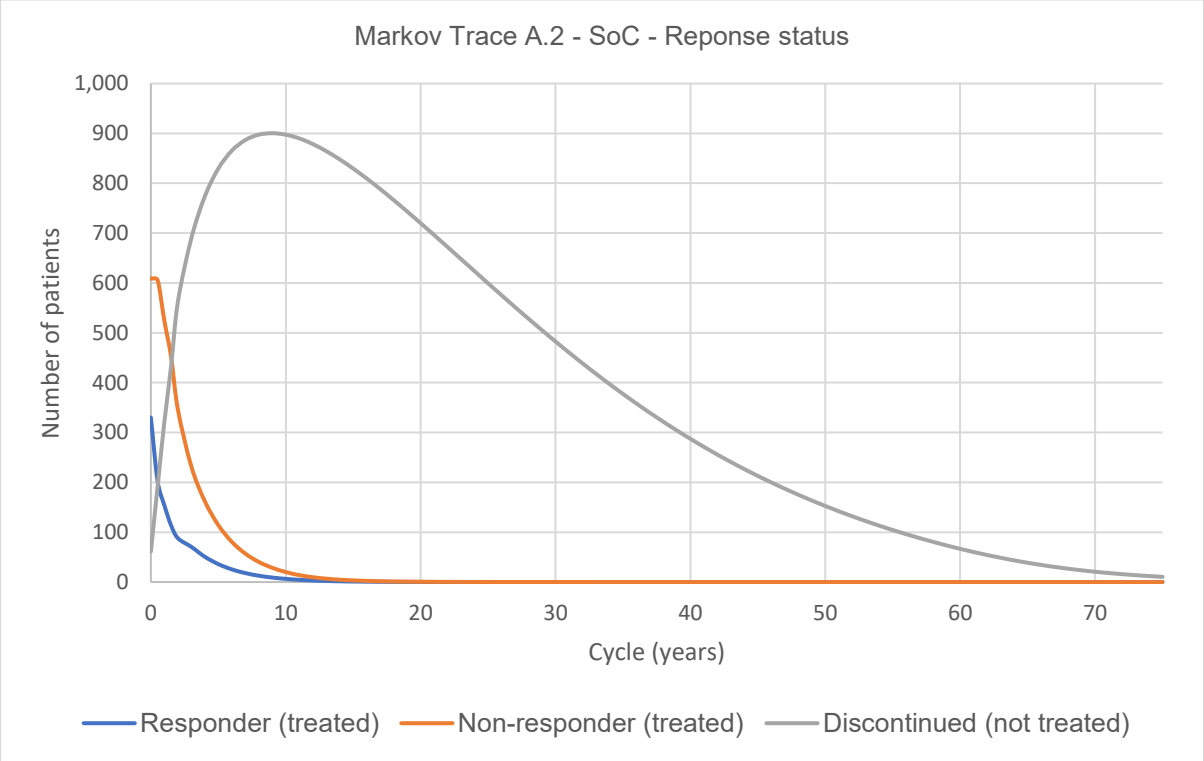
Technologies	Total Costs (£)	Total QALYs	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
Base case					
SoC	**£164,218**	**10.62**			
ADV7103	£357,605	19.42	£193,387	£8.80	£21,969
Age group 1-3					
SoC	£205,410	8.95			
ADV7103	£386,441	20.20	£181,031	11.25	£16,098
Age group 4-11					
SoC	£187,695	10.70			
ADV7103	£394,277	20.52	£206,582	9.82	£21,037
Age group 12-17					
SoC	£155,493	13.32			
ADV7103	£361,392	20.77	£205,899	7.45	£27,639
Age group 18+					
SoC	£148,980	9.92			
ADV7103	£333,922	18.29	£184,942	8.37	£22,095

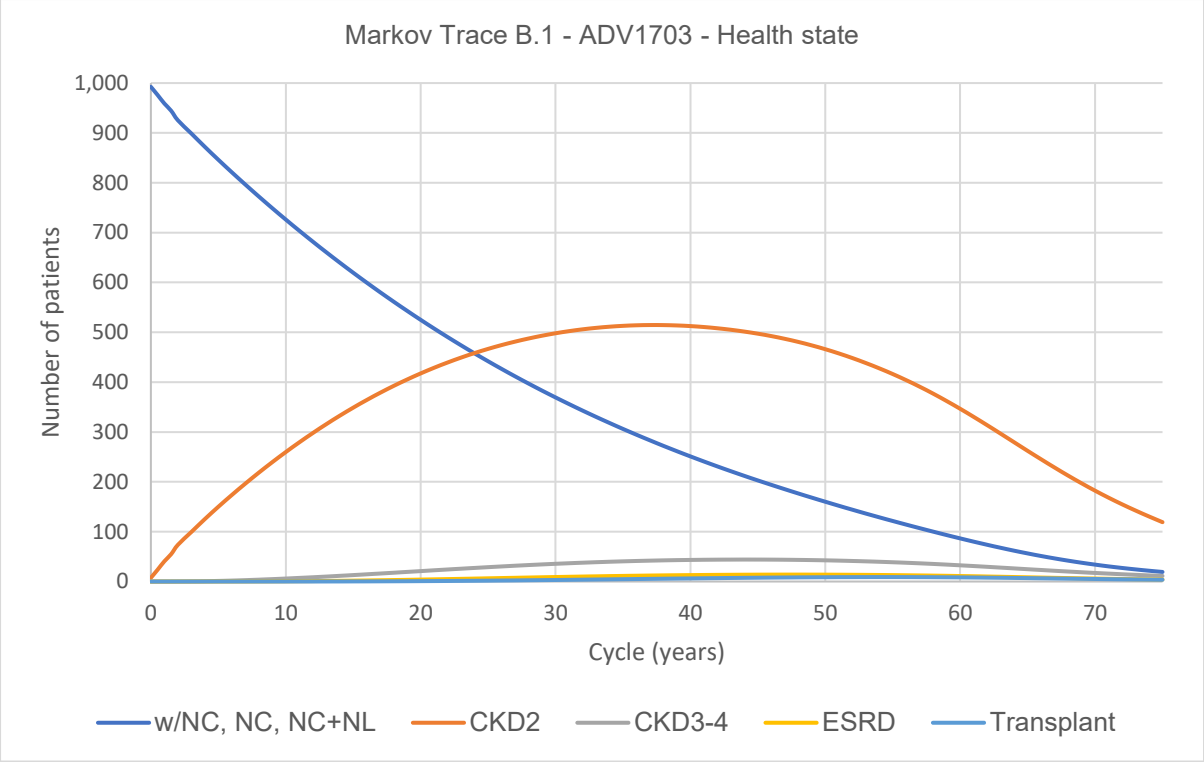
Table 22: Subgroup analysis - PAS price

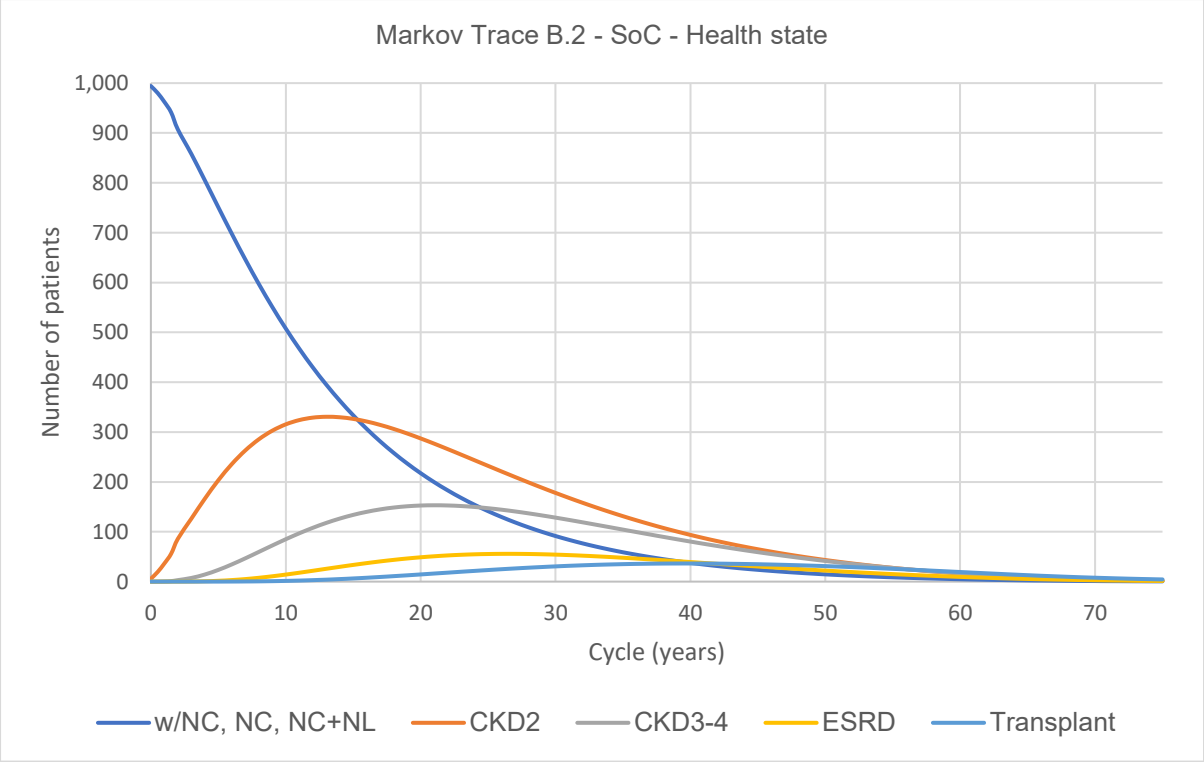
Technologies	Total Costs (£)	Total QALYs	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
Base case					
SoC	£164,218	10.62			
ADV7103	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age group 1-3					
SoC	£205,410	8.95			
ADV7103	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age group 4-11					
SoC	£187,695	10.70			
ADV7103	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age group 12-17					
SoC	£155,493	13.32			
ADV7103	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age group 18+					
SoC	£148,980	9.92			
ADV7103	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5. Updated Markov traces






Markov Trace B.1 - ADV1703 - Health state
Number of patients
1,000
900
800
700
600
500
400
300
200
100
0
0
10
20
30
40
50
60
70
Cycle (years)
w/NC, NC, NC+NL
CKD2
CKD3-4
ESRD
Transplant


Markov Trace B.2 - SoC - Health state
Number of patients
1,000
900
800
700
600
500
400
300
200
100
0
0
10
20
30
40
50
60
70
Cycle (years)
w/NC, NC, NC+NL
CKD2
CKD3-4
ESRD
Transplant

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15 July 2021

Re: Budget Impact Test non-submission

NHS England and NHS Improvement is writing to you to advise that as per the below BIT the budget impact is not expected to be significant.

ID3787 - slow-release potassium bicarbonate and potassium citrate for treating distal renal tubular acidosis

Therefore, please accept this letter as a non-submission.

Regards

Mohsin Ashraf
Commercial development support Pharmacist
Medicines Value Team
Commercial Medicines Directorate
NHS England and NHS Improvement

Confidential until published

Slow-release potassium bicarbonate and potassium citrate for treating distal renal tubular acidosis [ID3787]. A Single Technology Appraisal

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
	Emma Simpson, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK
	Geoff Holmes, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK
	Andrew Rawdin, Research Assistant, ScHARR, University of Sheffield, Sheffield, UK
	Ruth Wong, Information Specialist, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
Date completed	Date completed (08/03/2022)

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Declared competing interests of the authors:

None of the authors has any conflicts of interest to declare.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Slow-release potassium bicarbonate and potassium citrate for treating distal renal tubular acidosis [ID3787]. A Single Technology Appraisal. Stevenson M, Simpson E, Holmes G, Rawdin A and Wong R. School of Health and Related Research (ScHARR), 2022.

Contributions of authors

Andrew Rawdin and Matt Stevenson critiqued the health economic analysis submitted by the company. Emma Simpson summarised and critiqued the clinical effectiveness data reported within the company's submission. Geoff Holmes and Matt Stevenson critiqued the statistical aspects of the submission. Ruth Wong critiqued the company's search strategy. All authors were involved in drafting and commenting on the final report.

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Abbreviations

AEs	Adverse events
CEAC	Cost-Effectiveness Acceptability Curve
CKD	Chronic Kidney Disease
CS	Company Submission
CSR	Clinical Study Report
dRTA	Distal renal tubular acidosis
DSA	Deterministic Sensitivity Analyses
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EQ-5D	EuroQol 5 Dimensions
ERG	Evidence Review Group
ESKD	End-Stage Kidney Disease
ESRD	End-Stage Renal Disease
HRQoL	Health-Related Quality of Life
ICER	Incremental Cost Effectiveness Ratio
ITT	Intention To Treat
mEq	milliequivalent
mmol/L	Millimoles per Litre
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PAS	Patient Access Scheme
PP	Per Protocol
PSA	Probabilistic Sensitivity Analyses
PSS	Personal Social Services
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event(s)
SD	Standard Deviation
SLR	Systematic Literature Review
SmPC	Summary of Product Characteristics
SoC	Standard of care
SP	Study Period
SPI	Study Period 1
SPII	Study Period 2
SPIII	Study Period 3

STA	Single Technology Appraisal
UCa	Urine Calcium
UCi	Urine Citrate
UCr	Urine Creatine
VAS	Visual Analogue Scale
ypN	Post-surgical lymph node staging following Preoperative radiotherapy or chemotherapy

1. Executive summary

1.1 Overview of the ERG's key issues

The overarching ERG concern is that it does not have confidence that either the company's or the ERG's incremental cost effectiveness ratio (ICER) is robust. This is primarily due to: (i) the limited evidence related to the comparative efficacy of ADV7103 compared to standard of care (SoC); (ii) limitations in the conceptualisation and functionality of the model; (iii) the lack of targeted reviews to populate the model and the reliance on clinical opinion; (iv) inappropriate population of the model from the sources cited by the company; and (v) implementation issues within the model. These issues are listed in Table 1. The five broad issues comprise of many individual issues which are summarised, along with the location of the discussion within the ERG report in Section 1.5.

Table 1: Overview of the ERG's key issues

Issue Number	Description of Issue
1	Limited evidence related to the comparative efficacy of ADV7103 compared to SOC
2	Limitations in the conceptualisation and functionality of the model
3	Lack of targeted reviews to populate the model and the reliance on clinical opinion
4	Inappropriate population of the model from the sources cited by the company
5	Implementation issues within the model

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life, using QALYs.

ADV7103 is modelled to increase QALYs by increasing the proportion of patients with controlled disease which results in increased life expectancy and an increased average quality of life as complications associated with dRTA are delayed or do not happen.

ADV7103 is modelled to increase costs compared with SoC primarily due to the increased duration of treatment and the increased acquisition costs of ADV7103 compared with SoC. ADV7103 has an agreed patient access scheme (PAS) which is a simple discount of [redacted].

1.3 The decision problem: summary of the ERG's key issues

The company's submission (CS) includes an economic evaluation of ADV7103 compared to SoC for patients aged 1 year or over with distal renal tubular acidosis (dRTA). There is no one issue that is

believed to have a large (greater than [redacted]) impact on the ICER and in the ERG's exploratory analyses similar numbers increase the ICER, as decrease it. In combination, the impact on the company's base case ICER is substantial, increasing it to [redacted] in the ERG's indicative deterministic base case. However, the ERG cautions against accepting the ICERs in the company's base case or the ERG's indicative base case as there were a number of limitations in both that increase uncertainty. These are related to: the small number of patients included in BC21S and B22CS; the limited comparative efficacy data of ADV7103; the reliance on clinical opinion for numerous model parameters; the lack of a literature search or clear justification as to why the chosen sources were selected; insufficient details relating to how transition probabilities were calculated from the literature; multiple limitations that could not be addressed by the ERG within the timescales of the project; and some parameter values being set to zero in the ERG's indicative base case when the company's values were deemed implausible. A key advantage of ADV7103 treatment compared to SoC is the more convenient treatment regimen, which was not explicitly incorporated within the company's model which suggests that the ICER may be unfavourable to ADV7103.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The key evidence for clinical effectiveness within the CS comprised two open-label studies of ADV7103 in dRTA patients: B21CS; and B22CS. The ERG does not believe that any relevant published studies that could have provided effectiveness data of ADV7103 in dRTA have been missed or omitted from the CS. No randomised controlled trials were identified. Study B21CS (n=37) was a sequential study, which compared each patient on five days of the patient's prior SoC with five days on optimal dose of ADV7103. Study B22CS (n=30) was a single arm extension of B21CS where all patients received ADV7103.

B21CS primary outcome was bicarbonataemia, a surrogate outcome for long term complications of dRTA. In the per protocol set, mean (standard deviation (SD)) blood bicarbonate levels were 21.7 (3.06) mmol/L with SoC (n=29) and 23.1 (1.62) mmol/L with ADV7103 (n=30). Non-inferiority of ADV7103 versus SoC was demonstrated, mean difference (SD) 1.4195 (2.647), $p<0.0001$. There was a significant difference between SoC and ADV7103 treatment periods in both the per protocol (p=0.0037) and ITT sets (p=0.0008) when assessing the superiority of ADV7103. Within months 3 to 48 of B22CS, the percentage of patients with blood bicarbonate levels in the normal range was between 60.9% and 92.3%.

During the five days of treatment in B21CS, compliance was high for both SoC (91.9%) and ADV7103 (96.9%). During B22CS, compliance to ADV7103 was reported as ≥75 % being 93.3% (28/30) at month three, and 79.3% (23/29) at month 24.

For B21CS, there were similar adverse event rates SoC (7/37, 18.9%) and ADV7103 (6/32, 18.8%) and types. After 48 months of the B22CS study, AEs were experienced by 27/30 (90.0%) patients taking

ADV7103. The most frequently experienced types of AEs were: metabolism and nutrition disorders 60.0% and gastrointestinal disorders 53.3%. Most AEs were of mild, or moderate, intensity.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

Issue 1. Limited evidence related to the comparative efficacy of ADV7103 compared to SOC

Report section	Sections 3.2 and 4.3.3.2.16
Description of issue and why the ERG has identified it as important	There is little long-term comparative efficacy data for ADV7103. The B21CS study used patients as their self-control, but had a short duration (a maximum of 5 days of optimised treatment) and Study B22CS was single-armed. Both studies involved less than 40 patients.
What alternative approach has the ERG suggested?	None
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Larger studies that generated comparative efficacy data would help reduce uncertainty.

Issue 2. Limitations in the conceptualisation and functionality of the model

Report section	Section 4.3.3.1.1
Description of issue and why the ERG has identified it as important	This issue covers a multitude of sub-issues. Full details are provided in Section 4.3.3.1.1 with only headers provided here: • Patients responding to treatment cannot progress beyond CKD2 • Patients not-responding, but on treatment, cannot progress to end-stage kidney disease • Patients discontinuing treatment will never restart treatment • Patients who lose disease control or regain disease control remain in the same health state • No chronic utility gain associated with the more convenient dosing regimen of ADV7103 compared to SoC • Conditions that are chronic in nature have been modelled as transitory health states • Patients start the model in different health states dependent on initial treatment • The assumption that the QALY loss associated with those with acquired dRTA is not incurred when patients have controlled disease
What alternative approach has the ERG suggested?	The ERG could not undertake exploratory analyses to address the first six bullet points. Exploratory analyses have been undertaken to assess the impact of alternative approaches on the ICER for the bottom two bullet points. The first adds 5 days of ADV7103 costs to the intervention arm to approximate the costs associated with starting people in different health states. The second removes the additional QALY losses associated with acquired dRTA.
What is the expected effect on the cost-effectiveness estimates?	The impact of amending the model to address the first six bullets is unknown. The first of the two changes made by the ERG had little impact on the ICER, although removing the QALY losses associated with acquired dRTA increased the ICER for the weighted population by approximately [redacted]
What additional evidence	The model structure would need to be amended to facilitate the

or analyses might help to resolve this key issue?	exploration of the first eight bullet points, and a literature search conducted to find appropriate parameter estimates. A literature search would be required to inform the parameter estimate for the QALY losses of acquired dRTA and how this is modified by the level of a patient's disease control.

Issue 3. Lack of targeted reviews to populate the model and the reliance on clinical opinion

Report section	Section 4.3.3.2.1
Description of issue and why the ERG has identified it as important	It appears that there were no formal targeted reviews of the literature. There was additionally a considerable reliance on expert opinion for parameter values.
What alternative approach has the ERG suggested?	None
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Formal targeted literature reviews would allow a better characterisation of available evidence and potentially reduce the reliance on expert clinical judgement.

Issue 4. Inappropriate population of the model from the sources cited by the company

Report section	Section 4.3.3.2
Description of issue and why the ERG has identified it as important	This issue covers a multitude of sub-issues. Full details are provided in Section 4.3.3.1.2 with only headers provided here: • Inappropriate utilities used for the general population • Inappropriate calculations of utility multipliers related to health states • Potentially inappropriate QALY losses associated with transitory health states • The assumption that all patients with nephrolithiasis would have 1 percutaneous nephrolithotomy each year • Estimation of risk of death associated with fracture or with hypokalaemia • Estimation of the proportions of patients with disease control at the start of the model • The assumed dosages for ADV7103 • Assumption of equal disease control for patients regardless of age • Uncertainty in the proportion of patients with acquired dRTA • Applying a continuity correction due to small numbers of observed events
What alternative approach has the ERG suggested?	The ERG has used alternative approaches to assess the impact of changing the assumptions for all of the bullet points except the final three. The methods used are detailed in Section 4.2.2. The last three bullet points have been left as an additional source of uncertainty with no additional analyses provided by the ERG.
What is the expected effect on the cost-effectiveness estimates?	Two exploratory analyses were shown to noticeably increase the weighted population ICER: using the assumed dosage from Study B22CS rather than Study B21CS; and setting the QALY losses associated with transitory states to zero. One analysis noticeably reduced the ICER, which was assuming there was no death associated with fractures or hypokalaemia.
What additional evidence or analyses might help to resolve this key issue?	A formal targeted review would reduce the uncertainty associated with some of the issues raised.

Issue 5. Implementation issues within the model

Report section	Section 4.3.3.2
Description of issue and why the ERG has identified it as important	This issue covers a multitude of sub-issues. Full details are provided in Section 4.3.3.1.2 with only headers provided here: • Incorrect calculation of costs of fracture, failure to thrive and osteomalacia/rickets in the first four cycles of the model • Incorrect calculation of QALY losses associated with acquired dRTA • Incorrect calculation of the midpoint age for those in the children age group • Incorrect calculation of the costs for modified Shohl's solution in combination with sodium bicarbonate • Data entry/calculation error related to the percentage of people who regain disease control under SoC in the first four cycles • Apparent error in calculating the probability of moving from without nephrocalcinosis to nephrocalcinosis for patients who have discontinued treatment
What alternative approach has the ERG suggested?	The ERG has corrected what it believes are errors within the company's model.
What is the expected effect on the cost-effectiveness estimates?	The change in the ICER for each correction was less than [redacted]. Four of the changes decreased the ICER, with the remainder (related to the QALY losses associated with acquired dRTA) increasing the ICER.
What additional evidence or analyses might help to resolve this key issue?	Confirmation (or not) from the company that the errors identified by the ERG are actually errors.

1.6 Summary of ERG's preferred assumptions and resulting ICER

The individual components of the ERG's deterministic indicative base case ICER for a weighted population are shown in Table 2, together with all of these changes applied simultaneously. Only incremental costs and QALYs, together with the ICER are presented, with absolute values provided in Table 44. Results were also observed to differ in an adult population compared with a non-adult population with deterministic indicative ICERs of [redacted] and

[redacted] respectively. These subgroups may be of relevance if the committee deems that the adult patients have acquired dRTA whereas the non-adult patients have inherited dRTA.

Given the reasons detailed in Section 1.3, the ERG believes that its indicative ICER is likely to be unfavourable to ADV7103, although the extent of this possible bias is unknown. The model has a large number of limitations, and therefore the ERG has provided some bullet points that the Appraisal Committee may find informative:

- ADV7103 is licensed for the treatment of dRTA, whereas the components of SoC are not,
- ADV7103 has a much more convenient dosing regimen than SoC, than has not been formally captured in the estimates of QALYs.
- that the price premium for ADV7103 compared with SoC in terms of mEq is [redacted]%.

The ERG has been informed by NICE that there is are Commercial Medicines Unit prices for Shohl's solution, potassium bicarbonate and sodium bicarbonate which are used within SoC. Results incorporating these reduced prices are contained in a confidential appendix.

Table 2: Summary of ERG exploratory analyses and deterministic indicative ICER for ADV7103 compared to SoC

Exploratory analysis	Incremental QALYs	Incremental cost	ICER
Company's updated base case	[redacted]	[redacted]	[redacted]
EA1: Adding an additional 5 days of costs of ADV7103 to the ADV7103 arm	[redacted]	[redacted]	[redacted]
EA2: Setting the costs of the nephrocalcinosis and nephrolithiasis health state to that of nephrocalcinosis health state	[redacted]	[redacted]	[redacted]
EA3: Assuming that the QALY losses associated with acquired dRTA are set to zero	[redacted]	[redacted]	[redacted]
EA4: Using the general population utility for the full population and using alternative health state utility multipliers	[redacted]	[redacted]	[redacted]
EA5: Exploring the use of alternative QALY losses associated with transitory health states	[redacted]	[redacted]	[redacted]
EA6: Correcting errors relating to the costs of fracture, faltering growth, and osteomalacia/rickets in the first four six-month cycles	[redacted]	[redacted]	[redacted]
EA7: Correcting errors relating to the QALY losses associated with acquired dRTA in the first four six-month cycles	[redacted]	[redacted]	[redacted]
EA8: Correcting the midpoint age for those in the children age group	[redacted]	[redacted]	[redacted]
EA9: Correcting the cost of modified	[redacted]	[redacted]	[redacted]

Shohl's solution in combination with sodium bicarbonate			
EA10: Correcting the probability of percentage of people receiving SoC who regain disease control in the first four six-month cycles	[redacted]	[redacted]	[redacted]
EA11: Amending the formulae related to the probability of moving from the without nephrocalcinosis health state to the with nephrocalcinosis health state for patients not on treatment	[redacted]	[redacted]	[redacted]
EA12: Removing the risk of death for both fracture and hypokalaemia	[redacted]	[redacted]	[redacted]
EA13: Changing the proportions with disease control at the start of the model	[redacted]	[redacted]	[redacted]
EA14: Changing the assumed dose of ADV7103	[redacted]	[redacted]	[redacted]
ERG's preferred analysis (combining EA 1-14)*	[redacted]	[redacted]	[redacted]

EA – exploratory analysis; ICER - incremental cost-effectiveness ratio; QALY - quality-adjusted life year
** The probabilistic value was £30,584*

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The company provided an acceptable description of distal Renal Tubular Acidosis (dRTA) which is a rare disease characterised by a renal defect in hydrogen ion secretion. Other characterisations of dRTA include: hyperchloremic metabolic acidosis; inability to acidify urine pH less than 5.5; hypokalaemia (a deficiency of potassium in the bloodstream); nephrocalcinosis (where there is excess calcium deposited within the kidney tissues) and nephrolithiasis (kidney stones); skeletal abnormalities; and (inherited form) sensorineural hearing loss.[1] Patients with metabolic acidosis have blood pH levels below 7.35 with a bicarbonate blood concentration of less than 22mmol.[2] dRTA can be either hereditary, or acquired. Table 8 of the company's submission (CS) provides further details on which causes are hereditary and which are acquired, with this latter category broken down into those associated with systemic disease, those associated with nephrocalcinosis, and those associated with drugs. Most children with dRTA have the heredity form (and all survive to adulthood).

The company reports that: the prevalence of dRTA in England in 2017, estimated using Clinical Practice Research Datalink data, is between 0.46 and 1.60 per 10,000 people; 22% of confirmed cases were defined as hereditary; and the mean age of diagnosis was 46 years.[3] This prevalence estimate would equate to between 2760 and 9600 patients with dRTA in a population of 60 million.

For infants with inherited dRTA, symptoms include vomiting, diarrhoea, constipation and impaired growth/weight gain. Hospitalisation can be required for severe cases of dehydration, tachypnoea, loss of appetite, polydipsia and obtundation.[2, 4] Palazzo *et al*. report that common clinical consequences of dRTA in children include growth failure, sensorineural hearing loss, vomiting, obtundation, nephrolithiasis, and rickets.[5] Data from a retrospective study by Lopez-Garcia *et al.* reported that over one-third of children with dRTA had impaired estimated glomerular filtration rate (eGFR) rates.[6]

In adults, common clinical symptoms reported by Palazzo *et al.* include vomiting, diarrhoea, constipation, loss of appetite, muscle weakness, paralysis, nephrocalcinosis, nephrolithiasis, osteomalacia, polydipsia, polyuria, and rickets.[5] The company cites a recent comparison of chronic kidney disease (CKD) stages between people with dRTA versus those without showed a much larger proportion of patients at CKD stage 2 and above using National Health and Nutrition Survey III data (reference not supplied in the CS).

The company reports that life expectancy in UK patients with dRTA has been estimated to be 72 years, which is considerably shorter than general population values, although the ERG comments that the abstract[3] referenced in the CS does not mention mortality.

2.2 Critique of company's overview of current service provision

Table 10 of the CS, which is reproduced in Table 3, reports a summary of the BMJ best practice diagnostic path for patients with dRTA.[7, 8] Clinical advice to the ERG suggests that Patients with dRTA are almost invariably hypokalaemic rather than hyperkalaemic and require alkali therapy. Table 11 of the CS, which is reproduced in Table 4, reports a summary of the BMJ best practice for the recommended surveillance of individuals following diagnosis of dRTA. The clinical pathway of care for children with dRTA provided by the company is reproduced in Figure 1, with the pathway for adults provided in Figure 2.

Table 3: BMJ best practice diagnostic path for patients with dRTA (reproduced from Table 13 of the CS)

Laboratory evaluation	Determination of arterial pH, PCO_2 and bicarbonate. Plus, serum bicarbonate, chloride, sodium and potassium together with serum anion gap. In hyperkalaemia measurement of serum aldosterone is also taken to differentiate between aldosterone deficiency from aldosterone resistance
	Urine pH measured by pH electrode or blood gas analyses
	If diagnosis is uncertain or in which distal RTA is incomplete, physiological tests are used to confirm diagnosis of dRTA
Physiological tests of acidification	Response of Urine pH and potassium concentration to furosemide administration or alternatively the response to urine pH to furosemide and fludrocortisone (confirms hyper kalemic dRTA)
	Measurement of urine pH after ammonium chloride loading to include acidosis (unpleasant for patients), which confirms incomplete dRTA or dRTA
	Measurement of urine minus blood PCO_2, presence or absence of an increase I urine PCO_2 after phosphate loading, and /or the response to urine PH to sulphate loading – which confirms site of lesion in dRTA or the mechanism
Radiology evaluation	Radiological investigation to confirm nephrocalcinosis, osteopenia and osteopetrosis, cerebral calcifications in inherited carbonic anhydrase II deficiency
	Abdominal x-ray or CT scan
	Urinary tract obstruction by ultrasound, nuclear renal scan or spiral CT scan
	Radiological confirmation of rickets
Additional diagnostic tools	Discovery of abnormally low serum bicarbonate concentration and hyperchloremia
	Recognition of significant risk factors or consequences of RTA (e.g., nephrocalcinosis, diabetes, prostatism, growth retardation and renal calculi)
	Inherited testing
	Hearing tests

Table 4: BMJ best practice for surveillance of patients with diagnosed dRTA (reproduced from Table 14 of the CS)

System/ Concern	Evaluation	Comment
Renal	Venous blood gas	In rapidly growing individuals (infants & young children): at least every 3-4 months once blood pH is normalised w/out evidence of respiratory compensation; in older children & adults: at least every 6 months. Sample to be drawn in fasting conditions & immediately before scheduled dose of alkali
	Serum creatinine, urea, sodium, potassium, chloride, calcium, phosphate, alkaline phosphatase, albumin	In rapidly growing individuals (infants & young children), at least every 3-4 months once adequate control is achieved In older children & adults, at least every 6 months
	Urinalysis, urine creatinine, sodium, potassium, calcium, citrate	Annually; more frequently when adjusting treatment
	Renal ultrasound	Annual evaluation for nephrocalcinosis, urolithiasis, & cysts in asymptomatic individuals
ENT	Audiometry	Annual evaluation for hearing loss
Skeletal	Bone densitometry	There is no consensus on the benefit of follow-up bone densitometry.
Constitutional	Measurement of length/height, weight; calculation of body mass index	In infants, at least every 3 months in older children, at least every 6 months until achievement of final height

Figure 1: The current clinical pathway of care for children with dRTA provided by the company. (reproduced from Figure 9 of the CS)

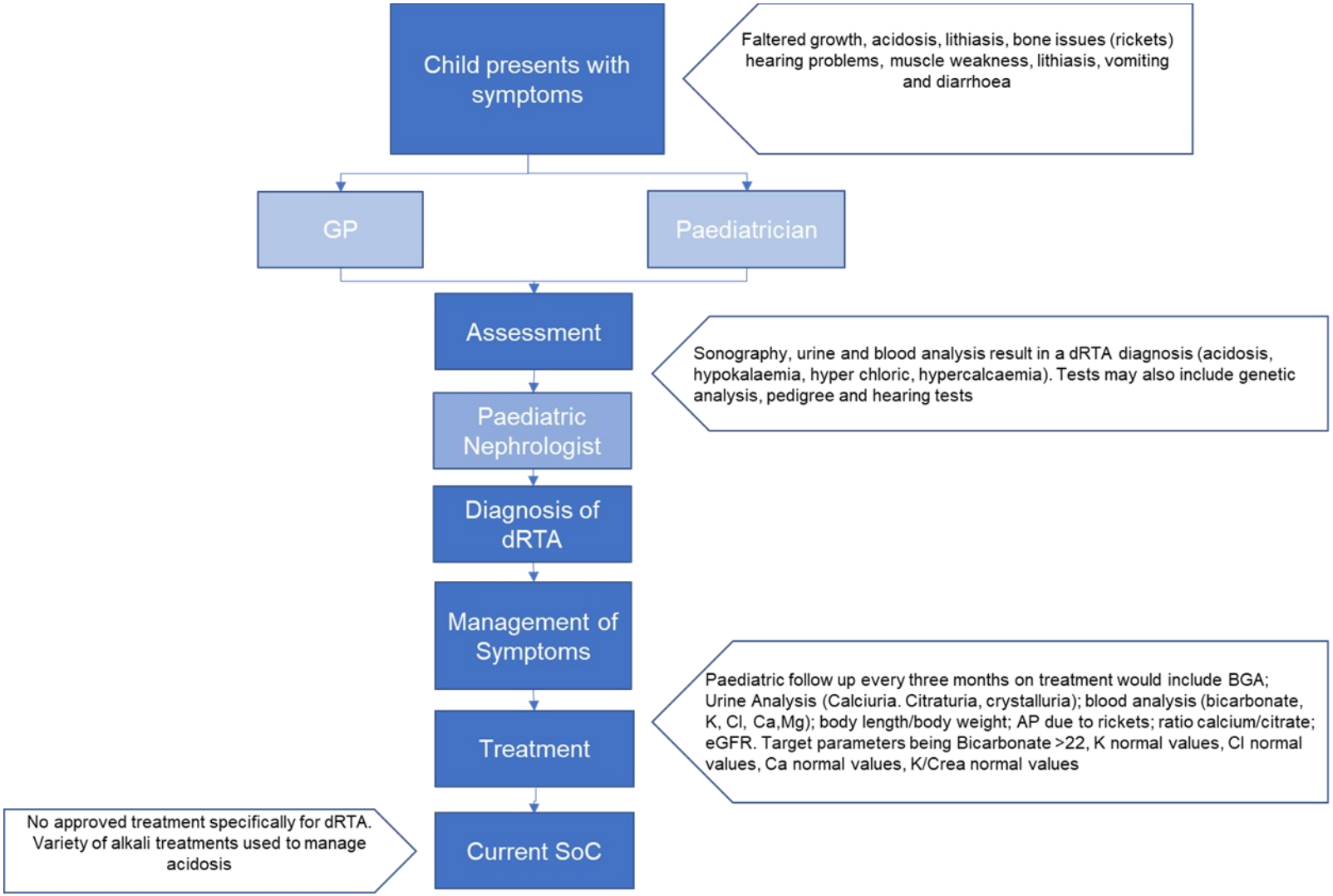
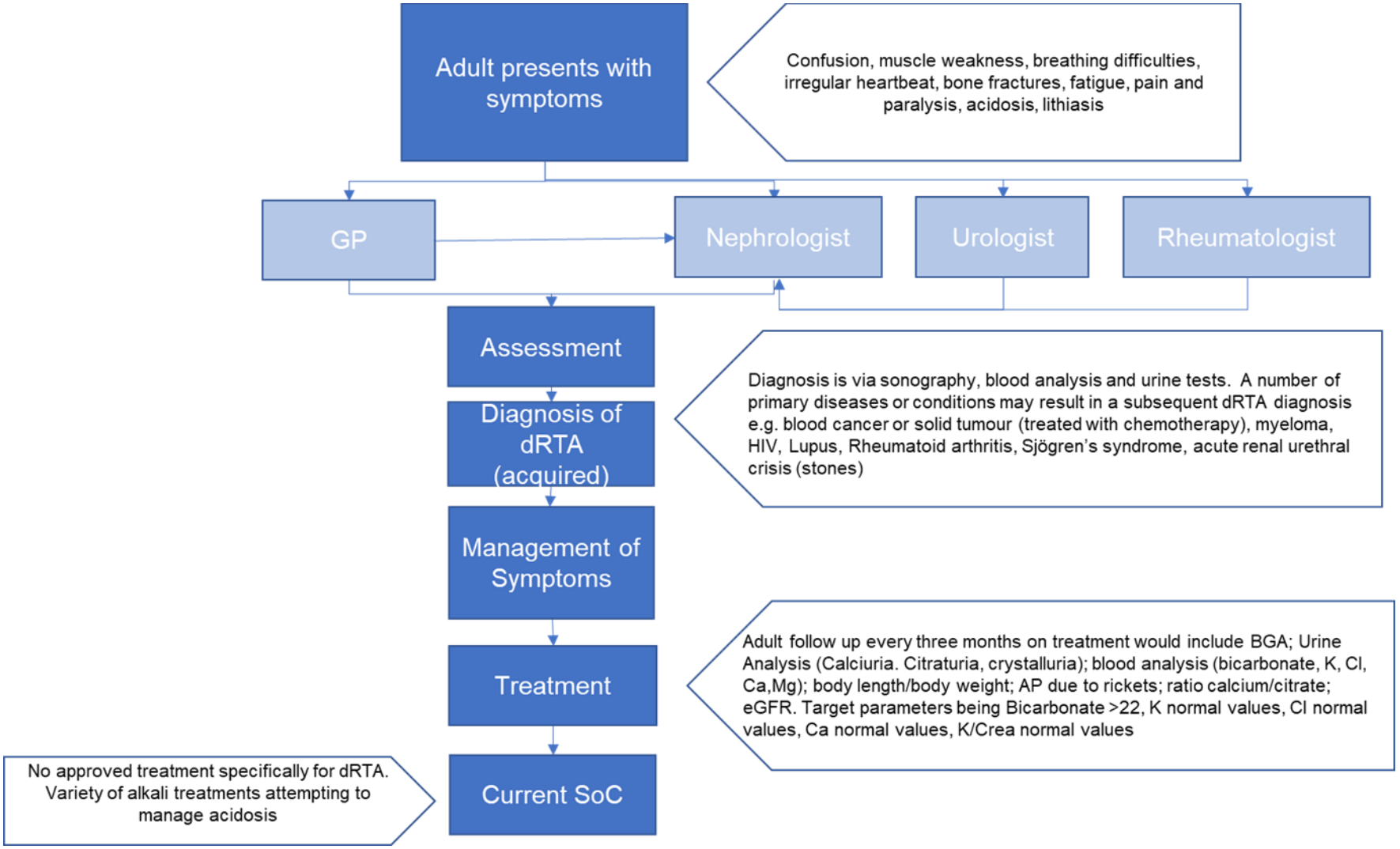


Figure 2: The current clinical pathway of care for adults with dRTA provided by the company. (reproduced from Figure 11 of the CS)



The primary aim of treatment for patients with dRTA is to correct metabolic acidosis and other biochemical abnormalities with the intention to avoid failure to thrive, rickets, osteoporosis, nephrolithiasis and nephrocalcinosis.[9] Avoidance of progressive nephrocalcinosis is highlighted by the company as particularly important as this could lead to kidney complications, such as CKD and end-stage kidney disease (ESKD). The company has used the older nomenclature, which is end stage renal disease (ESRD); on clinical advice, the ERG has used ESKD in this document.

Alkali replacement therapy is provided with a goal of maintaining normal serum bicarbonate concentration of >20 mEq/L in infants and >22 mEq/L in children and adults.[10] The CS states that '*there are no currently licensed treatments for dRTA. Current treatment are off label or pharmacy/hospital compounded products*'. The CS also states that 'v*arious existing alkali medicinal products are authorised for the prevention/partial prevention/treatment of dRTA but none of are specifically authorised for dRTA or were studied in appropriate clinical trials and are therefore not the preferred therapeutic options. Most often, pharmacy or magistral preparations are used*.' The ERG is unclear what was meant in the CS by the term authorised, but clinical advice received by the ERG confirms that products are not licensed by regulatory authority and are prescribed off-licence.

The wide variety of treatments currently used to treat patients with dRTA is shown in Lopez-Garcia *et al*.[6] This study collected data from clinicians contacted through European professional organisations in August 2017 via an online form, with adequate data collected on 340 patients. It was observed that more than 30 different alkali formations were used with 25% receiving oral bicarbonate, 42% oral citrate, 33% both oral bicarbonate and oral citrate and less than 1% remaining untreated. Sodium-containing salts were used in 21% of patients, potassium in 29% and a combination of both sodium-containing salts and potassium in 50%.

Current treatments need multiple intakes (three to six times a day, including at night) due to the immediate release formulations of citrate or bicarbonate salts that have a short duration of action. The nightly intake, which is reported to affect adherence to treatment, is stated to be particularly important in children as growth hormone is secreted mainly at night. Additionally, the company states that in patients with dRTA, decreased blood pH levels is correlated with lower growth hormone secretion, leading to growth impairment.

The company proposes that ADV7103, which provides a prolonged-release of potassium citrate and potassium hydrogen carbonate (also known as potassium bicarbonate) replaces the current variety of alkali treatments used in SoC in Figure 1 and Figure 2.

2.3 Critique of company's definition of the decision problem

The adherence of the CS to the scope issued by NICE is summarised in Table 5 with supplementary details provided in Sections 2.3.1 to 2.3.7.

Table 5: The adherence of the CS to the NICE scope (adapted from Table 1 of the CS)

	Scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with distal renal tubular acidosis aged 1 year and older	As per the NICE Scope	-
Intervention	Prolonged-release potassium citrate and potassium bicarbonate	As per the NICE Scope	-
Comparators	Established clinical management without prolonged-release potassium citrate and potassium bicarbonate (Sibnayal®), which may include alkalinising treatments alone or in combination with one another	As per the NICE Scope	-
Outcomes	The outcome measures to be considered include: bicarbonate level in the blood; potassium level in the blood; calcium level in the urine; citrate level in the urine; renal function; measures of impaired growth; and bone mineral density.	As per the NICE Scope	-
Economic Analysis	Cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective. Any commercial arrangements will be taken into account.	As per the NICE Scope	-
Subgroups to be considered	None	In sensitivity analyses the company provided results based on age groups: 1- 3 years; 4-11 years; 12 – 17 years; and 18 years and over.	Dosing of ADV7103 is dependent on both age and weight
Special Considerations	None	None	-

2.3.1 Population

The population includes all people aged 1 year of over who have dRTA.

2.3.2 Intervention

The intervention ADV7103 has the branded name of Sibnayal®. ADV7103 is a fixed-dose combination of potassium citrate and potassium hydrogen carbonate (also known as potassium bicarbonate) as prolonged-release granules. It has a marketing authorisation from the European Medicines Agency (EMA) for the treatment of dRTA in patients one year and older. Dosing of ADV7103 is based on age and weight and is administered twice daily, typically twelve hours apart, preferably during meals. The granules are recommended to be swallowed with water, although an alternative method is for the granules to be mixed (without crushing) with small amounts of soft food and swallowed without chewing. ADV7103 can be taken for a patient's remaining lifetime, unless contraindicated. Contraindications include patients with eGFR of 44 ml/min/1.73m^2 or lower, hyperkalaemia, and hypersensitivity to the active substances or excipients of ADV7103.

The list price for a box of 60 sachets of ADV is £360 for 24 milliequivalent (mEq) and £120 for 8 mEq. However, a simple Patient Access Scheme (PAS) which is a discount of [redacted] has been approved resulting in prices of [redacted] for 24mEq per box and [redacted] for 8mEq per box. For both doses, this equates to a cost of [redacted] per mEq.

2.3.3 Comparator

The comparator for ADV7103 is current SoC although the company states that the components of SoC are used off-label. As described in Section 2.2, SoC largely consists of oral bicarbonate and oral citrate use in conjunction with sodium-containing salts and potassium. Multiple intakes of treatment, including nightly doses, are required with SoC.

2.3.4 Outcomes

The NICE scope details multiple outcomes that should be considered, although the ERG notes that the majority of these are surrogate outcomes and that modelling assumptions will be required to estimate the percentage of patients that experience hard clinical endpoints such as ESKD, kidney transplant or death related to conditions caused by dRTA.

2.3.5 Economic analyses

The analyses in the CS were in line with the NICE scope, although results were presented both at the list price and when the PAS discount of [redacted]% is included. For brevity, only the results using the PAS price have been included in this report

2.3.6 Subgroups

The NICE scope did not list any subgroups that warranted exploration. However, in addition to the combined population, the CS provides sensitivity analyses based on four age bands: 1- 3 years; 4-11 years; 12 – 17 years; and 18 years and over. These analyses are relevant as the dosage of ADV7103 is dependent on both age and weight and could also be relevant if it is believed that adult patients have a different disease (acquired dRTA) to non-adult patients (inherited dRTA) as assumed in the model.

2.3.7 Special considerations

The NICE scope did not list any special considerations including issues related to equity or equality that should be explored. The company did not claim that special considerations were relevant to this Single Technology Appraisal (STA).

3 CLINICAL EFFECTIVENESS

Two studies of ADV7103 in dRTA are discussed in this section: B21CS; and B22CS.

3.1 Critique of the methods of review(s)

3.1.1 Searches

The company performed one clinical effectiveness search to identify all clinical effectiveness and safety studies of ADV7103 or comparator treatments of patients with dRTA aged one year and older.

In summary, the ERG has identified limitations in the company search strategy relating to:

- Sources searched
- Reporting
- Simultaneous searching in the Embase.com platform
- Limits applied
- Search filter terminology.

The company searched several electronic bibliographic databases in August 2021 (Appendix 2.3 Identification and selection of relevant studies): MEDLINE [via Embase.com], MEDLINE in Process [via PubMed.com], EMBASE [via Embase.com], Cochrane Central Register of Controlled Trials [via Wiley]. Database searching was supplemented with reference list searching of included studies, as is good practice for systematic reviews.

The company hand searched several key conference abstract websites in the last three years (dates unreported): Spanish Society of Nephrology (SEN) Annual Congress; Congress of the International Paediatric Nephrology Association; International Society for Pharmacoeconomics and Outcomes Research (ISPOR): Europe and International. The company did not report on the search terms or the results of the conference website sources.

The company did not search clinical trials registries for ongoing or complete and unpublished studies. Examples of trials registries include clinictrials.gov, WHO International Clinical Trials Registry Platform (ICTRP) and the EU Clinical Trials Register (EUCTR). The company's reasons for omitting searches for ongoing or unpublished trials are unclear from the CS. A cross-sectional study by Banno, Tsujimoto & Kataoka (2020)[11] compared the coverage of the two trials registry sources (clinicaltrials.gov and WHO ICTRP records) and CENTRAL. The conclusions from this study suggested that clinicaltrials.gov and ICTRP sources together with CENTRAL should be searched to

identify unpublished trials. The company has reported undertaking reference tracking and citation searches as supplementary source.

The search terms for the 'distal renal tubular acidosis' population only was considered comprehensive by the ERG and the concept combinations in the strategies are correct. The company have also conducted a search for clinical guidelines and epidemiological evidence.

The Embase.com platform allows MEDLINE and Embase to be searched simultaneously. The Cochrane Handbook[12] recommends that both free-text and vocabulary/index terms are used. However, in MEDLINE and Embase the indexed terms are not the same in each record (with Embase having more indexing terms attached to records compared to MEDLINE records). It is unclear to the ERG, whether the MeSH and Emtree terminology have been comprehensively included and mapped between MEDLINE and Embase i.e., MeSH terms will automatically map to Emtree terms. Conversely, Emtree terms do not map to MeSH terms. The ERG does not have access to the Embase.com platform to fully appraise the MEDLINE and Embase search headings.

The company has applied a Randomised Controlled Trial (RCT) and observational search filters to limit the search. Inconsequential and redundant terms were identified (e.g. (case* NEXT/1 control*)). The ERG recommends that both index terms and free-text terms should be present in the search filters (as seen in the cost-effectiveness search filter). For example:

- RCT search filter - 'single blind procedure'/de and 'single blind':ab,ti,; 'double blind procedure'/de and 'double blind':ab,ti,; 'randomized controlled trial'/exp and 'randomi*ed controlled trial':ab,ti,
- Observational studies filter - 'longitudinal study'/exp and 'longitudinal study':ab,ti,; 'prospective study'/exp and 'prospective study':ab,ti,; 'retrospective study'/exp and 'retrospective study':ab,ti,; 'observational study'/exp and observational NEXT/5 (study OR studies).

The company have applied an English language limit to the search and this could result in the language publication and geographical bias. Section 4.5.5. of the Cochrane Handbook[12] states that it is necessary to assess the eligibility of all relevant studies regardless of the publication language.

Having reviewed the search strategies, the ERG considers that the omission of searches in clinical trials registries and inconsistencies in the applied search filter is likely to impact search sensitivity compared to the other limitations described in this critique. The consequences on the findings of the review are unknown.

3.1.2 Inclusion criteria

The company conducted a systematic literature review (SLR) to identify key published data on dRTA (CS Appendix D). The review was broad, and included prevalence and incidence, current management strategies, and treatment effectiveness and safety (CS Appendix D). Within this, data for the decision problem would be covered.

The population included male and female patients of any age, and any current pharmacological treatment was included as an intervention (CS Appendix D). For effectiveness and safety data, study designs sought were RCTs, non-randomised controlled trials, cohort, case-control, cross-section and uncontrolled studies, or data from registries (CS Appendix D).

Abstract and full text screening were conducted by two reviewers (CS Appendix D), as is good practice for systematic reviews.

3.1.3 Critique of data extraction

Data extraction was conducted by two reviewers, as is good practice for systematic reviews. Relevant information about the studies of ADV7103 in dRTA were provided in the CS; this was checked by the ERG against the clinical study report (CSRs) and publications, [13-15] [16, 17] and was found to be accurate.

3.1.4 Quality assessment

Study B21CS was an open-label, non-inferiority, Phase II/III sequential study, which compared each patient on 5 days of SoC with 5 days of optimised ADV7103 treatment (CS Section B.2.3). Study B22CS was an open label extension study of B21CS, with patients taking ADV7103 assessed for up to 48 months (CS Section B.2.3).

No formal risk of bias assessment was conducted on the included studies of ADV7103 in dRTA in the CS SLR (CS Appendix D), however CS Section B.2.5 addresses some issues of quality regarding the study design.

The CS assessment indicates the following: B21CS is statistically powered for non-inferiority analysis of the primary outcome of bicarbonataemia (blood bicarbonate levels); bicarbonataemia is predictive of long-term consequences of dRTA; a placebo-controlled study would be unethical; B21CS is limited in terms of quality-of-life evidence but this was an outcome for B22CS (CS Section B.2.5). The CS also indicates there are few data on comparators available (CS Section B.2.5).

The ERG agrees that a placebo-controlled study would be unethical, however a parallel group study design could have allowed long-term follow-up of SoC, and addressed the lack of data on comparators. The ERG accept that it may be difficult to recruit enough patients for a long-term parallel group study in the case of a rare disease. The CS states that the goal of B22CS was not to compare treatments but to assess safety of ADV7103. Effectiveness outcomes are measured in B22CS, but the only data comparing against SoC are from B21CS.

Blood bicarbonate level is a surrogate outcome measure. Surrogate outcome measures may result in bias if they are not reliable predictors for what they are intending to measure.[18] [19] The ERG's clinical advisors commented that bicarbonataemia is a reasonable surrogate for long term complications of dRTA (CS Section B.2.3).

B21CS had a sequential, non-randomised design. A potential problem of sequential treatments is that prior treatment may not have sufficient time to leave a patient's system,[20] however the ERG's clinical advisors commented that the short half-life of SoC would mean that there was no residual benefit that would affect the estimation of benefit for the subsequent ADV7103 treatment. Table 6 includes risk of bias items from the public health NICE methods guide for assessing the quality of quantitative interventions,[18] with items regarding non-randomised studies[22-29] and non-inferiority trials.[30] Table 6 shows the ERG's quality assessment based on study information provided in the CS and the B21CS CSR.[13]

The comparator treatment for B21CS was current SoC. This is only assumed to be at optimal dose, based on prior treatment, as the trial did not include a titration phase for SoC [21].

B21CS compares five days SoC with five days of optimised ADV7103. This was endorsed by Committee for Medicinal Products for Human Use (CHMP) to be adequate time for the primary outcome (blood bicarbonate level) (CS Section B.2.3). It would not be adequate time to compare treatment effects on long-term consequences of dRTA, or to assess compliance with treatment. B22CS addresses longer-term follow-up for patients receiving ADV7103 treatment.

Selection bias is avoided by having clearly defined eligibility criteria, and recruiting consecutive patients who meet these criteria. The eligibility criteria for B21CS were clearly defined. B21CS recruitment was described as patients being "enrolled in a staggered approach into four age subsets" (CS Section B.2.3). It is unclear if this involved all consecutive patients meeting eligibility criteria being recruited.

Missing data have the potential to introduce bias. Not all patients provided data for all outcomes. The ITT set did not include all enrolled patients. For the primary outcome, a modified ITT analysis was used for patients with valid pre-dose plasma bicarbonate values. The company's response to clarification question A2 explained there were 35 patients in the modified ITT set for the primary outcome, 34 patients on five days SoC, and 31 patients on five days optimised ADV7103 treatment.

B21CS and B22CS were open-label studies. Lack of blinding can lead to a high risk of performance and detection bias. Subjective measures, such as health-related quality-of-life (HRQoL), are more likely to be biased than objective measures.[31] B22CS measured treatment acceptability by visual analogue scale (VAS) 0-100mm (CS Section B.2.6). Patients and/or parents were asked to score improvement over previous alkalising treatment in terms of: efficacy; safety; formulation; number of daily doses; taste (CS Section B.2.6). The scales asked for improvement, that is, the lowest score possible would assume equivalence of current and prior treatments, with option to report if there was any worsening of treatment acceptability, therefore biasing in favour of ADV7103. There is also the potential for recall bias, as the comparison was with prior treatment.[29]

Table 6: Quality assessment of Study B21CS and OLE extension B22CS

Question	ERG assessment
Is the objective of the study clearly described?	Yes
Were eligibility criteria adequately defined?	Yes
Were patients recruited consecutively?	Unclear
Do the selected participants represent the eligible population?	Yes
Were exposures to interventions accurately measured?	Yes
Was there bias due to missing data?	Unclear
Was the primary outcome assessed using accurate, valid and reliable measures?	Yes
Were methods of outcome assessment comparable for both interventions?	Yes
Was follow-up long enough?	B21CS Primary outcome – yes, but not for all outcomes B22CS addresses this for ADV7103, but no long-term follow-up for SoC
Was primary outcome relevant? (If surrogate, is this appropriate?)	Bicarbonataemia is a surrogate outcome, however it is deemed to be reasonable surrogate for long term complications of dRTA
Were the outcome assessors blinded to the intervention?	No
Were all participants accounted for at study conclusion?	Yes
Were data for this outcome available for all, or nearly all, participants?	Primary outcome – nearly all patients Other outcomes varied in number of patients with data recorded
Was the study sufficiently powered? Was sample size was determined, detailing whether it was calculated using a non-inferiority or equivalence criterion and specifying the margin of equivalence?	For the primary outcome, yes

Explanation of rationale for using a non-inferiority or equivalence design?	Yes
For the primary outcome, a summary of results for each group and the estimated effect size and its precision (e.g., 95% confidence interval)?	Yes

3.2 Included studies of ADV7103 in dRTA

The company's SLR identified 33 publications from Europe providing background information about dRTA (CS Appendix D). Within this, the company identified two published studies of ADV7103 in dRTA; B21CS and B22CS (CS Appendix D).

The company reported finding published articles of alkali treatment for dRTA. However, none of the published articles identified of comparator treatments were considered by the company as providing evidence suitable for an indirect comparison (CS B.2.9). Reasons given for this were that the articles were discussion papers, or that the studies did not provide data for the same outcome measures as those evaluated in the B21CS or B22CS studies (clarification response, question A10).

The CS provided an indirect comparison with historical controls of eighteen untreated people with dRTA from Thailand (CS B.2.9). According to clinical advice received by the ERG, the intention is that patients would not be left untreated; instead, adjustments to treatment would keep being made, as untreated patients have poorer outcomes. However, some patients may not take medication because SoC is unpalatable and impractical.

The key evidence for clinical effectiveness within the CS comprised two studies of ADV7103 in dRTA patients: B21CS; and B22CS. The CS also described B03CS, a study of ADV7103 in healthy subjects. As this was in healthy subjects rather than dRTA patients, it is not described here.

Study B21CS was an open-label, non-inferiority, Phase II/III sequential study, which compared each patient taking 5 days of SoC with 5 days taking ADV7103 (CS Section B.2.3).[16] Study B22CS was an open label extension study of B21CS, with patients on ADV7103 assessed over 24 months, with the option for patients to continue beyond 24 months (CS Section B.2.3).[17]

The company identified two ongoing studies of ADV7103 in dRTA; Study B23CS (NCT03644706, ARENA-2) a planned RCT of withdrawal from ADV7103; and Study B24CS (NCT03831152) a planned open label extension of B23CS (CS Section B.2). At the time at which the CS was submitted (29th November 2021), both of these studies were reported to be on hold (CS Section B.2). These studies are due to be conducted in North America (CS Section B.2).[32, 33]

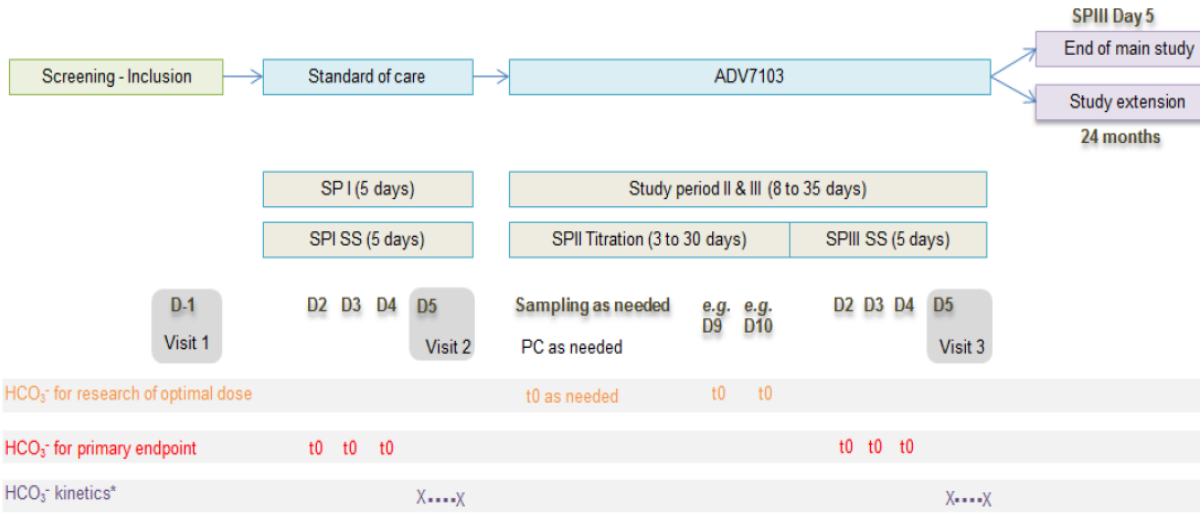
Following advice from clinicians, the ERG does not believe that any relevant published studies, that could have provided effectiveness data of ADV7103 in dRTA, have been omitted from the CS.

3.2.1 Study design B21CS

Study B21CS was a multicentre, open-label, non-inferiority sequential study. It used a self-controlled design, that is each patient was given SoC followed by ADV7103, and acted as their own control (rather than having a parallel control group) (CS Section B.2.3). Planned recruitment was at least four patients in each of four age subsets. Study characteristics are shown in Table 7. (CS Section B.2.2).

SoC was given for five days (study period 1 (SPI)); this was the patient's usual SoC alkalising treatment at their usual therapeutic dose without modification (Figure 3). This was followed by a titration period of ADV7103 twice a day, which could last three to 30 days (study period 2 (SPII)). "*Titration was performed to determine the optimal dose based on patients' bicarbonataemia*" (CS Section B.2.3). This was followed by 5 days of ADV7103 twice a day at the patient's optimum dose (study period 3(SPIII)).

Figure 3: B21CS study design (reproduced from CS Figure 14)



Blood and urine were sampled at local laboratories. Hospital visits were planned for days 1 and 5 of SPI, and day 5 of SPIII. There was additional testing of 24-hour bicarbonataemia fluctuation of some patients (all aged ≥18 years, or 12 to 17 years, and some of younger-aged patients) during hospitalisation at day 5 of SPI, and day 5 of SPIII (CS Section B.2.3 and CS Figure 14). Samples for blood bicarbonate levels were taken prior to the first dose on a given day (referred to as t0); samples were taken and analysed at local laboratories (CS Section B.2.3).

Of the 13 centres in the study, 11 centres were in France, one was in Slovakia and one was in Serbia. The patients enrolled in Serbia were hospitalised throughout the three SPs, unlike for centres in other countries (CS Section B.2.3). There were no patients from the United Kingdom. Clinical advice to the ERG suggests that SoC in these countries are likely to be representative of SoC in England.

ADV7103 and SoC were compared on the following outcomes. The primary outcome was blood bicarbonate levels (measured on days 2, 3 and 4 of SPI and SPIII) (CS, Section B.2.3). Secondary outcomes were after 4 to 5 days of treatment at steady state: reduction of hypercalciuria; and correction of hypocitraturia. After 5 days of treatment at steady state: other blood bicarbonate derived parameters (fluctuation, response vs nonresponse); safety and tolerability including gastrointestinal tolerability; acceptability (palatability, swallowing, ease of administration); and compliance.

Table 7: Characteristics of Study B21CS

Study	Population	Intervention	Comparator	Primary outcome
B21CS EudraCT Number: 2013-002988-25[34]	Patients with an established diagnosis of dRTA with metabolic acidosis. Four age subsets (≥18 years, 12 to 17 years, 4 to 11 years, and 6 months to 3 years)	ADV7103: a combination of potassium citrate (ADV7103-CK) and potassium bicarbonate (ADV7103-BK) prolonged-release granules	SoC	Blood bicarbonate levels

Key study eligibility criteria are shown in Table 8 which reproduces Table 18 of the CS. Patients were male or female and had an established diagnosis of dRTA with metabolic acidosis, in four age subsets (≥18 years, 12 to 17 years, 4 to 11 years, and 6 months to 3 years) (CS, Section B.2.3). Patients were excluded if they presented with kalaemia or a severe or moderate renal impairment; these reflect contraindications in the marketing authorisation. Patients were excluded if they were "*at risk of non-compliance in the judgement of the Investigator*" (CS, Section B.2.3). There was no inclusion criterion about the time on stable dose of SoC prior to study entry (CS, Section B.2.3).

Table 8: Inclusion and exclusion criteria for Study B21CS (reproduced from CS, Table 18)

Key inclusion criteria	Key exclusion criteria
Patient who had a diagnosis of dRTA (acquired or inherited form) with metabolic acidosis Patient male or female, including child aged between 6 months and 17 years old and adult aged ≥18 years old and ≤55 years old For female patients (maiden after puberty or woman), non-childbearing potential had to be confirmed, for example using a contraceptive method judged effective by the Investigator (or surgically sterilised) if sexually active and having a negative pregnancy test at inclusion Patient and/or parents or legal representative(s) who was (were) willing and able to participate in the study, to understand and to comply with study procedures for the entire length of the study Patient or parents or legal representative(s) who had provided a signed written informed consent For patients of ≤17 years of age, collection or attempt to collect assent had to be confirmed Patient who was affiliate to a social health insurance system and/or in compliance with the recommendations of the national law in force relating to biomedical research	Patient who presented associated proximal tubular signs (i.e., presenting for example hypophosphoraemia, urinary betamicroglobulin, hyponatraemia) Patient who presented a kalaemia (i.e., plasma potassium concentration) >5.0 mmol/L Patient who presented a severe or moderate renal impairment (creatinine clearance <45 mL/min/1.73m^2 according to Schwartz formula for the children and both Cockcroft & Gault and MDRD formulas for adults) Patient who presented – barring the study disease – 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 Patient who took or could not stop (last dose on day 1) potassium-sparing diuretics (e.g., Spironolactone, aldactone, amiloride, triamterene), angiotensin converting enzymes inhibitors, angiotensin II receptor antagonists, tacrolimus, potassium desodic salts Female patient who was pregnant or breast-feeding Patient who received any medication within the 4 weeks before the inclusion in the study that could interfere with the study treatment Patient who presented contraindications to the administration of the study treatment such as known allergic reactions or hypersensitivity to the active pharmaceutical ingredients or other excipients of the formulations of the study treatment, 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, malabsorption, delayed gastric emptying, oesophageal compression, intestinal obstruction or other chronic gastrointestinal disease) Patient who was admitted to hospital in emergency settings Patient who had participated in a clinical trial within the last 3 months before enrolment Patient who was at risk of non-compliance of the study procedure in the judgement of the investigator Patient who presented any other condition, which in the opinion of the investigator, would preclude participation in the study Patient who could not be contacted in case of emergency Patient under any administrative or legal supervision

MDRD=Modification of Diet in Renal Disease; mmol/L= Millimoles per Litre

3.2.2 Study design B22CS

Study B22CS (EudraCT Number: 2013-003828-36)[35] was an open-label extension study of B21CS, with patients on ADV7103 assessed over 24 months, with the option for patients to continue beyond 24 months (CS, Section B.2.3). To be included, patients were required to have satisfactory efficacy, safety and tolerability of ADV7103 during B21CS (CS, Section B.2.3). The participants were patients who

had completed B21CS and agreed to continue ADV7103, at the dose used in B21CS SPIII (with allowance for some dose adjustment), instead of their SoC. Recruitment was planned for up to 32 patients (CS, Section B.2.3).

The primary outcome was AEs. The secondary outcomes were: bicarbonataemia; hypocitraturia; hypercalciuria; crystalluria; paraclinical and biological safety; compliance; kalaemia; hyperphosphaturia; hypermagnesuria. B22CS also had exploratory objectives: nephrocalcinosis; nephrolithiasis; bone remodelling; rickets (in children); osteomalacia (in adults); growth and pubertal maturity in the relevant paediatric populations; treatment acceptability; and HRQoL (VAS 0-100).

The first assessment of Study B22CS was the same date as B21CS study period III, day 5. Further outcome assessments were scheduled at months 3, 6, 12, 18 and 24. If patients continued after 24 months, then annual assessments were planned (CS, Section B.2.3).

Subgroups

No subgroups of interest were listed in the final NICE scope. For B21CS and B22CS, age subsets were assessed separately (≥18 years; 12 to 17 years; 4 to 11 years; and 6 months to 3 years); however, other planned subgroup analyses were not deemed possible (CS, Section B.2.7). Subgroup analyses by dRTA type were not performed, because only one enrolled patient had the acquired form of dRTA (CS, Section B.2.7).

3.2.3 ADV7103 in dRTA study results

For B21CS, 37 patients were screened, and all 37 were enrolled in the study (Table 25 CS) (CS Section B.2.3). Baseline characteristics of patients enrolled in B21CS are shown in Table 9 along with the baseline characteristics of patients from B21CS who continued in B22CS. Patients in B21CS were recruited from 11 centres France, one in Slovakia and one in Serbia. According to clinical advice received by the ERG, there are likely to be no significant differences between the study baseline characteristics, and those of dRTA patients in England and that there is no reason to assume any association between ethnicity and treatment effect. Whilst the study design has intended to recruit patients as young as 6 months, none of the study participants were aged under 1 year, hence the marketing authorisation agreed by the EMA and the company was for patients aged more than one year old;[36] therefore the baseline ages of patients in the study are relevant to the population eligible for treatment.

Table 9: Baseline characteristics for Study B21CS (adapted from CS Table 30)

Baseline characteristic	**B21CS N=37**	**B22CS** (n=30)
Age Mean (SD) years	11.5 (8.15)	11.2 (5.9)
Age Median years	11.5	10.3
Age Range years	1-46	1-22
Female	23 (62%)	17 (56.7%)
Male	14 (38%)	13 (34.3%)
Weight (kg) Mean (SD)	37.4 (22.30)	37.30 (19.17)
Weight (kg) Median	39.0	41.05
Weight (kg) Range	9-114	12.0-87.0
Height (cm) Mean	133.5 (27.79)	135.1 (26.5)
Height (cm) Median	139.0	141.0
Height (cm) Range	75-170	86-170
Type of dRTA Acquired – n (%)	1 (2.7%)	0 (0)
Type of dRTA Inherited - n (%)	35 (94.6%)	29.0 (100%)
Type of dRTA Not specified – n (%)	1 (2.7%)	1.0 (0%)

SoC, as taken prior to study B21CS, and during SPI, is shown in Table 10. SoC was the patient's usual alkalising treatment, at their usual therapeutic dose, without modification (CS, Section B.2.3). Data were not available for all patients about duration of prior SoC. For the 25 patients with available data, patients had received their usual type of SoC alkalising treatment for a mean duration of 4 years (range 8 months to 4.7 years), and without dose modification for a mean duration of 18 months (range 0.5 to 4.3 years) (CS Section B.2.3), and had received between one and six lines of SoC prior to study entry.

Table 10: Study B21CS - SoC in SPI (adapted from CS Tables 19 and 20)

SoC	**(N=37)**
Taking >1 medication, n(%)	18 (48.6%)
Taking alkali + K^+ supplement, n(%)	3 (8.1%)
Sodium load (mean ± SD)	1.08 ± 0.47 g/day
≤ 2 intakes per 24 hours, n(%)	5 (13.5%)
≥ 3 intakes per 24 hours, n(%)	32 (86.5%)
At least one intake at night, n(%)	10 (27%)
Average dose Adult: ≥18 years (n=7)	2 ±1.5 mEq/kg/day
Average dose Adolescents: 12 to 17 years (n=10)	2.2±1.4 mEq /kg/day
Average dose Children: 4 to 11 years (n=15)	2.7±1.2 mEq /kg/day
Average dose Infants: 6 months to 3 years (n=5)	5.3±2.5 mEq /kg/day

mEq = milliequivalent

In Study B21CS, of the 37 patients starting SPI, 35 completed SPI and started SPII. Thirty-two patients completed SPII (Table 11). The 32 patients who started SPIII all completed the study (CS, Section B.2.3).

Two patients did not complete SPI: one patient requested to withdraw from study; one withdrew for an "*other*" reason (from CSR, difficulty swallowing ADV7103 first intake attempt)[13]. Three patients did not complete SPII: one due to lack of efficacy; two patients requested withdrawal from study. In B21CS SPII, the median titration period of ADV7103 was ten days (mean 12.76 days).

In B21CS SPIII, ADV7103 was administered twice daily, typically twelve hours apart. Mean (SD) doses of ADV7103 in SPIII were: adults 1.7 ±1 mEq /kg/day; adolescents 2.8±1.7 mEq /kg/day; children 3.8±1.1 mEq /kg/day; and infant 6.1±2.3 mEq /kg/day (CS Section B.2.3).

Data were not provided by all patients for all outcomes (CS, Section B.2.5) (CS clarification response, question A2). The ITT and acceptability analysis sets were taken from all 37 patients but depended on those providing data for a particular outcome, while the PP set included 30 patients (2 patients were excluded due to major protocol deviations and five patients due to early study discontinuation) (CS Section B.2.3) (clarification response, questions A2 and C2).

Blood bicarbonate levels were only accepted for blood samples drawn pre-morning dose (t0), some samples were not collected, and some samples were classed as missing if the time of sampling was after the morning dose or unknown (CS, Section B.2.5).

Table 11: Patient disposition in Study B21CS (reproduced from CS, Table 25)

	Adults (≥ 18 years)	**Adolescents (from 12-17 years inclusive)**	**Children (from 4-11 years inclusive)**	**Infants (from 6 months – 3 years inclusive)**	**Total**
Screening					
Entered phase, N	7	10	15	5	37
Completed phase, n (%)	7 (100)	10 (100)	15 (100)	5 (100)	37 (100)
SPI					
Entered phase, N	7	10	15	5	37
Completed phase, n(%)	7 (100)	10 (100)	14 (93.3)	4 (80)	35 (94.6)
Discontinued prior to phase completion, n (%)	-	-	1 (6.7)	1 (20)	2 (5.4)
Primary reason for non-completion of study phase (n[%])	-	-	Withdrawal by subject (1 [6.7])	Other (1[20])	Other (1[2.7]) Withdrawal by subject (1[2.7])
SPII/SPIII					
Entered phase, N	7	10	14	4	35
Completed phase, n(%)	7 (100)	8 (80)	14 (100)	3 (75)	32(91.4)
Discontinued prior to phase completion, n (%)	-	2 (20)	1	1(25)	3 (8.6)
Primary reason for non-completion of study phase (n[%])	-	Lack of efficacy (1[10]) Withdrawal by subject (1[10])	-	Withdrawal by subject (1[25])	Lack of efficacy (1[2.9]) Subject withdrawal (2[5.7])
Overall total					
Screened, N	7	10	15	5	37
Completed study, n(%)	7 (100)	8(80)	14 (93.3)	3 (60)	32 (86.5)

Compliance, palatability and tolerability

In B21CS, compliance was high. 34/37 patients (91.9%) were compliant during SoC treatment (SPI), and 31/32 patients (96.9%) were compliant during ADV7103 treatment (SPIII) (CS, Section B.2.6). Results were similar in the different age subsets (CS, Section B.2.6). These treatment periods were only five days in duration. Longer-term compliance with optimised ADV7103 treatment was an outcome measure in B22CS.

Palatability and gastrointestinal tolerability were measured by a VAS or a facial hedonic scale depending on age. In B21CS, palatability was considered to be worse for SoC than ADV7103, with

patient-reported "*dislike very much*" for 24.2% (n=35) of SoC-treated patients and 3.0% (n=31) of optimal ADV7103-treated patients (CS, Section B.2.6) (clarification response, question A14).

In Study B21CS, gastrointestinal tolerability was considered to be worse for SoC than ADV7103, with 54.5% (n=35) of SoC-treated patients reporting "*No Complaint*", and 78.8% (n=32) of ADV7103-treated patients reporting "*No Complaint*" (CS, Section B.2.6) (clarification response, question A14).

For each patient, Study B22CS was to start on the last day of inclusion in Study B21CS. For B22CS, 32 patients from B21CS were eligible to continue with B22CS (CS, Section B.2.3), of whom 30 patients started the B22CS study. Two patients chose not to participate in B22CS: one adult who preferred prior treatment and did not want to participate in study procedures; and one child, decision not explained to study investigators (clarification response, question A1). Twenty-nine patients provided data up to 24 months into B22CS, and one patient withdrew from the study at patient request (CS, Section B.2.3).

In B22CS, eleven patients (36.7%) were taking concomitant medication throughout the study duration, the most common being cholecalciferol (n=6, 20.0%). Concomitant medication at any point in B22CS was taken by n=29 patients (96.7%.).

Study B22CS measured percentage compliance at 3-monthly visits (CS, Section B.2.6). Compliance was reported as ≥75% for n=28/30 (93.3%) patients at month 3, and n=23/29 (79.3%) patients at month 24 (CS, Section B.2.6). Clinical advice provided to the ERG suggested that these compliance levels are very good compared to SoC.

Bicarbonate level in the blood

In the PP set, 29 patients provided data for SoC treatment (SPI), and 30 patients for the ADV7103 treatment of SPIII (Table 12) (CS, Section B.2.6). The mean (SD) blood bicarbonate levels were 21.7 (3.06) mmol/L with SoC and 23.1 (1.62) mmol/L with ADV7103 (CS, Section B.2.6).

Non-inferiority of ADV7103 vs. SoC was demonstrated in the PP set ("*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"*) (CS, Section B.2.6). ADV7103 was shown to be superior to SoC in both the PP (p=0.0037) and ITT sets (p=0.0008) (Table 12). Patients providing data were analysed together, that is across age subsets. According to clinical advice received by the ERG, it is reasonable to assume the drug has the same ability to normalise blood bicarbonate levels across age groups, provided the dose is tailed to patient age/size. This appears to be the case from mean blood bicarbonate levels from Study B21CS (Table 13). The ITT analysis in Table 12 shows results with data assumed missing at random. There were still significant differences with last observation carried forward

imputation (LS mean difference 1.28 (95% CI 0.419, 2.144 p=0.0024)); or worst observed case imputation (LS mean difference 1.24 (95% CI 0.397, 2.088, p=0.0026)) (CS, Section B.2.5). The ERG concluded that the method of imputation did not significantly affect the conclusions.

Table 12: Study B21CS - blood bicarbonate levels compared (adapted from CS Table 37 and CS Table 38)

	PP set		ITT set	
	SP I (SoC)	**SP III (ADV7103)**	**SP I (SoC)**	**SP III (ADV7103)**
Blood bicarbonate levels				
N in analysis set	N=30		N=35	
N with recorded data	29	30	34	31
Mean (SD) mmol/L	21.7 (3.06)	23.1 (1.62)	21.2 (3.11)	23.0 (1.62)
Min-Max mmol/L	17-29	19-27	16-29	19-27
Non-inferiority and superiority analyses				
N in analysis	29	29	34	31
Difference	Mean difference (SD) 1.4195 (2.647)		LS mean 1.636	
95% CI	(0.4128, 2.4263)		(0.6679, 2.6034)	
Non-inferiority *p*-value	<0.0001		Not applicable	
Superiority *p*-value	0.0037		0.0008	

Table 13: Study B21CS - blood bicarbonate levels by age subset (adapted from CS, Table 37)

Age subset	**PP set mmol/L**	
	SP I (SoC)	**SP III (ADV7103)**
Adults, ≥18 years old (n=7) Mean (SD)	24.1 (4.39)	23.8 (1.69)
Adolescents, 12-17 years old inclusive (n=8) Mean (SD)	22.5 (1.42)	23.3 (1.64)
Children, 4-11 years old inclusive (n=11 SPI, 12 SPIII) Mean (SD)	19.9 (2.04)	22.8 (1.66)
Infants, six months-3 years old inclusive (n=3) Mean (SD)	20.0 (1.32)	21.8 (0.76)

Two methodologies were used for defining non-responders; one was provided in the CS, and another was used in the model. The first method defined a non-responder as a patient recording at least one value of bicarbonataemia below the lower normal range, as defined by local laboratories, across Day 2, Day 3 and Day 4. The proportions of patients who were classified as responders are shown in Table 14 (CS, Section B.2.6). In the ITT set, 19/30 patients (63.3%) were non-responders to SoC, and 7/30 patients (23.3%) were non-responders to ADV7103; the complement values were assumed to be responders.

Table 14: Study B21CS - non-responder number/proportion of patients with at least one value of bicarbonataemia below lower normal range (adapted from CS, Table 39)

PP Set			ITT Set		
SoC	**ADV7103**	**n/N (%)**	**SoC**	**ADV7103**	**n/N (%)**
Response	Response	10/29 (34%)	Response	Response	10/30 (33%)
Non-response	Response	12/29 (41%)	Non-response	Response	13/30 (43%)
Response	Non-response	1/29 (3.4%)	Response	Non-response	1/30 (3.3%)
Non-response	Non-response	6/29 (21%)	Non-response	Non-response	6/30 (20%)
p-value[a]		0.003	*p*-value[a]		0.002

ITT=intent-to-treat, PP=per protocol, SoC=standard of care
Note: Post-dose samples are excluded from the analysis. [a]exact p-value obtained from a McNemar's test

A second definition of non-responder was used in the model. In this, patients were classified as non-responders where the mean bicarbonataemia levels of the measurements taken across Days 2 to 4 was below with the lower normal range, as defined by local laboratories. These results are shown in Table 15. In the ITT set, 17/30 patients (56.6%) were non-responders to SoC, and 3/30 patients (10.0%) were non-responders to ADV7103;[16] the complement values were assumed to be responders.

Table 15: Study B21CS - non-responder number/proportion of patients with at least one value of bicarbonataemia below lower normal range (taken from the company's CSR[37])

PP Set			ITT Set		
SoC	**ADV7103**	**n/N (%)**	**SoC**	**ADV7103**	**n/N (%)**
Response	Response	13/29 (45%)	Response	Response	13/30 (43%)
Non-response	Response	13/29 (45%)	Non-response	Response	14/30 (47%)
Response	Non-response	0/29 (0.0%)	Response	Non-response	0/30 (0.0%)
Non-response	Non-response	3/29 (10%)	Non-response	Non-response	3/30 (10%)
p-value[a]		<0.001	*p*-value[a]		<0.001

ITT=intent-to-treat, PP=per protocol, SoC=standard of care
Note: Post-dose samples are excluded from the analysis. [a]exact p-value obtained from a McNemar's test

Study B22CS measured blood bicarbonate levels in patients taking ADV7103 in the longer-term. Within months 3 to 48, the percentage of patients with blood bicarbonate levels in the normal range was from 60.9% to 92.3% (Table 16) (CS, Section B.2.6). Most of the low bicarbonate levels were mild. One case was considered linked to low compliance, and two to reduced doses of ADV7103 (CS, Section B.2.6). There were ten recordings considered clinically significant bicarbonataemia in Study B22CS (CS, Section B.2.6).

Table 16: Study B22CS - bicarbonataemia status by visit (blood test prior to ADV7103 intake) (reproduced from CS, Table 44)

Analysis Visit	n	Low n (%)	Normal n (%)	High n (%)
Baseline	25	11 (44.0)	13 (52.0)	1 (4.0)
Month 3	23	2 (8.7)	21 (91.3)	0
Month 6	19	7 (36.8)	12 (63.2)	0
Month 12	18	4 (22.2)	14 (77.8)	0
Month 18	19	3 (15.8)	16 (84.2)	0
Month 24	23	8 (34.8)	14 (60.9)	1 (4.3)
Month 36	22	4 (18.2)	18 (81.8)	0
Month 48	19	6 (31.6)	13 (68.4)	0

Potassium level in the blood

For the Study B21CS ITT population, the majority of patients, n=22/29 (76%), had normalised potassium (that is, they did not present with hypokalaemia (below 3.5 mmol/L) after 4 to 5 days of treatment) for both the SoC treatment (SPI) and ADV7103 treatment (SPIII) (CS, Section B.2.6) (clarification response, question A15). Some patients were hypokalaemic with one treatment but not the other, and this was the same percentage of patients (n=2/29, 6.9%) for being either hypokalaemic on SoC but not ADV7103, or being hypokalaemic on ADV7103 but not SoC. The rest of the patients 3/29 (10%) were hypokalaemic for both the SoC treatment (SPI) and treatment with ADV7103 (SPIII) (CS, Section B.2.6).

At baseline in Study B22CS, 16/19 (84.2%) patients had normal plasma potassium levels. Throughout Study B22CS, most patients had normalised plasma potassium across the 3-monthly visits for the 24 months on ADV7103 (as assessed in 19-23 patients with pre-dose measurements) (CS, Section B.2.6). Only one patient (4.3%) had hypokalaemia which was considered to be clinically significant (CS, Section B.2.6).

Citrate level in the urine

For Study B21CS, hypocitraturia was defined as at least one value of UCi/UCr (urinary ratio of citrate/creatinine) inferior to the age-specific lower normal limit on day 4 or day 5 during treatment with either SoC (SPI) or ADV7103 (SPIII) (CS, Section B.2.6).

For the B21CS ITT population, data were provided for 17 patients. All 17 patients experienced hypocitraturia during either one or both study periods. Nine (53%) of 17 patients had hypocitraturia during both treatments. Seven patients (41%) had hypocitraturia during treatment with SoC but not ADV7103. One patient (5.9%) had hypocitraturia during treatment with ADV7103 but not SoC (CS, Section B.2.6). There was no statistically significant difference between SPI and SPII, p=0.070 for the

ITT population n=17 (p=0.125 for the PP set, n=16) (CS Section B.2.6) although the midpoint favoured ADV7103 treatment.

For Study B22CS, 13 patients (65.0%) had hypocitraturia at baseline. Between month 3 and month 48, the percentage of patients with hypocitraturia ranged from 47.4% (9/19) to 80.0% (16/20) (CS, Section B.2.6).

Calcium level in the urine

For Study B21CS, hypercalciuria was defined as at least one value of UCa/UCr (urinary ratio of calcium/creatinine) superior to the age-specific upper normal limit on day 4 or day 5 of SPI or SPIII (CS, Section B.2.6).

For the Study B21CS ITT population, three patients presented with hypercalciuria: n=1/30 (3.3%) after SoC (SPI), n=1/30 (3.3%) after ADV7103 (SPIII), and n=1/30 (3.3%) after both treatments (SPI and SPIII) (no statistically significant differences between treatments, p=1.0) (CS, Section B.2.6).

A *post hoc* analysis in Study B21CS (in the "ITT" set, n=20 patients) of (urine calcium/citrate (UCa/UCi) ratio) above the risk threshold for lithogenesis (>3 mmol/mmol) after 4 to 5 days of treatment, suggested that there were more patients above the risk threshold on SoC but not ADV7103 (9/20 (45%), than above the risk threshold on ADV7103 but not SoC (1/20 (5.0%) (p=0.021). There were 7/20 patients (35%) above the risk threshold for lithogenesis on both treatments (CS, Section B.2.6).

For Study B22CS, at baseline 27/27 (100%) patients had normal range UCa/UCr (CS, Section B.2.6). Throughout B22CS, most patients (84.6%-96.3%) had normal range UCa/UCr across the 3-monthly visits for the 24 months on ADV7103 (as assessed in 26-29 patients) (CS, Section B.2.6).

For B22CS, the percentage of patients above the UCa/UCi risk threshold for lithogenesis ranged from 36.8% to 70.0% across the 24 months (CS, Section B.2.6). Clinical advice provided to the ERG suggests that this is better than would be expected with SoC.

Nephrocalcinosis and nephrolithiasis

At baseline in Study B22CS, 86.2% patients had nephrocalcinosis, and at month 48, 90.9% patients had nephrocalcinosis (Table 17). For Study B22CS, at baseline 20.7% patients had nephrolithiasis (renal stones), and at month 48, 31.8% had nephrolithiasis (Table 17). Clinical advice provided to the ERG suggests that longer follow-up would be required to assess that effect on nephrocalcinosis which tends to improve or improve over years rather than weeks.

One child had renal stones only at baseline in B22CS (CS, Section B.2.6). Five patients had nephrolithiasis at baseline, that recurred throughout follow-up. Nine other patients did not have nephrolithiasis at baseline but did during follow-up (of which six patients had one event, and three patients had recurrent events).[15] [redacted]

Table 17: Study B22CS - nephrocalcinosis and nephrolithiasis (adapted from CS, Tables 56 and 57)

Analysis Visit	Nephrocalcinosis		Nephrolithiasis	
Baseline, n(%)	n	29	n	29
	No	4 (13.8)	No	23 (79.3)
	Yes	25 (86.2)	Yes	6 (20.7)
Month 24, n(%)	n	29	n	29
	No	1 (3.4)	No	24 (82.8)
	Yes	28 (96.6)	Yes	5 (17.2)
Month 36, n(%)	n	26	n	26
	No	2 (7.7)	No	19 (73.1)
	Yes	24 (92.3)	Yes	7 (26.9)
Month 48, n(%)	n	22	n	22
	No	2 (9.1)	No	15 (68.2)
	Yes	20 (90.9)	Yes	7 (31.8)

Renal function

Study B22CS measured eGFR. For the overall population (n=27) there was a mean (SD) change from baseline in eGFR of -6.8 (28.5) from baseline to month 48 (CS, Section B.2.6). At month 48, the mean (SD) eGFR was 118.3 (23.0) (CS, Section B.2.6).

Throughout Study B22CS follow-up, there were no recorded cases of a moderate/severe decrease in eGFR (according to KDIGO 2013[38]) (CS, Section B.2.6). Mild decreased eGFR was present in 4.3% patients at baseline; and throughout months 3 to 48, ranged from 3.4% to 13.3% (CS, Section B.2.6).

Measures of impaired growth

For Study B22CS, most patients were in the two standard deviations range for height and weight throughout study follow-up (CS, Section B.2.6).

For Study B22CS, most patients had a normal estimated adult stature, including 100% of adults and infants (CS, Section B.2.6). For the adolescent subset (aged 12-18; n=8), one patient had high estimated adult stature from baseline to month 24, and all others had normal estimated adult stature throughout follow-up. For the child subset (aged 4-12; n=13), five patients had below normal estimated adult stature at baseline, and two at month 48.

Bone mineral density

Study B22CS measured the Z-score of the bone mineral density of the spine. Defining normal as ≤-2.0 according to International Society for Clinical Densitometry criterion,[39] most patients were within the normal range. There were low values reported for 7/25 (28%) at baseline, 4/27 (14.8%) at month 12 and 3/21 (14.3%) at month 24 (CS, Section B.2.6). Clinical advice provided to the ERG suggests that the trend in improvement of bone mineral density was as expected.

During Study B22CS follow-up, of the six adults, none had osteomalacia at baseline or 24 months (CS, Section B.2.6). Of three infants, one infant had rickets at baseline, but no infants had rickets at 24 months or 48 months (CS, Section B.2.6). At baseline, no adolescents (0/8) or children (0/13) had rickets, and at month 48 one adolescent (1/6 providing data, 16.7%), and one child (1/9 providing data, 11.1%) had rickets (CS, Section B.2.6).

HRQoL

HRQoL was measured in Study B22CS, but not Study B21CS. The analysis population in Study B22CS comprised patients who had at least one dose of study drug, and at least one treatment acceptability or HRQoL assessment.[15]

HRQoL was measured by VAS 0-100mm, rated by patients and/or parents depending on patient age. Baseline HRQoL was not recorded. Mean HRQoL (Table 18) was high at month 6 of Study B22CS, mean 80.7 (SD 20.7), and also at month 24, mean 88.9 (SD 18.9) (CS, Section B.2.6).

All Study B22CS patients had inherited dRTA. According to clinical advice received by the ERG, patients with acquired dRTA have lower utility than people with other forms of dRTA as they have additional conditions/co-morbidities from the condition causing secondary dRTA.

Table 18: Study B22CS - HRQoL at 6 months and 24 months as measured by VAS 0-100mm (adapted from CS, Table 66)

		Overall
HRQoL of the patient	**Statistics**	**(N=30)**
HRQoL of the patient at M6	N	30
	Mean±SD	80.7±20.7
	SEM	3.8
	Min/Median/Max	25/87.0/100
HRQoL of the patient at M24	N	29
	Mean±SD	88.9±18.9
	SEM	3.5
	Min/Median/Max	23/97.0/100
HRQoL of the patient change M24-M6	N	29
	Mean±SD	7.0±16.3
	SEM	3.0
	Min/Median/Max	-22/7.0/42

Study B22CS measured treatment acceptability by VAS 0-100mm, at month 24 (CS, Section B.2.6).[15] Patients and/or parents were asked to score improvement over previous alkalising treatment in terms of: efficacy; safety; formulation; number of daily doses; taste; and other improvements to be specified by patient.[15] The scales asked the respondent to measure improvement, that is, the lowest score possible would assume equivalence of current and prior treatments. An improvement of 75% or greater was reported by: 21/30 (91.3%) for efficacy; 19/30 (65.5%) for safety; 24/30 (82.8%) for formulation; 25/30 (86.2%) for number of daily doses; and 17/30 (58.6%) for taste (CS, Section B.2.6).

3.2.3 Adverse events

The safety population of Study B21CS comprised: 37 patients for SPI (SoC treatment); 34 patients for SPII (ADV7103 titration); and 32 patients for SPIII (ADV7103 treatment) (CS, Section B.2.10).

The safety population of Study B22CS comprised 30 patients for months 1 to 18, 29 patients for months 18 to 36, and 27 patients for months 36 to 48 (CS, Section B.2.10).

Table 19: Number of patients with at least one AE (adapted from CS, Tables 74 and 77, and Section B.2.10)

	B21CS SPI SoC steady state	B21CS SPII ADV7103 titration	B21CS SPIII ADV7103 steady state	B22CS ADV7103 long-term
Sample size	**N=37**	**N=34**	**N=32**	**N=30**
Duration	5 days	Median 10 days (range 4-25 days)	5 days	Up to 48 months
Overall all-cause AEs, n(%)	7 (18.9%)	19 (55.9%)	6 (18.8%)	27 (90.0%)
AEs considered treatment-related, n(%)	4 (10.8%)	9 (26.5%)	1 (3.1%)	5 (16.7%)
Severe AEs, n(%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	3 (10.0%)
Severe AEs considered treatment-related, n(%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)
Serious adverse events any cause	0 (0.0%)	1 (2.9%)	0 (0.0%)	10 (33.3%)
SAEs considered treatment-related, n(%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
All-cause AEs leading to discontinuation or interruption n(%)	0 (0.0%)	0 (0.0%) discontinuation [n=2 treatment interruption]	0 (0.0%)	2 (6.7%) (temporary discontinuation of 3-7days) [n=0 permanent discontinuation]

There were no AEs leading to death during Study B221CS or Study B22CS (CS, Section B.2.10). There were no AEs leading to permanent discontinuation of ADV7103 during Study B221CS or Study B22CS (CS, Section B.2.10). ADV7103 treatment was interrupted during SPII of Study B21CS for two patients (one due to acute gastroenteritis, one due to vomiting) (CS, Section B.2.3), and during Study B22CS for two patients (three occasions, associated with eight AEs) (CS, Section B.2.10).

Throughout Study B21CS, AEs were experienced by 24/37 (64.9%) patients (CS, Section B.2.10). There was a higher rate of AEs during the titration period SPII (19 of 34 patients [55.9%]), than for the other study periods, Rates of AEs for the 5-day study periods of Study B21CS were: SPI (SoC) 7/37 (18.9%); and SPIII (ADV7103) 6/32 (18.8%) (Table 19).

For SPII in Study B21CS (the ADV7103 titration phase), the most frequently experienced type of AE was gastrointestinal disorders, which occurred in 13 of 34 patients (38.2%). Other classes of AE

experienced during SPII were: nervous system disorders 7/34 (20.6%); general disorders and administration site conditions 6/34 (17.6%) and infections and infestations 2/34 (5.9%).

Gastrointestinal disorders were the most common type of AE for SPI (SoC treatment); these occurred in 5 of 37 patients (13.5%). Two patients (5.4%) experienced headache during SPI. For SPIII (ADV7103 treatment), classes of AE were: gastrointestinal disorders 1/32 (3.1%); general disorders and administration site conditions 2/32 (6.3%); nervous system disorders 2/32 (6.3%); and infections and infestations 1/32 (3.1%).

Severe AEs were defined as those requiring systemic drug therapy or other treatment; causing a significant impairment of functioning, interrupting usual activity, usually incapacitating (CS and clarification response, question A22). Serious AEs were defined as meeting one of the following conditions: death; life-threatening event; requiring inpatient hospitalisation or prolongation of existing hospitalisation; congenital anomaly or birth defect; persistent or significant disability/incapacity; or other medical condition of major clinical significance (CS and clarification response, question A22). The only severe/serious AEs reported for Study B21CS were during SPII (ADV7103 titration) and were in adolescents (age 12-17 years). One patient (2.9%) experienced two severe AEs (one of which was possibly related to study treatment), and one patient (2.9%) experienced a serious AE (considered unrelated to study treatment) (CS, Section B.2.10).

Throughout 48 months of the ADV7103 OLE Study B22CS (Table 19), AEs were experienced by 27 of 30 patients (90.0%) (CS, Section B.2.10). For Study B22CS, the most frequently experienced types of AE were: metabolism and nutrition disorders 18/30 (60.0%) and gastrointestinal disorders 16 (53.3%). Other classes of AE experienced during Study B22CS were: infections and infestations 11/30 (36.7%); musculoskeletal and connective tissue disorders 9/30 (30.0%); renal and urinary disorders 9/30 (30.0%); nervous system disorders 6/30 (20.0%); skin and subcutaneous tissue disorders 6/30 (20.0%); general disorders and administration site conditions 2/30 (6.7%) (CS, Section B.2.10).[15]

Three patients in Study B22CS experienced severe AEs, none of which were considered related to ADV7103. Ten patients (33.3%) in Study B22CS experienced serious AEs, none of which were considered related to ADV7103 (CS, Section B.2.10).

Five patients (16.7%) experienced AEs considered related to ADV7103, all of which were gastrointestinal disorders of mild/moderate severity (CS, Section B.2.10).

The Summary of Product Characteristics (SmPC)[40] lists for ADV7103: "*Gastrointestinal disorders: abdominal pain as very common*" (occurring in one or more patient per ten treated); "*abdominal pain*

upper, diarrhoea, dyspepsia, gastrointestinal disorder, gastrointestinal pain, nausea and vomiting as common" (occurring in one or more patients per 100 treated, but less than one in ten). The SmPC clarifies that these gastrointestinal disorders were generally of mild, or moderate, intensity.[40]

3.3 Critique of the indirect comparison and/or network meta-analysis

The company did not undertake any indirect or network meta-analysis that was used within the modelling. A naïve indirect comparison was provided showing that bicarbonate levels were significantly higher in patients who had treatment with ADV7103 compared with historic untreated patients. The ERG comments that these data would be confounded if patients on SoC had higher bicarbonate levels than untreated patients.

3.4 Additional work on clinical effectiveness undertaken by the ERG

No additional work was undertaken by the ERG.

3.5 Conclusions of the clinical effectiveness section

The ERG does not believe that any published RCTs relevant to the decision problem that could have provided effectiveness data have been omitted from the CS. The key evidence for clinical effectiveness within the CS comprised two open-label studies of ADV7103 in dRTA patients: Study B21CS; and Study B22CS.

With dRTA being rare, sample sizes were small. Study B21CS was a sequential study, which compared each patient on five days of patient's prior SoC (n=35) with five days on optimised ADV7103 treatment (n=32), with optimal ADV7103 dose decided by a titration period. Study B22CS was a single-arm extension with 30 patients taking ADV7103. Study populations were considered by clinical advice provided to the ERG to be representative of UK population eligible for treatment with ADV7103.

Despite the small sample size, Study B21CS was statistically powered to detect non-inferiority of ADV7103 compared to SoC in the primary outcome of bicarbonataemia. Bicarbonataemia is a surrogate outcome measure; however, clinical advice provided to the ERG suggests it is a reasonable surrogate for long-term complications of dRTA. In the PP set, mean (SD) blood bicarbonate levels were 21.7 (3.06) mmol/L with SoC (n=29) and 23.1 (1.62) mmol/L with ADV7103 (n=30). Non-inferiority of ADV7103 vs. SoC was demonstrated, mean difference (SD) 1.4195 (2.647), $p<0.0001$. There was a significant difference between SoC and ADV7103 treatment periods in superiority analysis in both the PP ($p=0.0037$) and ITT sets ($p=0.0008$). Within months 3 to 48 of B22CS, the percentage of patients with blood bicarbonate levels in the normal range was from 60.9% to 92.3%.

During B21CS, compliance was high for both SoC (91.9%) and optimised ADV7103 treatment (96.9%) across the five days of treatment. During Study B22CS, compliance to ADV7103 was reported as ≥75

% for n=28/30 (93.3%) at month 3, and n=23/29 (79.3%) at month 24. According to clinical advice received by the ERG, compliance during studies is generally greater than compliance in real world clinical practice.

For B21CS, there were similar AE rates and types for five days SoC (7/37, 18.9%) compared with five days on optimised ADV7103 treatment (6/32, 18.8%). For 48 months of ADV7103, in Study B22CS, AEs were experienced by 27/30 (90.0%) patients. The most frequently experienced types of AE were: metabolism and nutrition disorders 60.0% and gastrointestinal disorders 53.3%. Most AEs were of mild, or moderate, intensity.

4 COST EFFECTIVENESS

The company undertook an SLR to identify relevant cost-effectiveness studies from published literature and a pragmatic review to identify evidence from previous NICE Technology Appraisals.

4.1 Company's review of published cost-effectiveness studies

4.1.1 Company's search objective and methods

The company performed a three-in-one systematic literature search in August 2021 (CS, Appendix 2.3 Identification and selection of relevant studies) for: (i) published cost-effectiveness studies of patients dRTA; (ii) HRQoL studies and (iii) cost and resource use studies.

The following sources were searched: MEDLINE [via Embase.com], MEDLINE in Process [via PubMed.com], EMBASE [via Embase.com], Cochrane Central Register of Controlled Trials [via Wiley] and NHS Economic Evaluation Database [via CRD]. The ERG does not have access to MEDLINE or Embase via the Embase.com host platform. The company hand-searched several key conference abstract websites in the last three years (dates unreported): SEN; Congress of the International Paediatric Nephrology Association; and ISPOR. The company did not report on the search terms and results in the conference website sources.

The search terms for the 'distal renal tubular acidosis' population only was considered comprehensive by the ERG and the concept combinations in the strategies are correct. The ERG has reviewed both the cost-effectiveness (combined with resource allocation terms) and the quality-of-life search filters and considers these to be comprehensive in the MEDLINE and Embase search. Study design filters were not applied in MEDLINE-in-process database, CENTRAL or NHS EED. The limitation of applying English language limits to the search, which have been described previously in Section 3.1.1, also apply to these searches.

The company states in Appendix D of the CS that '*for the purposes of the HTA submission further targeted searching of the literature was required to source utility and disutility values associated with each health state and to confirm some of the transition values not available from clinical trial data or dRTA specific literature from this SLR. These values were verified with a dRTA health care professional.*' The search strategies for targeted searches were not provided by the company.

4.1.2 Eligibility criteria for the company's review of published economic evaluations

The inclusion criteria for studies are presented in CS Appendix D. The ERG considers the inclusion criteria to be appropriate to capture recent and relevant evidence related directly to dRTA.

4.1.3 Findings of the cost effectiveness review

The company's SLR identified 20 studies reported across 33 publications. None of these publications described a cost-effectiveness analysis of treatments for patients with dRTA.

A broader search to identify published economic models within CKD identified a systematic literature review[41] that was undertaken to inform the design of future conceptual models for economic evaluations of interventions for people with CKD. This paper reported that the majority of CKD models were Markov models and that many did not consider patient heterogeneity. Within the CKD models, eGFR was typically utilised as a key prognostic factor.

4.1.4 Conclusions of the cost effectiveness review

Due to the limited evidence identified by the searches, the company decided to build a *de novo* model, as detailed in Section 4.2 of this report. The ERG agrees that constructing a new model is appropriate.

4.2 Description of company's health economic analysis

4.2.1 Model overview

The company submitted a revised model in response to clarification questions, which addressed many limitations identified by the ERG in its initial inspection of both the CS and the mathematical model. The ERG's critique focusses only on the company's model provided post-clarification. All analyses presented incorporate the agreed PAS.

The model evaluates the use of ADV7103 for the treatment of dRTA compared with SoC in four different population of patients conditional on age at diagnosis. These were infants (aged between 1 year and 3 years), children (aged between 4 and 11 years), adolescents (aged between 12 and 17 years) and adults (aged 18 years and over). Cost-effectiveness is measured in terms of incremental cost-effectiveness ratios (ICERs) which are expressed in terms of the incremental cost per QALY gained. In addition to providing ICERs for each age group, the company also provides a weighted ICER for all patients assuming that 8.82% are infants, 23.53% are children, 17.65% are adolescents and 50.00% are adults. The company's economic analysis adopts an NHS and Personal Social Services (PSS) perspective and considers costs and health outcomes over a 75-year (lifetime) horizon. The model uses a state transition approach with the following health states: without nephrocalcinosis; with nephrocalcinosis; nephrocalcinosis in combination with nephrolithiasis; chronic kidney disease stage 2 (CKD2); chronic kidney disease stages 3 and 4 combined (CKD3-4); ESKD; kidney transplant; and death. Treatment status is also modelled with patients being on treatment (either ADV7103 or SoC) or assumed to have discontinued treatment. Treatment status influences the likelihood of disease control, with patients on treatment characterised as either having controlled disease (responders) or uncontrolled disease (non-responders), whilst patient not on treatment are assumed to be non-responders. Disease

control status affects the probability of disease-progression, with non-responders having a worse prognosis than responders. Patients who have discontinued treatment have the worst prognoses as only this group are modelled to progress to ESKD.

4.2.2 Model structure

The company's model structure (Figure 19 of the CS) is reproduced in Figure 4. Each of the four age groups are modelled separately and each has a lifetime horizon. The progression of patients has been appropriately modelled so that infants will progress to being children, adolescents and adults when calculating the ICER for infants. The model uses six-month time cycles for the first two years with one-year time cycles used subsequently; half cycle correction is included. Both costs and QALYs were discounted at 3.5% per annum as recommended by NICE with costs inflated to 2019/2020 values using Personal Social Services Research Unit inflation indices.[42]

Patients enter the model in one of three states (without nephrocalcinosis, with nephrocalcinosis, or with both nephrocalcinosis and nephrolithiasis), all of which are associated with chronic kidney disease stage 1. All patients are assumed to be on treatment, with one cohort receiving treatment with ADV7103 and one cohort receiving treatment with SoC. Patients are allocated into responders and non-responders, based on disease control. Through the course of the model, patients on ADV7103 and SoC can move between the responder and non-responder categories, whilst they remain on treatment.

Responder status influences the transition probability between the following health states: without nephrocalcinosis; with nephrocalcinosis; with both nephrocalcinosis and nephrolithiasis; progression of disease to CKD2 and progression of disease to CKD3-4. Patients responding to treatment are assumed never to transition to CKD3-4, whilst patients who are not responding to treatment, but who remain on treatment, cannot progress beyond CKD3-4.

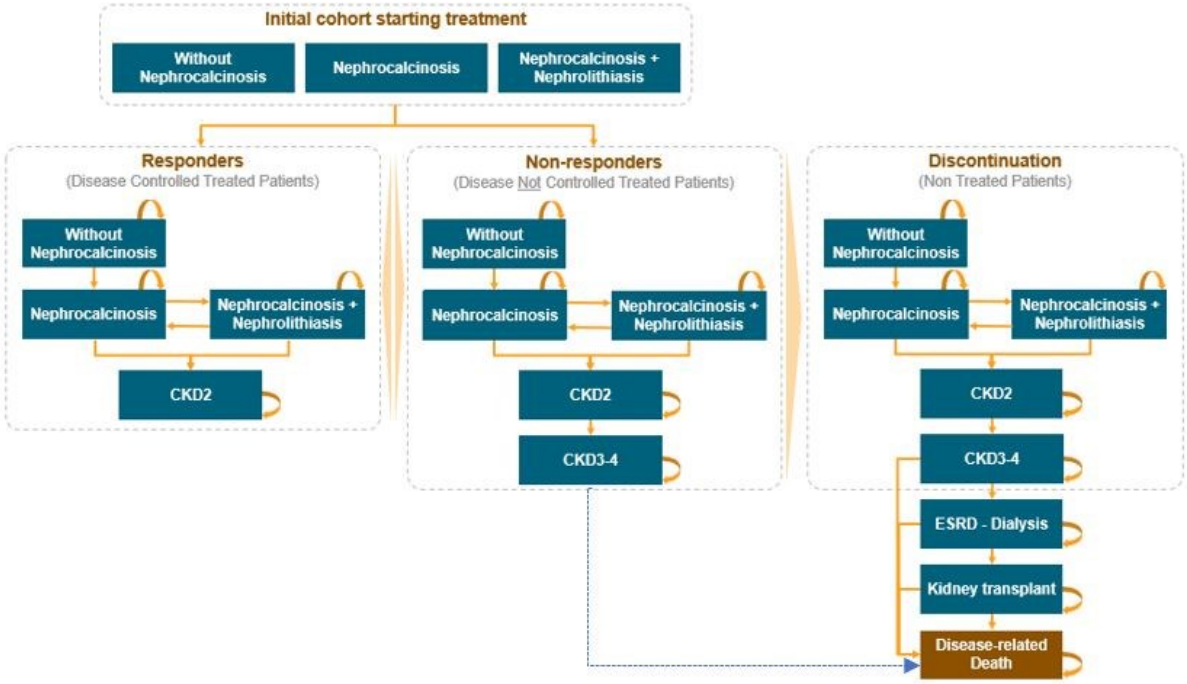
A limitation is that patients who receive no treatment are assumed never to restart active treatment (either with SoC or ADV7103).

The model assumes that patients who receive no treatment can experience more severe kidney-related disease, than patients remaining on treatment, potentially progressing to ESKD and dialysis, and kidney transplant.

The model assumes that disease-related death can happen from CKD3-4, ESKD, and kidney transplantation; the ERG has amended the company's model structure diagram to show that disease-related death is possible from the non-responder health state, as confirmed in the company's

clarification response (question B10).[43] Death from other causes can occur at any point within the model from any health state/treatment status combination.

Figure 4: Company's model structure (adapted to show disease-related death from CKD3-4)



The model also simulates transitory health events. These include fracture, failure to thrive, osteomalacia (for adult patients) and rickets (for children), gastrointestinal events and hypokalaemia, all of which are associated with QALY decrements and costs. Failure to thrive can only occur as an event in patients aged less than 15 years.

In addition, patients starting the model as adults are assumed to have acquired dRTA which is associated with a persistent QALY losses, per cycle, if patients were non-responders or have discontinued treatment. This assumption does not match the characteristics of patients in the key studies as no patients in Study B22CS had acquired dRTA, and only 1 patient had acquired dRTA in Study B21CS.

Although the model is comprised of four distinct age groups, the company presented an overall weighted ICER as its base case, which assumed that the proportions of the total population were: infants (8.8%); children (23.5%); adolescents (17.6%); and adults (50%). The split of patients amongst the group appears from the CS to have been informed by clinical opinion and Clinical Practice Research Datalink data published in Bianic *et al*.[44]

4.2.3 Evidence used to inform the company's model parameters

The evidence used to inform the company's model is described in Section 4.2.3.1 through to Section 4.2.3.8. The ERG noted that there is considerable reliance on clinical opinion which was obtained using Delphi panels. The methods used were detailed in response to clarification questions A5 and B5.[43]

The ERG notes that the evidence required to populate the model which considers the long-term prognoses of patients has not been shown in the CS to be systematically captured. For example, no Preferred Reporting Items for Systematic reviews and Meta-Analysis diagrams were provided and the criteria for choosing particular sources to populate model parameters has not been provided. As such, the estimates used in the company's base case model are subject to considerable uncertainty.

4.2.3.1 Patient ages and weights at model entry

The mean age and weight assumed for each of the four modelled age groups is shown in Table 20. Mean age was taken as the midpoint for each age band, although the ERG notes that this was not accurately calculated for children (age group from 4 to 11 years) which should be 7.50 years rather than 8 years. The mean weight for adults was assumed to be constant throughout the time horizon of the model. No systematic or targeted review appeared to have been undertaken to estimate the studies used to estimate the mean weight, as such, these values may not be the best estimates, although any error may not make a material difference to the ICERs.

Table 20: Initial patient characteristics

Patient group	Mean Age	Mean Weight (kg)	Source for weight
Infants	2	12.78	So *et al*.[45]
Children	8	32.00	Tinning and Acworth[46]
Adolescents	15	59.70	Calculated from data in Tinning and Acworth[46]
Adults	25	70.80	Walpole *et al*.[47]

4.2.3.2 Health states on model entry

The initial health states of patients in the model are presented in Table 21 based on data from Study B21CS. The company has grouped infants, children and adolescents together, where it is assumed that

a small proportion of patients do not have nephrocalcinosis. In contrast, all adult patients are assumed to start with nephrocalcinosis, some of whom also have nephrolithiasis.

Table 21: Initial health state for patients in the model

Patient group	Without nephrocalcinosis	Nephrocalcinosis	Nephrocalcinosis + nephrolithiasis
Infants/children/adolescents	6.66%	86.67%	6.67%
Adults	0.00%	85.71%	14.29%

4.2.3.3 Disease control on model entry

A patient was classified as a responder or non-responder based on disease control. Patients with bicarbonate values within the normal range for an age- and sex-matched population were classified as a responder. The remainder, those patients with bicarbonate values outside of the normal range for bicarbonataemia, were classified as non-responders. The data informing this parameter came from B21CS.

Contrary to standard health economic models, the company's model does not begin with identical cohorts in both arms of the model, but assumes that more people have controlled disease (90%) in the ADV7103-treated arm than in the SoC-treated arm (43%). In response to clarification question B11,[43] the company stated that no initial cycle was included due to the short period of time of the initial response (5 days). The ERG has adjusted the results from the company's model to attempt to redress the limitation of the company's assumption of different profiles of disease control by treatment on model entry.

The ERG highlights that the values used in the company's model appear erroneous assuming that disease control is defined on the mean bicarbonataemia values across Days 2-4, as the value for SoC should be 43.33% as reported in Bertholet-Thomas *et al*.[16] rather than 43.00%. Additionally, the choice of this definition rather than requiring patients to have normal bicarbonataemia on all of the three days was not justified.

Further, the transition probabilities associated with maintaining disease control or regaining disease control (Sections 4.2.3.4.1 and 4.2.3.4.2) imply a different proportion of responders at the beginning of the model than the 90% and 43% used by the company. The proportion of patients maintaining disease control between 0 and 6 months was 16/19 and those regaining disease control in this period was 7/11 which suggests that 19/30 (63.33%) of patients had controlled disease at Month 0 which appear incompatible with the values presented in Table 14 and Table 15.

4.2.3.4 Transition probabilities between the health states

Where possible the company used patient-level data from the B21CS and the B22CS studies to inform transition probabilities. However, given that patients only had five days of SoC treatment in B21CS and that some variables appeared not to be collected in these studies, there needed to be a large number of assumptions made. The transition probabilities and the methods/sources used to derive these are detailed in Section 4.2.3.4.1 to 4.2.3.4.10. A summary table, adapted from Table 90 in the CS taking into account changes made in the clarification process, is provided in Table 22.

Table 22: Summary of annual transition probabilities between model health states

Transition from:	Transition to	Responders on treatment (ADV7103 or SoC)	Source	Non-responders on treatment (ADV7103 or SoC)	Source	Patients on no treatment	Source
w/NC	NC	12.56%	Clinical opinion	25.13%	Palazzo *et al*.[5]	90.00%	Clinical opinion
NC	NC+NL	4.66%	Clinical opinion	9.23%	Lopez-García *et al*.[6]	40.00%	Clinical opinion
NC+NL	NC	20.00%	Clinical opinion	20.00%	Clinical opinion	20.00%	Clinical opinion
NC	CKD2	3.82%	Clinical opinion	4.27%	Lopez-García *et al*.[6] and Excel Solver	7.69%	Clinical opinion
NC+NL	CKD2	3.82%	Clinical opinion	4.27%	Lopez-García *et al*.[6] and Excel Solver	7.69%	Clinical opinion
CKD2	CKD3-4	n/a	Clinical opinion	3.00%	Clinical opinion	7.80%	Clinical opinion
CKD3-4	ESKD	n/a	Clinical opinion	3.00%	Clinical opinion	7.80%	Clinical opinion
ESKD	Transplant	n/a	Clinical opinion	n/a	Not appropriate	5.50%	Sugrue *et al.*[41]

CKD: chronic kidney disease; ESKD: end-stage kidney disease; n/a: not allowed; NC: nephrocalcinosis; NL: nephrolithiasis; w/NC: without nephrocalcinosis

4.2.3.4.1 Probability of remaining with controlled disease

As stated in Section 4.2.3.3, the model assumes at entry, 90% of patients receiving ADV7103 have controlled disease (responders) compared with 43% of patients receiving SoC. The probability that responders remain with controlled disease and on treatment for patients receiving ADV7103 was estimated using patient-level data from the B21CS and B22CS studies; these values were assumed applicable to all ages. The probabilities of people remaining with controlled disease and on treatment are shown in Table 23. For all cycles after 48 months, the probability for the 36-to-48-month period was used. In order to estimate the values for patients remaining on SoC, the ratio of patients with controlled disease assumed at day 5 between SoC and ADV7103, 0.478 (43%/90%), could be applied to all ADV7103 values; these values are provided in Table 23. The validity of this assumption is not known. The ERG highlights that there is no clear pattern within the ADV7103 data in Table 23, as such the robustness of the 36–48-month data in reflecting the probability for the remaining lifetime of patients in unknown.

Table 23: Probability of remaining a responder on treatment

Time period	Probability – ADV7103	Probability – SoC[†]
0-6 months	0.842 (16/19)	0.402
6-12 months	1.000 (23/23)	0.478
12-18 months	0.920 (23/25)	0.440
18-24 months	0.720 (18/25)	0.344
24-36 months	0.889 (16/18)	0.425
36-48 months	0.818 (18/22)	0.391

[†]Assumed to be the ADV7103 value multiplied by 43/90

For both ADV7103 and SoC, the complements of the values were assumed to be the probabilities that responders became non-responders on treatment. As detailed in Section 4.2.3.4.2, it is possible for patients on treatment to regain disease control whilst remaining on treatment. Patients who move to the uncontrolled disease state are classified as non-responders but do not change their underlying disease state, instead these were assumed to remain in the health state in which they started the cycle.

4.2.3.4.2 Probability of regaining disease controlled.

As can be calculated from Section 4.2.3.3, the company's base case model assumes that at entry, 10% of patients receiving ADV7103 have uncontrolled disease (non-responders) compared with 57% of patients receiving SoC. In the ADV7103 group, the probability that non-responders regain disease control was estimated using patient-level data from the B21CS and B22CS studies. For patients

receiving SoC, clinical opinion suggested that 10% of non-responders would become responders each year. These probabilities are shown in Table 24. For all cycles after 48 months, the probability for the 36-to-48-month period was used. Patients whose disease becomes controlled are assumed to remain in the same health state that they were in during the cycle in which they became a responder.

The ERG noted that in the company's base case model the probabilities for disease recovery in the initial four six-month cycles had used the yearly probabilities erroneously.

Table 24: Probability of regaining disease control on ADV7103 treatment

Time period	Probability of regaining disease control
0-6 months	0.636 (7/11)
6-12 months	0.286 (2/7)
12-18 months	0.400 (2/5)
18-24 months	0.500 (2/4)
24-36 months	0.667 (6/9)
36-48 months	0.400 (2/5)

4.2.3.4.3 Probability of discontinuing treatment

Within the model all responders were assumed to continue with treatment. For patients who were non-responders, the yearly probability of discontinuation for those within states up to CKD2 in severity was assumed conditional on: response status; whether a patient remained on treatment; and on age group (adult or non-adult). For patients on ADV7103, who disease was not controlled, discontinuation rates per year of 0% for non-adults and 3.3% per year for adults were assumed. People discontinuing ADV7103 treatment were assumed to have a 50% chance of receiving SoC, and a 50% chance of assuming no treatment. For SoC-treated patients whose disease was not controlled, based on clinical opinion, it was assumed that 39% of non-responding non-adults and 45% of non-responding adults would discontinue treatment per year; these people would receive no further treatment.

In addition to the discontinuation rates detailed in the previous paragraph patients were assumed to discontinue treatment (either ADV7103 and SoC) noting that patients have to stop ADV7103 treatment when their eGFR reaches a level of 44 ml/min/1.73m^2 or lower. Clinical opinion received by the company suggested that an 20% of patients in the CKD3-4 health state would discontinue per year. Patients assumed to discontinue from the CKD3-4 health state are assumed to have no further treatment. All patients entering the ESKD health state are assumed to discontinue treatment, either ADV7103 or SoC.

4.2.3.4.4 Probability of moving from the without nephrocalcinosis health state to the nephrocalcinosis health state

The annual probability of moving from the without nephrocalcinosis health state to the nephrocalcinosis health state in patients not responding to treatment was assumed to be informed by Palazzo *et al*.[5] which reported data on 89 Italian patients with dRTA in whom next-generation sequencing was applied. The company have assumed that this is a probability of 25.13%; however, the ERG could not find this value in the source paper. For patients with controlled disease, clinical advice to the company suggested the probability for non-responders was half that of non-responders (12.56%). For patients on no treatment, the company assumed that 90% of patients develop nephrocalcinosis every year. The ERG believes that the formulae used to apply this transition probability for those that have discontinued treatment have been incorrectly implemented in the company's economic model referencing irrelevant cells.

4.2.3.4.5 Probability of moving from the nephrocalcinosis health state to the nephrocalcinosis health state with nephrolithiasis

The annual probability of moving from nephrocalcinosis to nephrocalcinosis with nephrolithiasis was sourced from Lopez-Garcia *et al*.[6] In patients not responding to treatment, this value was reported to be 9.23%. For patients with controlled disease this probability was assumed to be halved (to 4.66%) with this reduction based on clinical expert opinion provided to the company. For patients not taking any treatment, the probability per year was assumed to be 40% based on clinical opinion.

4.2.3.4.6 Probability of moving from the nephrocalcinosis health state with nephrolithiasis to the nephrocalcinosis health state

The probability of moving from nephrocalcinosis with nephrolithiasis to nephrocalcinosis was estimated from clinical opinion and was assumed to be 20% per year. It is unclear from the CS whether these values have explicitly considered the assumption in the model that patients with nephrolithiasis have one percutaneous nephrolithotomy each year which may be associated with a loss of nephrolithiasis.

4.2.3.4.7 Probability of moving from the nephrocalcinosis health state, or the nephrocalcinosis with nephrolithiasis health state to CKD2

The annual probability of moving from nephrocalcinosis to CKD2 was calibrated, using the Excel Solver add-in procedure, such that the proportion of patients who are non-responders that move from nephrocalcinosis to CKD2 or to CKD3-4 matched that reported for 11-year-old patients in Lopez-Garcia *et al*.[6] CS Section B.3.3 and the company's clarification response to question B45[43] provide further details on the use of Solver. This calibration resulted in an estimated annual transition probability

from nephrocalcinosis to CKD2 of 4.27% for non-responders. For responders, clinical opinion was used to estimate that 7.5% of patients would develop CKD2 over a 2-year period (3.82% per year). Clinical opinion also suggested that the rate for people who discontinued treatment was twice that of non-responders resulting in a probability of 7.69% per year. The values relating to progressing to CKD2 for nephrocalcinosis were assumed generalisable to patients with nephrocalcinosis and nephrolithiasis. The Excel Solver add-in procedure was not re-run when undertaking sensitivity analyses to recalibrate the probability of moving from the nephrocalcinosis health state, or the nephrocalcinosis with nephrolithiasis health state to CKD2. This could cause inaccuracy in these sensitivity analyses.

4.2.3.4.8 Probability of moving from CKD2 to CKD3-4

The probability of moving from CKD2 to CKD3-4 was estimated from clinical opinion conditional on disease control and whether a patient had discontinued treatment. For those with controlled disease on treatment it was assumed that no-one would progress beyond CKD2; for those with uncontrolled disease on treatment, it was assumed that there was a probability of progressing from CKD2 to CKD3-4 of 3.00% per year; for those not on treatment, clinical opinion suggested that the probability would be 2.6 times that of non-responders, resulting in an annual probability of 7.80%.

4.2.3.4.9 Probability of moving from CKD3-4 to ESKD

The probabilities of moving from CKD3-4 to ESKD was estimated from clinical opinion conditional on disease control and whether a patient had discontinued treatment. For those with controlled disease on treatment it was assumed that no-one would progress beyond CKD3-4; for those with uncontrolled disease on treatment, it was assumed that there was a probability progressing from CKD3-4 to ESKD of 3.00% per year; for those not on treatment, clinical opinion suggested that the probability would be 2.6 times that of non-responders, resulting in an annual probability of 7.80%. It is unclear whether the clinicians deliberately set these transition probabilities to the same as those when moving from CKD2 to CKD3-4 or whether this is a coincidence. The ERG highlights that the review undertaken by Sugrue *et al.*[41] estimated a 7.1% chance of moving from CKD2 to CKD3 each year; the CS provided no explanation whether the values provided to the company by clinical experts were informed by the Sugrue *et al.* review.

4.2.3.4.10 Probability of moving from ESKD to kidney transplant

All patients in the ESKD state were assumed to have discontinued treatment. The annual probability of moving to transplant was taken from Sugrue *et al*.[41] and was estimated to be 5.50% per year.

4.2.3.5 Probabilities of transitory events

The model assumes that transitory events would not occur if a patient's disease is controlled, but that they could occur if a patient has uncontrolled disease whilst on treatment or if they have discontinued treatment. These annual probabilities are provided in Table 25. The ERG has concerns with the derivation of the values used in the model as these could not be found when consulting the cited papers and the company did not provide details on its calculations to allow the ERG to check these. An example of apparent discrepancies is for failure to thrive where the values in Table 5 of Palazzo *et al.*[5] suggest a greater percentage of patients have failure to thrive than the 12.91% used in the model. For Jha *et al*.,[48] the company assumed that the annual probability of osteomalacia and rickets was equal to the reported prevalence estimates for both conditions, which may be incorrect.

Table 25: Probability of transitory events for patients with uncontrolled disease or patients not taking treatment

	Uncontrolled disease on treatment		Discontinued treatment	
Time period	**Annual probability (%)**	**Source**	**Annual probability (%)**	**Source**
Hypokalaemia	9.39	Clinical opinion	72.00	Clinical opinion
Failure to thrive	12.91	Palazzo *et al*.[5]	12.91	Palazzo *et al*.[5]
Fracture	0.17	Zhang *et al*.[49]	0.34	Clinical opinion
Osteomalacia	9.62	Jha *et al*.[48]	19.23	Clinical opinion
Rickets	59.09	Jha *et al*.[48]	80.00	Clinical opinion

4.2.3.6 Probability of mortality

Life expectancy tables reported for the UK in 2019[50] were used to estimate the background risk of mortality. Some health states, or transitory events were assumed to be associated with increased risk of death. These are summarised in Table 26. For death associated with hypokalaemia, the values are additional risks, such that a patient with ESKD would have a 10.65% risk plus a 5.82% risk if they were hypokalaemic.

Table 26: Probability of death associated with health states and transitory events

Health State / transitory event	Annual probability of death (%)	Source
CKD3-4	4.72	Gibertoni *et al*.[51]
ESKD	10.65	Gibertoni *et al*.[51]
Transplant	5.30	Sugrue *et al*.[41]
Fracture	3.54	Center *et al*.[52]
Hypokalaemia		
Without CKD	0.67	Collins *et al*.[53]
CKD2 and CKD3-4	2.28	Collins *et al*.[53]
ESKD	5.82	Ohnishi *et al*.[54]

No rationale was provided for the selection of the studies used to source these transition probabilities or an assessment of whether the results reported are generalisable to the decision problem. For information, a brief summary of the sources used to populate the risk of death in the model is provided: Gibertoni *et al*.[51] reports estimates of the incidence of COVID-19 and mortality in CKD patients in four nephrology units in Italy; Sugrue *et al*.[41] reported the results of an SLR that was undertaken to inform the design of future conceptual models for economic evaluations of interventions for people with CKD; Center *et al*.[52] was an prospective five-year cohort study of all residents aged 60 years and over in Dubbo, Australia; Collins *et al*.[53] summarises cardiovascular mortality in ESKD; and Ohnishi *et al*.[54] was a cohort study set in Japan estimating the association between post-dialysis hypokalaemia and all-cause mortality in patients undergoing maintenance haemodialysis. The research of Center *et al*.[52] and Collins *et al*.[53] were dated, being published in 1999 and 2003, respectively.

4.2.3.7 Health-related quality of life

In Section B.2.6 of the CS, the company cited patient-reported benefits associated with ADV7103 treatment. Within B22CS, it was reported that quality of life improved in the following aspects: school/work (100%); social/family (94.7%); emotional functioning (63.2%) and physical health (94.7%). From the CS, the number of patients responding for each aspect was not clear. All patients in B22CS declared they were satisfied with ADV7103 treatment, with 14 of 17 patients (82.4%) stating that the treatment either met or was above their expectations.

The results of patient-/parent-reported VAS outcomes were presented for gastrointestinal tolerability; appropriate formulation; convenience of the number of daily doses; long-term treatment acceptability; and the quality of life of patients and parents, with all appearing to favour ADV7103 compared with SoC. However, these potential benefits were not quantified within the company's model with utility

within health states being independent of treatment. The ERG would have liked to have explored the impact on the ICER by applying a chronic utility advantage for ADV7103 over SoC, by allowing patients on SoC to have a worse utility associated with SoC treatment but did not have time within the timelines of the appraisal.

In the company's model, the utility value for patients without nephrocalcinosis was stated to be taken from Ara and Brazier,[55] "*assuming no history of a health condition*", with values ranging from 0.963 for people under 30 years of age to 0.819 for patients greater than 85 years of age. As discussed in Section 4.3.3.2.3, the ERG believes that these values are not appropriate for use in the model.

Utility multipliers are used in the company's model to account for underlying health states and QALY decrements are used for transitory events (including having acquired dRTA) apart from fractures which use a utility multiplier. The midpoint utility multipliers associated with health states are presented in Table 27. As discussed in Section 4.3.3.2.3, the ERG believes that there are considerable limitations in the utility multiplier values used by the company. For information, a brief summary of the sources used to populate the health state utility multipliers is provided: Jesky *et al.*[56] was a UK-based study, where pre-dialysis CKD patients completed an EQ-5D at baseline; Polotti *et al.*[57] aimed to estimate the HRQoL in patients with renal stones and included the EQ-5D questionnaire; Neri *et al.*[58] was a cross-sectional study based in the UK and the US (with results provided separately for each country) aiming to evaluate the relationship between CKD and the EQ-5D; Laupacis *et al.*[59] was a prospective study set in Canada that followed up patients for two years after renal transplant, although this study is dated as it was published in 1996. Further details on the studies, where relevant, are provided in Section 4.3.3.2.3 which describes the alternative utility multipliers preferred by the ERG.

Table 27: Health state utility multipliers used in the company's base case analysis

Health state	Utility multiplier	Source
Without nephrocalcinosis	1.000	assumed
Nephrocalcinosis†	0.907	Jesky *et al.*[56]
Nephrolithiasis	0.880	Polotti *et al.*[57]
Chronic kidney disease stage 2	0.907	Jesky *et al.*[56]
Chronic kidney disease stages 3-4	0.822	Jesky *et al.*[56]
End stage renal disease	0.541	Neri *et al.*[58]
Kidney transplant		
In year of transplant	0.736	Laupacis *et al.*[59]
In each subsequent year	0.736	

† Assumed equal to chronic kidney disease stage 2

The QALY decrements and utility multipliers associated with transitory states and acquired dRTA are provided in Table 28. As discussed in Section 4.3.3.2.3, the ERG believes that there are considerable limitations in the values used by the company For information, a brief summary of the sources used to populate the QALY losses associates with transitory events and acquired dRTA is provided: Kanis *et al.*[60] is a detailed 339-page report of a World Health Organization Scientific Group meeting convened in 2004; NICE published developed a clinical guideline in 2017 on the recognition and management of faltering growth in children;[61] Yanes *et al.*[62] report HRQoL for children and adults with X-linked hypophosphatemia and severe rickets; de Groot *et al.*[63] aimed to characterise HRQoL and its determinants in patients with metastatic renal cell carcinoma; Palaka *et al.*[64] is an abstract estimating the impact of hyperkalaemia on HRQoL in patients with CKD; and Ahlstrom *et al.*[65] was a cross-sectional study set in a tertiary-care facility in Finland which treated patient for acute renal failure (during 1998-2002) with renal replacement therapy and administered the EQ-5D questionnaire. Further details on the studies are provided in Section 4.3.3.2.3 where these are relevant in explaining alternative QALY losses preferred by the ERG.

Table 28: QALY losses associated with transitory events and acquired dRTA

Event	QALY losses	Source
Fracture	0.977ˆ	Kanis *et al.*[60]
Failure To Thrive	0.130	NICE Guidelines[61]
Osteomalacia/rickets	0.352	Yanes *et al.*[62]
Gastrointestinal event	0.001	de Groot *et al.*[63]
Hypokalaemia	0.050	Palaka *et al.*[64]
Acquired distal renal tubular acidosis†	0.180	Ahlstrom *et al.*[65]

ˆ Utility multiplier rather than a QALY loss

† Only for patients starting the model as adults and who have uncontrolled disease

4.2.3.8 Resource use and costs

The following sections detail the drug acquisition costs, drug administration costs, disease management costs, subsequent treatment costs, and the costs associated with managing adverse events used within the model.

4.2.3.8.1 Drug acquisition costs

As stated in Section 2.3.2, the unit cost for ADV7103 including the PAS is [redacted] per mEq. SoC was assumed by the company to consist of a number of different treatments; the proportion of patients receiving each treatment in the B21CS study is presented in Table 29, alongside

the unit cost per mEq as taken from the BNF.[66] Where two products were used in combination the company assumed that an average of the costs of the two individual drugs was applicable. The company states that the mean cost of SoC is £0.1628 per mEq. The ERG comments that the unit cost per mEq for modified Shohl's solution with sodium bicarbonate was not correctly calculated.

Table 29: Percentage of patients in the B21CS study receiving each SoC treatment and the cost per mEq for each SoC treatment used in the company's model

Treatment	Percentage receiving treatment	Unit cost per mEq (p)
1 Product	51.4%	
Potassium bicarbonate	8.1%	3.84
Potassium citrate	21.7%	0.23
Sodium bicarbonate	18.9%	39.80
Modified Shohl's solution	2.7%	7.75
2 Products	48.6%	
Potassium bicarbonate + potassium citrate	8.1%	2.04
Potassium bicarbonate + sodium bicarbonate	13.5%	21.82
Potassium citrate + sodium bicarbonate	24.3%	20.02
Modified Shohl's solution with sodium bicarbonate	2.7%	7.75

The company's model assumes that the dose of ADV7104 and SoC is dependent of the patient's weight. The company has assumed the dose in terms of mEq/Kg/day used in the B21CS study to be generalisable to future usage of ADV7103 and SoC. These dosages are presented in

Table **30** alongside the resulting annual costs. The company used the dosages from B21CS in its base case, although performed sensitivity analyses using the dosages from B22CS.

Table 30: Mean weight of patients, dose and annual cost of ADV7104 and SoC for patients at different ages

Age (years)	Weight (kg)	ADV7103 (B21CS study)		SoC		ADV7103 (B22CS study)	
		Dose (mEq/kg/day)	Annual cost (PAS price)	Dose (mEq/kg/day)	Annual cost	Dose (mEq/kg/day)	Annual cost (PAS price)
1 to 3	12.78	6.11	[redacted]	5.27	£4,005	4.81	[redacted]
4 to 11	32.00	3.80	[redacted]	2.70	£5,138	3.41	[redacted]
12 to 17	59.70	2.79	[redacted]	2.20	£7,810	2.61	[redacted]
18 and above	70.80	1.74	[redacted]	1.99	£8,378	2.26	[redacted]

4.2.3.8.2 Drug administration costs

As both ADV7103 and the comparator drugs are taken orally, the company assumes that there are no costs associated with their administration.

4.2.3.4.3 Disease management costs

The resource use, unit costs and annual costs for both the responders and non-responders are presented in

Table **31**. Annual management costs for each health state, which are assumed independent of treatment are presented in

Table **32**. Sources for the costs shown in

Table **32** are provided in Table 98 of the CS; the ERG is content that any inaccuracies in these values would not materially affect the ICER. The ERG also notes that for nephrolithiasis it is assumed that all patients would have 1 percutaneous nephrolithotomy each year, which may be an overestimate.

The costs associated with transitory events are presented in Table 33. As detailed in Section 4.3.3.2.5, the ERG believes that the costs associated with fracture, faltering growth and osteomalacia/rickets have been implemented incorrectly in the model for the initial two years.

Table 31: Type of resources, frequencies and unit costs for disease management costs used in the model for both responders and non-responders

Resource	Annual frequency of resource use	Unit cost (£)	Annual total (£)
Responders			
Doctor's visit	2.00	180.77	361.54
Blood test	2.00	6.94	13.87
Urine test	2.00	4.41	8.81
CT scan	1.00	106.42	106.42
Ultrasound	0.50	32.50	16.25
DEXA scan	0.10	66.34	6.63
Total			513.53
Non-responders / Those on no treatment			
Doctor's visit	4.00	180.77	723.08
Blood test	4.00	6.94	27.74
Urine test	4.00	4.41	17.63
CT scan	2.00	106.42	212.85
Ultrasound	1.00	32.50	32.50
DEXA scan	0.50	66.34	33.17
Urine infection treatment (adults only)	0.50	2.70	1.35
Total			1,048.32[†]

CT: Computerised tomography; DEXA: Dual energy x-ray.
[†] £1046.97 for non-adults, as they do not receive urine infection treatment

Table 32: Annual health state costs used in the model.

Health state	Annual cost	Source
Responder	£514	See Table **31** **Table 31**
Non-responder / patients who have discontinued treatment	£1048	See Table **31** **Table 31**
Nephrocalcinosis	£1211	Kent *et al*.[68] Inflated using Curtis & Burns[42]
Nephrolithiasis	£6241	2019/20 National Cost Collection.[67] Weighted average of LB75A & LB75B
Chronic kidney disease stage 2	£1211	Kent *et al*.[68] Inflated using Curtis & Burns[42]
Chronic kidney disease stages 3-4	£4422	Kent *et al*.[68] Inflated using Curtis & Burns[42]
End stage renal disease	£32,360	NICE NG107.[69] Inflated using Curtis & Burns[42]
Kidney transplant		
In year of transplant	£14,361	2019/20 National Cost Collection.[67] Weighted average of LA01A, LA01B, LA02A, LA02B, LA03A, LA03B plus weighted average of LA11Z, LA12A, LA12B
In each subsequent year	£5914	NHS blood & transplant fact sheet 7 (reference not provided). Inflated using Curtis & Burns [42]

Table 33: Costs associated with transitory events.

Event	Cost (£)	Source
Cost per year		
Fracture	2126	2019/20 National Cost Collection.[67] Weighted average of HD39D, HD39E, HD39F, HD39G, HD39H
Faltering growth	2089	2019/20 National Cost Collection.[67] Weighted average of PX30A, PX30B, PX30C
Osteomalacia/rickets	3183	Zipitis *et al*. (reference not provided). Inflated using Curtis & Burns[42]
Cost per event		
Gastrointestinal event	148	2019/20 National Cost Collection.[67] WF01A
Hypokalaemia	1,330	2019/20 National Cost Collection.[67] Weighted average of KC05G, KC05H, KC05J, KC05K, KC05L, KC05M, KC05N

4.2.4 Model evaluation methods

The CS presents the ICER for ADV7103 versus SoC. Both deterministic and probabilistic estimates (based on 1,000 iterations) are presented. The distributions used for the PSA undertaken by the company are presented in Table 13 of the company's clarification response, [43] and for brevity are not reproduced here. The results of the PSA are additionally presented as points on a cost-effectiveness plane and as cost-effectiveness acceptability curves (CEACs). The company also presented a range of one-way deterministic sensitivity and scenario analyses to explore the uncertainty in parameters and structural assumptions.

4.2.5 Company's model validation and verification

The CS reports that assumption and parameter values used in the models were validated by clinical experts and that internal model validation was carried out by the same company that produced the model.

4.2.6 Company's cost-effectiveness results

The deterministic estimate of cost-effectiveness for ADV7103 versus SoC presented by the company, incorporating the PAS for ADV7103, is shown in Table 34. The company estimates that for a weighted population, ADV7103 provides [redacted] more QALYs at an additional cost of [redacted] resulting in an ICER of [redacted].

The absolute values for life years, QALYs and costs were not reported in the probabilistic analysis, although the incremental values, were not markedly different from those of the deterministic analysis (incremental QALYs of [redacted] and incremental costs [redacted] resulting in an ICER of [redacted] for the weighted population).

Table 34: Company's deterministic ICER (weighted population)

Description	Life years†	QALYs	Costs	Incremental			ICER
				Life years†	QALYs	Costs	
ADV7104	24.52	[redacted]	[redacted]				
SoC	18.18	[redacted]	[redacted]	6.34	[redacted]	[redacted]	[redacted]

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years
SoC: Standard of Care †Undiscounted (all other values are discounted)

A breakdown of the components of total costs in the deterministic company analysis is presented in Table 35.

Table 35: Components of total discounted costs in the company's base case

Description	ADV7104	SoC	Incremental
Mean cost per patient			
Treatment costs	[redacted]	[redacted]	[redacted]
Management cost	[redacted]	[redacted]	[redacted]
Nephrolithiasis + nephrocalcinosis costs	[redacted]	[redacted]	[redacted]
Chronic kidney disease costs	[redacted]	[redacted]	[redacted]
End stage renal disease costs	[redacted]	[redacted]	[redacted]
Kidney transplant costs	[redacted]	[redacted]	[redacted]
Musculoskeletal costs	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]

Results presented in the company's model are replicated in Figure 5 (the cost-effectiveness plane) and in Figure 6 (the CEAC) with the addition of axis titles which were added by the ERG.

Figure 5: Company's cost-effectiveness plane. ADV7103 versus SoC (weighted population)

[redacted]

Figure 6: Company's CEAC ADV7103 versus SoC (weighted population)

Whilst the summary results presented by the company was for the entire dRTA population, it was possible to extract results individually for each of the four age groups. The results estimated by the company for each age group are shown in Table 36 through to Table 39. An additional analysis, generated by the ERG, using the company's base case assumptions for non-adults (infants/children/adolescents) is shown in Table 40. Non-adults are assumed by the company to have inherited dRTA, and could thus have different results than adult patients who are assumed by the company to have acquired dRTA. It can be seen that the ICERs increase as non-adults age, such that the ICER for infants is lower than the ICER for children, which is lower than the ICER for adolescents. The ICER for adults is smaller than that for adolescents, which the ERG believes is due to the added impact of QALY losses associated with dRTA when patients have uncontrolled disease and the greater dose assumed to be taken by adolescents than adults in the company's base case (see

Table **30**). The company's estimate of the ICER for non-adults is [redacted] and the ICER for adults is [redacted].

Table 36: Company's deterministic ICER (infants)

Description	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
ADV7104	25.79	[redacted]	[redacted]				
SoC	18.48	[redacted]	[redacted]	7.30	[redacted]	[redacted]	[redacted]

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years
SoC: Standard of Care †Undiscounted (all other values are discounted)

Table 37: Company's deterministic ICER (children)

Description	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
ADV7104	25.42	[redacted]	[redacted]				
SoC	18.44	[redacted]	[redacted]	6.98	[redacted]	[redacted]	[redacted]

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years
SoC: Standard of Care †Undiscounted (all other values are discounted)

Table 38: Company's deterministic ICER (adolescents)

Description	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
ADV7104	24.80	[redacted]	[redacted]				

SoC	18.31	[redacted]	[redacted]	6.49	[redacted]	[redacted]	[redacted]

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years
SoC: Standard of Care †Undiscounted (all other values are discounted)

Table 39: Company's deterministic ICER (adults)

Description	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
ADV7104	23.77	[redacted]	[redacted]				
SoC	17.96	[redacted]	[redacted]	5.81	[redacted]	[redacted]	[redacted]

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years
SoC: Standard of Care †Undiscounted (all other values are discounted)

Table 40: Company's deterministic ICER (non-adults)

Description	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
ADV7104	24.52	[redacted]	[redacted]				
SoC	18.18	[redacted]	[redacted]	6.34	[redacted]	[redacted]	[redacted]

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years
SoC: Standard of Care †Undiscounted (all other values are discounted)

4.2.7 Company's deterministic sensitivity analyses

The company undertook deterministic scenario analyses for the full population changing key parameters. The results indicated that the model appeared robust to the changes evaluated. The tornado diagram contained in the model has been reproduced in Figure 7. The ICER was only observed to rise above [redacted] when the discount rate was set to 1.5%. For non-discount rate variables, the bounds were estimated using +/- 20% of the mean value.

Figure 7: Tornado diagram showing the company's DSA

4.2.8 Company's scenario analyses

The company provided scenario analyses in Table 20 of its clarification response. For brevity, these have not been reproduced here. The ERG notes none of the scenarios presented by the company led to an ICER which was greater than £20,000.

4.3 Critical appraisal of the company's health economic analysis

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analyses and the underlying health economic model upon which this was based. These included:

- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the ERG.
- Examination of the correspondence between the description of the model reported in the CS and the company's executable model.
- Replication of the base case results, PSA, DSAs and scenario analyses presented within the CS.
- Where possible, checking of parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic evaluation and the assumptions underpinning the model.

4.3.1 Model verification

On scrutinising the model, the ERG identified a large number of limitations that relate to the structure of the model/conceptualisation of the decision problem, the sources for the parameterisation of the model, the calculation of parameter values from these sources, and the implementation of the intended model. These are discussed fully in Section 4.3.3.

4.3.2 Adherence of the company's model to the NICE Reference Case

The ERG's summary of the adherence of the company's model to the NICE Reference Case is provided in Table 41. The company's economic analysis of ADV7103 treatment for people with dRTA is in line with the NICE Reference Case, although the limitations of the model stated in Section 4.3.1 remain.

Table 41: Adherence of the company's economic analyses to the NICE Reference Case

Element	Reference case	ERG comments (a ✔ denotes the company's analyses are in line with the reference case)
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	✔
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	✔
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	✔
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	✔
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	✔
Perspective on costs	NHS and PSS	✔
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	✔
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	✔
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	✔

4.3.3 Key issues and uncertainties identified within the critical appraisal

The key issues and uncertainties identified in the ERG's critique of the company's model have been divided into two sections to aid readability. The headings are '*conceptual modelling issues and uncertainties*' and '*issues and uncertainties related to the population of the economic model*'. Where the ERG could not address these limitations within the timescale of the appraisal this has been explicitly noted.

4.3.3.1 Conceptual modelling issues and uncertainties

4.3.3.1.1 Patients responding to treatment cannot progress beyond CKD2

Within the model it is considered impossible for patients responding to treatment, either with ADV7103 or SoC, to move to the CKD3-4 health state. Whilst rare, clinical advice suggests that this could occur. The ERG could not amend the model within the timescales of the appraisal and thus this remains a limitation of the model.

4.3.3.1.2 Patients not-responding, but on treatment, cannot progress to ESKD

Within the model it is considered impossible for patients not responding to either ADV7103 or SoC but remaining on treatment, to move to the ESKD health state. Clinical advice suggests that this could occur, but is rare. The ERG could not amend the model within the timescales of the project and thus this has been left as a limitation of the model.

4.3.3.1.3 Patients discontinuing treatment will never restart treatment

Within the model, once patients discontinue treatment it is assumed that this decision is final and that patients will never seek retreatment (with either ADV7103 or SoC) later on in life. Clinical advice suggests that this could happen, although some patients may not resume SoC treatment due to its palatability. The ERG could not amend the model within the timescales of the appraisal and thus it remains a limitation of the model.

4.3.3.1.4 Patients start the model in different health states dependent on initial treatment

In economic evaluations it is good practice to ensure that the cohorts entering the model are identical such that any difference in simulated costs and QALYs are solely due to the different outcomes produced by each treatment option. This was not the case in the company's model. In response to clarification question B11[43] the company declined to amend the model stating that '*The initial response was assessed at day 5, therefore no initial cycle was included for such a short period of time, considering a cycle length of 6 months.*' The ERG does not believe this is an adequate response and has added the cost of an additional 5 days' worth of ADV7103 treatment to approximate the answers that would have been produced if the initial cycle had been included.

4.3.3.1.5 Patients who lose disease control or regain disease control remain in the same health state

In the model, patients who lose disease control are assumed to become a non-responder but remain in the same health state. This creates the possibility that patients who maintain disease control can have their health state worsen, whereas this is not possible for patients who lose disease control. The reverse scenario also exists, where patients regain disease control are assumed not to lose nephrolithiasis, whereas this happens for a proportion of patients with uncontrolled disease. The ERG could not amend the model within the timescales of the appraisal and thus this remains a limitation of the model.

4.3.3.1.6 No chronic utility gain associated with the more convenient dosing regimen of ADV7103 compared to SoC

As discussed in Section 4.2.3.7, the company has provided some data to indicate that ADV7103 could plausibly be associated with a chronic improvement in HRQoL compared with SoC; clinical advice provided to the ERG supports this hypothesis. In the model HRQoL is assumed independent of treatment; therefore, any benefits to the patient are not captured if patients receiving SoC and ADV7103 are in the health states. The ERG has not been able to assess a loss in utility associated with SoC treatment within the timescales of the appraisal.

4.3.3.1.7 The assumption that all adults entering the model had acquired dRTA

The company's model assumed that all patients aged 18 years or over have acquired dRTA, justification for this assumption was not provided in the CS. The ERG comments that no patients in the B22CS study had acquired dRTA and that 1 patient had acquired dRTA in the B21CS study, which is a considerably lower proportion than that assumed in the model. The ERG has not explicitly changed the proportions of patients with acquired dRTA, but has effectively assumed that no patients have acquired dRTA in the exploratory analyses conducted for Section 4.3.3.1.9.

4.3.3.1.8 The assumption that the QALY loss associated with those with acquired dRTA is not incurred when patients have controlled disease

The model assumes that on entry, adult patients have acquired dRTA. The company's response to clarification question B49 states that '*Acquired forms of the disease are usually associated with autoimmune diseases, such as Sjögren's syndrome, systemic lupus erythematosus or autoimmune chronic liver disease.*' In the model this is assumed to be associated with a QALY decrement each year of 0.180 if disease is uncontrolled, but associated with no QALY loss if patients have controlled disease. No evidence was provided relating to why these diseases would have no impact on patients who have controlled disease. On investigating the cited source for the QALY loss, Ahlstrom *et al.,*[65] it appears that the value of 0.180 may be the difference between an age- and sex- matched population and that of patients receiving renal replacement therapy for acute renal failure at a tertiary centre in Finland; it is unclear how generalisable these results are to people with acquired dRTA.

Clinical advice received by the ERG supported the fact that the HRQoL in patients with acquired dRTA would on average be worse than in patients with inherited dRTA. However, the ERG has explored the impact on the ICER of assuming that there is no additional QALY loss associated with acquired dRTA apart from that associated with health states and transitory events.

4.3.3.1.9 Conditions that are chronic in nature have been modelled as transitory health states

Osteomalacia/rickets have been modelled as transitory health states although the QALY loss assumed for this condition has been taken from patients with severe, chronic disease. If the company believes that osteomalacia/rickets will be persistent then a model structure with osteomalacia/rickets defined as health states would have been preferable. The ERG could not amend the model within the timescales of the appraisal; hence, this remains a limitation of the model.

4.3.3.2 Issues and uncertainties related to the population of the economic model

4.3.3.2.1 Lack of systematic reviews to populate the model

The model includes a large number of parameters. It appears that few, if any, systematic literature reviews have been undertaken with the aim of establishing the most appropriate source to use in the model. The model relies substantially on expert clinical opinion and as such, it is not clear to what extent the sources selected or clinical estimates used to populate the model may influence the results of the model. The ERG could not undertake targeted systematic literature reviews within the timescales of the appraisal; hence, this remains a limitation of the model. As such, all results, both those presented by the company and those presented by the ERG should be treated with caution.

4.3.3.2.2 Inappropriate utilities used for the general population

Following the clarification process the company used Ara and Brazier[55] to estimate the utility in the general population. However, the values taken were stated by the company to be associated with "*people with no history of a health condition*", and as such, were higher than the more relevant values which are for the entire general population. The ERG has used the general population values in its exploratory analyses; for comparison this approach estimates values of 0.948 for people aged below 30 years and 0.653 for patients aged 85 years and over compared with the values of 0.963 and 0.819 respectively that were used in the company's base case analysis.

4.3.3.2.3 Inappropriate calculations of utility multipliers related to health states

The utility multipliers estimated by the company (see Table 27) would be influenced by the change in the underlying general population utility (see Section 4.3.3.2.2). In addition, the ERG identified limitations in the way that the utility multipliers had been calculated. The alternative multipliers

preferred by the ERG are provided in Table 42. The derivations of the ERG's values are detailed in the following text. The ERG stresses that it has not undertaken an SLR but has assumed that the company's chosen sources are the most appropriate sources; however, this is subject to considerable uncertainty.

Table 42: Alternative health state utility multipliers explored by the ERG

Health state	Utility multiplier
Without nephrocalcinosis	1.000
Nephrocalcinosis†	0.976
Nephrolithiasis	0.976
Chronic kidney disease stage 2‡	0.951
Chronic kidney disease stages 3-4	0.951
End stage renal disease	0.809
Kidney transplant	
In year of transplant	0.619
In each subsequent year	0.619

† Assumed equal to nephrolithiasis. ‡ Assumed equal to CKD 3-4
For sources of the derived values see main text

For the without nephrocalcinosis state, the ERG maintained the company's assumption that utility would be the same that as for the general population.

For nephrolithiasis, the Polotti *et al.* study[57] reports data on the current renal stones status of patients (Yes/No/Unsure) and current symptoms status (Yes/No/Unsure) for 104 patients with urolithiasis (who are assumed generalisable to patients with nephrolithiasis). EQ-5D values were not significantly different between current renal stone status, but did differ based on symptom status. Polotti *et al.* report the EQ-5D values for renal stone patients (0.83) and for controls (0.92) although the direct comparison is confounded by the different mean ages for the groups which were 50 years and 24 years respectively. To calculate the multiplier, the ERG multiplied the 0.92 by the ratio of utility between 50-year-olds and 24-year-olds (also 0.92) to estimate a utility for controls, had they been 50 years of age, of 0.85 (0.92 x 0.92), and then calculating the multiplier as 0.83 divided by 0.85 (0.976). For nephrocalcinosis, the company assumed that the multiplier would be equal to that of CKD2, however, if the ERG maintained this assumption, then nephrolithiasis would be assumed to be less severe than nephrocalcinosis, which clinical advice provided to the ERG suggested was implausible. As such, the utility multiplier for nephrocalcinosis was set equal to nephrolithiasis.

For CKD stages, Jesky *et al*.[56] was used by the ERG which reports the EQ-5D score and mean age for patients by CKD stage. For those with CKD stages 1-2, an EQ-5D score of 0.85 was reported for patients with a mean age of 41; comparing with Ara and Brazier,[55] this suggests a multiplier of 0.950. For

CKD3-4, weighted data from Jesky *et al*. suggests a utility of 0.76; comparing with a weighted utility from Ara and Brazier of 0.80, this suggests a multiplier of 0.951. The ERG considers it implausible that the utility multiplier for CKD3-4 is higher than for CKD2. As the sample size was much larger for the CKD3-4 group (n=641) compared with CKD2 (n=29) the multiplier for CKD2 was set to that for patients with CKD3-4. For ESKD, a utility of 0.73 was reported for patients aged 64 years; comparing with Ara and Brazier, this suggests a multiplier of 0.809; the ERG prefers this estimate to the one provided by Neri *et al*.,[58] as this was taken for patients who had received a kidney transplant, whereas the model assumed that those in the CKD3-4 health state did not have a transplant.

For patients who have a transplant the company used data from Laupacis *et al*.[59] which the ERG believes has a number of limitations; these include being relatively dated, using a Canadian population and applying a time-trade-off approach rather than the EQ-5D. As an alternative source, the ERG has used data from Neri *et al*.[58] which estimated a mean EQ-5D value from 144 UK patients approximately five years after transplantation. Patients had a mean age of 52 years and a weighted EQ-5D score of 0.53; compared with Ara and Brazier,[55] this suggests a multiplier of 0.619. This value has been used across all time points post-transplant although the ERG highlights that this is likely to underestimate the utility loss in the first year of transplant.

Whilst the ERG believes that its utility multiplier values are methodologically more appropriate than the company's, the ERG stresses that its values may be inaccurate as it plausible that better data sources exist than the ones identified by the company which were used by the ERG.

4.3.3.2.4 Potentially inappropriate QALY losses associated with transitory health states

The company uses QALYs losses to account for transitory health states, except for fracture where a utility multiplier is used. Examining the publications cited by the company, the ERG has concerns relating to the appropriateness of some values. However, the ERG believes that the utility multiplier associated with fracture, which were those associated with rib, forearm, clavicle, scapula and sternum fractures, and the QALY decrement associated with GI events, which was the average of constipation, nausea and vomiting, appear appropriate.

For osteomalacia/rickets, the company has used a high QALY loss (of 0.352), the ERG comments that this is taken from an adult population with severe rickets in which, 93% had problems walking, with 3% unable to walk independently, 86% had problems with pain with 3% experiencing extreme pain, 65% reporting symptoms of anxiety and/or depression and 80% reporting problems with their usual activities. This population does not appear aligned with either the patient population with dRTA, or assuming that osteomalacia/rickets is a transitory condition rather than a permanent condition. If osteomalacia/rickets was deemed to be such a significant problem then this should have been formally

incorporated as a health state within the model. The ERG has explored the impact of assuming no QALY loss for osteomalacia/rickets.

For hypokalaemia, the company assumed a QALY loss of 0.05 from Palaka *et al*. The results for non-dialysis CKD patients indicate that EQ-5D values are 0.03 lower in patients with hypokalaemia than those without and thus the ERG prefers a QALY loss of 0.03.

For failure to thrive, the company assumed a QALY decrement of 0.130 which was taken from NICE guidelines on faltering growth (NG75)[61] which states that '*In keeping with other NICE Guidelines, it is assumed the utility decrement for increased anxiety is 0.07, representing a transition from 'mild' to 'moderate' anxiety on the standard EQ-5D form. This may be an overestimate of the effect as parents of children who are diagnosed with faltering growth may be very anxious to begin with*'. NG75 assumes that this utility decrement is applied to 1.85 parents resulting in 0.130 combined utility for parents. The ERG highlights that these numbers appear not to have an empirical foundation and also that these relate to carers not the person with dRTA. Whilst direct health effects for carers can be considered in the NICE Reference Case '*when relevant*', the relevance of utility losses associated with transitory states, together with the uncertainty in the actual utility loss, meant that the ERG performed exploratory analyses assuming no QALY loss from failure to thrive.

4.3.3.2.5 Incorrect calculation of costs of fracture, failure to thrive and osteomalacia/rickets in the first four cycles of the model

In the model, the costs of fracture, failure to thrive, and osteomalacia/rickets, have been implemented such that the value is dependent on the length of the time cycle, rather than the occurrence of the event. This results in the costs in a six-month cycle being half that in a one-year cycle. The ERG has amended the model such that the costs are independent of time-cycle and are constant at the annual cost.

4.3.3.2.6 Incorrect calculation of QALY losses associated with acquired dRTA

In the model, the calculation of the absolute QALY losses associated with acquired dRTA, has been implemented such that the value is dependent on the length of the time cycle. This results in the QALY losses in two six-month cycles being double that in a one-year cycle. The ERG has amended the model such that the QALY losses in the six-month cycles are half those for the 1-year cycles.

4.3.3.2.7 Incorrect calculation of the midpoint age for those in the children age group

The company has used a midpoint age for children (those aged between 4 and 11 years) as 8 years, rather than 7.5 years. The ERG has used 7.5 years in its exploratory analyses.

4.3.3.2.8 Incorrect calculation of the costs for modified Shohl's solution in combination with sodium bicarbonate

The company estimated that the costs of modified Shohl's solution in combination with sodium bicarbonate is 7.75p per mEq (see Table 29) The ERG believes that this should be the average of modified Shohl's solution (7.75p per mEq) and sodium bicarbonate (39.80p per mEq) which is 23.78p per mEq. The ERG has undertaken exploratory analyses using this cost per mEq for modified Shohl's solution and sodium bicarbonate.

4.3.3.2.9 The assumption that all patients with nephrolithiasis would have 1 percutaneous nephrolithotomy each year

The model assumes that every patient with nephrolithiasis would have one percutaneous nephrolithotomy each year. The CS does not provide evidence to support this assumption, nor does it provide any discussion on how this procedure would affect the patient's health state, for example whether the patient would not have nephrolithiasis after the procedure. Procedures for nephrolithiasis in Study B22CS were not reported which would have been informative data. The ERG has undertaken exploratory analysis to show the impact on the ICER if no percutaneous nephrolithotomies were assumed and the health state costs of nephrolithiasis were assumed equal to the health state costs assumed for nephrocalcinosis.

4.3.3.2.10 Data entry/calculation error related to the percentage of people who regain disease control with SoC in the first four cycles

The ERG believes that annual probabilities have been used for the first four six-month cycles rather than six-monthly values for the percentage of people who regain disease control with SoC. The ERG has performed exploratory analyses assuming that the probability of regaining disease control in the first four cycles is 5.13% rather than the 10% as in the company's base case.

4.3.3.2.11 Apparent error in calculating the probability of moving from without nephrocalcinosis to nephrocalcinosis for patients who have discontinued treatment

As mentioned in Section 4.2.3.4.4, the ERG believes that the formulae for estimating the probability of moving from the without nephrocalcinosis health state to the nephrocalcinosis health state for patients who have discontinued treatment is incorrect, as they link to cells related to the probability of moving from non-response in the CKD2 health state to becoming a responder. The ERG has performed exploratory analyses amending the formulae for all time points.

4.3.3.2.12 Estimation of risk of death associated with fracture or with hypokalaemia

The model assumes that the risk of death after fracture was 3.54% (approximately 1 in 33 people). The source for this estimate was Center *et al*.[52] which was a study set in Australia where the mean age of

patients who had a fracture was 75 years. This population is significantly older than the patients in this decision problem, who have a mean age of approximately 17 years on entry to the model. The ERG believes that the risk of death after fracture is substantially over-estimated and has undertaken exploratory analyses setting the risk of death after fracture to zero.

The ERG could not identify the sources of the risks of mortality from hypokalaemia for people without CKD and with CKD; the company cites Collins[53] although this paper does not mention hypokalaemia. For patients with ESKD, the company cites Ohnishi *et al*.[54] although this paper presents results in terms of hazard ratios and not absolute risk as is implied by the company's estimate of 5.82%. The ERG did not identify the values used to generate the company's estimate. In exploratory analyses, the ERG has assumed no additional mortality related to hypokalaemia, noting that it is unclear whether these deaths would also be included in the mortality probability associated with ESKD as reported by Gibertoni *et al*.[51]

4.3.3.2.13 Estimation of the proportions of patients with disease control at the start of the model

The company assumes that at the start of its base case model 90% of patients have controlled disease with ADV7103 treatment and 43% of patients have controlled disease on SoC. The ERG has adjusted the value for SoC to be 43.33% as reported in Bertholet-Thomas *et al*.[16]

Furthermore, the ERG has undertaken a scenario analysis using an alternative definition for disease control based on the requirement of having normal bicarbonataemia on all of Days 2 to 4 which estimates disease control rates of 76.67% for ADV7103 and 36.67% for SoC. An additional scenario analysis for initial disease control based on the patient numbers used to calculate the probabilities of maintaining and regaining disease control for ADV7103 uses 63.33% for ADV-7103, with the value for SoC kept at 43.33%. See Section 4.2.3.3 for further information.

4.3.3.2.14 The assumed dosages for ADV7103

The company's model assumes that dosing for ADV7103 follows the dose within Study B21CS. The ERG prefers to use the dosing from Study B22CS, which is a much longer study (48 months rather than 35 days or less which includes a titration period) and deemed more likely to represent the long-term doses when ADV7103 is used.

4.3.3.2.15 Assumption of equal disease control for patients regardless of age

The company's model assumes that the probability of maintaining or recovering disease control is independent of age. This assumption was supported by clinical advice received by the ERG, but the data for patients receiving ADV7103 in B22CS (shown in

Table 43) suggest that a difference could be plausible, although the sample size is small. The ERG has maintained the company's assumption but highlights that this assumption is subject to uncertainty.

Table 43: Disease control for adults and non-adults

	Adults	Non-adults
Probability of maintaining controlled disease		
24 to 36 months	100%	86.67%
36 to 48 months	100%	78.95%
Probability of recovering disease control		
24 to 36 months	0%	85.71%
36 to 48 months	0%	66.67%

4.3.3.2.16 Small sample sizes and limited comparative efficacy data

Study B21CS was of short duration (a maximum of 5 days of optimised treatment) and generated comparative efficacy using patients as their own controls. Study B22CS was of much longer duration (up to 48 months) but was a single-arm study. In both studies the number of patients observed was small, with less than 40 patients. These limitations mean that there is considerable uncertainty in the true efficacy of ADV7103, particularly if there is uncertainty in the most appropriate definition of disease control (see Sections 4.2.3.3 and 4.3.3.2.13).

4.3.3.2.17 Applying a continuity correction due to small numbers of observed events

Given that the low numbers of observations relating to disease controlled in the B21CS and B22CS studies, the ERG asked the company to perform continuity correction by dividing one additional unit equally across all possible outcomes when there were less than five observations in an outcome measure. The company attempted to do this, although it was not as the ERG requested. However, given the small impact on the ICER of the analyses undertaken by the company, the uncertainty within the decision problem and the timescales of the STA the ERG was content to use the observed data directly.

4.4 Exploratory analyses undertaken by the ERG

4.4.1 Overview of ERG's exploratory analyses

The ERG's exploratory analyses relate to the issues and uncertainties raised in Section 4.3.3.1 and Section 4.3.3.2 that the ERG could address within the timescales of the appraisal. These are detailed in Section 4.4.2. All analyses are presented deterministically apart from the ERG's indicative base case, which is a culmination of all of the ERG's individual changes, which has also been run probabilistically. The list price for all interventions, except ADV7103 has been used in these analyses. The ERG has been

informed by NICE that there is are Commercial Medicines Unit prices for Shohl's solution, potassium bicarbonate and sodium bicarbonate which are used within SoC. Results incorporating these reduced prices are contained in a confidential appendix.

4.4.2 ERG's exploratory analyses - methods

ERG exploratory analysis (EA) 1: Adding an additional 5 days' worth of costs to the ADV7103 arm

The company's model starts with patients in different health states for ADV7103 treatment and SoC treatment compared with the traditional approach of having identical cohorts for each treatment arm. The change in health states is assumed to happen at 5 days and therefore the ERG has added 5 days' worth of ADV7103 treatment costs to the ADV7103 arm to consider these additional costs.

ERG EA2: Setting the costs of the nephrocalcinosis and nephrolithiasis health state to that of nephrocalcinosis health state

The company's model assumes an annual cost of £6241 for people with nephrocalcinosis and nephrolithiasis to account for one percutaneous nephrolithotomy each year. This procedure was not linked to changes in health state and no information on the number of such procedures in Study B22CS were reported. The ERG has reduced the cost of being in the nephrocalcinosis and nephrolithiasis state to that of being in the nephrocalcinosis state (£1211).

ERG EA3: Assuming that the QALY loss associated with dRTA applies to those with controlled disease

The company's model assumes that the QALY loss associated with acquired dRTA (applied to adults entering the model) does not apply if the patients have controlled disease. No evidence was provided to support this assumption. The ERG has explored the impact on the ICER of assuming that there is no additional QALY loss from acquired dRTA.

ERG EA4: Using the general population utility from the full population and using alternative health state utility multipliers

The company used data from Ara and Brazier[55] to estimate the utility in the general population. However, the values taken were associated with people with no history of a health condition. The ERG has used the values for the entire population which it believes are more appropriate. As detailed in Section 4.3.3.2.2, the ERG prefers alternative health state utility multipliers to those used in the company's model. The values used by the ERG are shown in Table 42.

ERG EA5: Exploring the use of alternative QALY losses associated with transitory health states
As detailed in Section 4.3.3.2.4, the ERG believes that there were limitations with the QALY losses associated with some transitory states. The ERG has conducted an analysis, using a utility loss of 0.03 for patients with hypokalaemia, which is the difference in EQ-5D values for CKD patients with hypokalaemia and those without reported in Palaka *et al.*[64], and assuming no utility loss associated with failure to thrive or osteomalacia/rickets.

ERG EA6: Correcting errors relating to the costs of fracture, failure to thrive, and osteomalacia/rickets in the first four six-month cycles.
As detailed in Section 4.3.3.2.5, the ERG believes that the formulae for the costs of fracture, failure to thrive and osteomalacia/rickets in the four six-month cycles are incorrect and result in only half of the costs being applied. The ERG has amended these formulae to use the intended costs.

ERG EA7: Correcting errors relating to the QALY losses associated with acquired dRTA in the first four six-month cycles
As detailed in Section 4.3.3.2.6, the ERG believes that the formulae for the QALY losses associated with dRTA in the four, six-month cycles are incorrect and result in double the intended QALY losses being applied. The ERG has amended these formulae to use the intended QALY losses.

ERG EA8: Correcting the midpoint age for those in the children age group
The ERG has used a midpoint age of 7.5 years for people aged between 4 and 11 years of age instead of the 8 years used by the company.

ERG EA9: Correcting the cost of modified Shohl's solution in combination with sodium bicarbonate
The ERG has used a cost of 23.78p per mEq for modified Shohl's solution in combination with sodium bicarbonate instead of the company's estimate of 7.75p per mEq.

ERG EA10: Correcting the probability of percentage of people receiving SoC who regain disease control in the first four six-month cycles.
The ERG has used a value of 5.13% for these six-month cycles rather than the annual rate of 10% used by the company.

ERG EA11: Amending the formulae related to the probability of moving from the without nephrocalcinosis health state to the with nephrocalcinosis health state for patients not on treatment
The ERG has amended these formulae to remove the link to the probabilities of patients with CKD2 in the non-responder health state moving to the response state.

ERG EA12: Removing the risk of death following fracture or hypokalaemia

As detailed in Section 4.3.3.2.12, the ERG believes that the risk of death following fracture is overestimated, and the ERG could not locate the values used by the company relating to the risks of hypokalaemia. The ERG has undertaken exploratory analyses assuming that neither fracture nor hypokalaemia would cause death.

ERG EA13: Changing the proportions of patients with disease control

The ERG has used a value of 43.33% for SoC rather than the 43.00% used in the company base case to align with data presented in Bertholet-Thomas *et al.*[16]

The ERG preferred indicative base case was a combination of all of the ERG's exploratory analyses. The adjective indicative is used for the following reasons:

1) The sample sizes within the B21CS and B22CS studies are small, additionally Study B22CS was non-comparative, whereas Study B21CS had a short duration and used patients as their own control. This will add uncertainty regarding the true comparative efficacy of ADV7103 compared to SoC. Alternative definitions of responders would also change the ICER.
2) The model relies considerably on clinical opinion rather than empirical estimates obtained from clinical studies of patients with dRTA. This clinical judgment could be prone to error.
3) The literature sources chosen to populate the model have not been justified. Without a formal systematic literature review or clear justification for the source chosen the ICER will be subject to an unknown degree of uncertainty.
4) Details of the derivation of values used in the model from the cited publications were not provided by the company and the ERG could not determine how many of the parameter values had been derived. This means that the ICER is subject to uncertainty.
5) Many issues and limitations identified by the ERG (see Sections 4.3.3.1 and 4.3.3.2) could not be addressed within the timescales of the STA, and therefore add uncertainty to the ICER
6) Where the company's chosen base case parameter value was deemed implausible, for example QALY losses associated with osteomalacia/rickets, or risk of death from fracture, the ERG has set the value to zero in its indicative base case, effectively removing the QALY losses from these conditions from the model. This will add uncertainty to the ICER.

In addition to providing an indicative base case ICER for the full population, the ERG has provided indicative base case ICER for adults, who are assumed by the company to have acquired dRTA, and for non-adults who have inherited dRTA.

Two further scenario analyses were run by the ERG. ERG Scenario Analysis 1 (SA1) used the definition of disease control where patients had to have bicarbonataemia values at least as high as the lower normal range, as defined by local laboratories on all of Days 2, 3 and 4 (Table 14) rather than the mean across the three days being greater than the threshold (Table 15). This resulted in an initial disease control of 76.67% for ADV7103 and 36.67% for SoC.

In ERG SA2, the values of disease control implied by the transition probabilities for maintaining disease control and regaining disease control in Months 0 to 6 were used for ADV7103. This resulted in an initial disease control of 63.33% for ADV7103, the assumed disease control for SoC was kept at 43.33%. The results for SoC in ERG SA2 differ from those in the ERG's base case because the relative efficacy between ADV7103 and SoC is used within the model for disease control and this has changed in the scenario analysis.

4.4.3 ERG's exploratory analyses – results

This section is divided into two subsections. The first details the results produced when the company's base case model is amended by the ERG, with the second describing analyses that the ERG would have run but could not due to the structure/functionality of the model and/or the timescales of the STA.

4.4.3.1 Quantitative changes to the company's base case

The results of the ERG's exploratory analyses are presented in Table 44Error! Not a valid bookmark self-reference.. It can be seen that none of the individual exploratory analyses lead to a substantial change in the ICER with only using the dosage of ADV7103 from Study B22CS rather than from Study B21CS increasing the ICER by more than [redacted]. A relatively similar proportion of the ERG's exploratory analyses lead to reductions in the ICER as did the proportion that decreased the ICER. However, when all of the ERG's exploratory analyses were combined, the company's base case ICER of [redacted] increased to [redacted] in the ERG's indicative deterministic base case for the weighted population. Table 45 provides the deterministic indicative ICER for an adult population which is [redacted] whilst Table 46 provides the deterministic indicative ICER for a non-adult population [redacted]). Probabilistic estimates of the ICER were slightly lower than deterministic estimates, being £[redacted] for the weighted population, £[redacted] for the adult population and [redacted] for the non-adult population.

Alternative scenario analyses that use different estimates of disease control at the start of the model were run by the ERG with the deterministic results presented in

Table 47 and Table 48; neither of these scenarios markedly changed the ICER, with the ICER increasing by less than £[redacted] in the most unfavourable scenario for ADV7103.

The ERG cautions that the ICERs presented by both the company and the ERG may be inaccurate due to two reasons. Firstly, there were a large number of changes that the ERG could not undertake (see Section 4.4.3.2); some of these changes would be clearly favourable to the intervention, such as applying a disutility associated with SoC treatment, however, the impacts of other changes are unknown. Secondly, the value for some parameters have been set to zero, where the company's estimate appeared implausible; it is unlikely that the correct value is zero, but the ERG did not undertake reviews to ascertain more accurate parameter values.

Table 44: Results of the ERG's deterministic exploratory analyses (weighted population)

Analysis	Life years†	QALYs	Costs	Incremental			ICER
				Life years†	QALYs	Costs	
Company's updated base case							
ADV7103	24.52	[redacted]	[redacted]				
SoC	18.18	[redacted]	[redacted]	6.34	[redacted]	[redacted]	[redacted]
EA1: Adding an additional 5 days of costs of ADV7103 to the ADV7103 arm							
ADV7103	24.52	[redacted]	[redacted]				
SoC	18.18	[redacted]	[redacted]	6.34	[redacted]	[redacted]	[redacted]
EA2: Setting the costs of the nephrocalcinosis and nephrolithiasis health state to that of nephrocalcinosis health state							
ADV7103	24.52	[redacted]	[redacted]				
SoC	18.18	[redacted]	[redacted]	6.34	[redacted]	[redacted]	[redacted]
EA3: Assuming that the QALY losses associated with acquired dRTA are set to zero							
ADV7103	24.52	[redacted]	[redacted]				
SoC	18.18	[redacted]	[redacted]	6.34	[redacted]	[redacted]	[redacted]
EA4: Using the general population utility for the full population and using alternative health state utility multipliers							
ADV7103	24.52	[redacted]	[redacted]				
SoC	18.18	[redacted]	[redacted]	6.34	[redacted]	[redacted]	[redacted]
EA5: Exploring the use of alternative QALY losses associated with transitory health states							
ADV7103	24.52	[redacted]	[redacted]				

Analysis	Life years†	QALYs	Costs	Incremental			ICER
				Life years†	QALYs	Costs	
SoC	18.18	[redacted]	[redacted]	6.34	[redacted]	[redacted]	[redacted]
EA6: Correcting errors relating to the costs of fracture, faltering growth, and osteomalacia/rickets in the first four six-month cycles							
ADV7103	24.52	[redacted]	[redacted]				
SoC	18.18	[redacted]	[redacted]	6.34	[redacted]	[redacted]	[redacted]
EA7: Correcting errors relating to the QALY losses associated with acquired dRTA in the first four six-month cycles							
ADV7103	24.52	[redacted]	[redacted]				
SoC	18.18	[redacted]	[redacted]	6.34	[redacted]	[redacted]	[redacted]
EA8: Correcting the midpoint age for those in the children age group							
ADV7103	24.54	[redacted]	[redacted]				
SoC	18.18	[redacted]	[redacted]	6.35	[redacted]	[redacted]	[redacted]
EA9: Correcting the cost of modified Shohl's solution in combination with sodium bicarbonate							
ADV7103	24.52	[redacted]	[redacted]				
SoC	18.18	[redacted]	[redacted]	6.34	[redacted]	[redacted]	[redacted]
EA10: Correcting the probability of percentage of people receiving SoC who regain disease control in the first four six-month cycles							
ADV7103	24.51	[redacted]	[redacted]				
SoC	18.07	[redacted]	[redacted]	6.45	[redacted]	[redacted]	[redacted]
EA11: Amending the formulae related to the probability of moving from the without nephrocalcinosis health state to the with nephrocalcinosis health state for patients not on treatment							
ADV7103	24.52	[redacted]	[redacted]				
SoC	18.18	[redacted]	[redacted]	6.34	[redacted]	[redacted]	[redacted]
EA12: Removing the risk of death for both fracture and hypokalaemia							
ADV7103	24.92	[redacted]	[redacted]				
SoC	20.62	[redacted]	[redacted]	4.30	[redacted]	[redacted]	[redacted]
EA13: Changing the proportions with disease control at the start of the model							
ADV7103	24.52	[redacted]	[redacted]				
SoC	18.18	[redacted]	[redacted]	6.33	[redacted]	[redacted]	[redacted]
EA14: Changing the assumed dose of ADV7103							

Analysis	Life years†	QALYs	Costs	Incremental			ICER
				Life years†	QALYs	Costs	
ADV 7103	24.52	[redacted]	[redacted]				
SoC	18.18	[redacted]	[redacted]	6.34	[redacted]	[redacted]	[redacted]
ERG indicative base case (incorporating all of the above exploratory analyses (EA1-EA14))							
ADV 7103	24.94	[redacted]	[redacted]				
SoC	20.55	[redacted]	[redacted]	4.39	[redacted]	[redacted]	[redacted]
ERG indicative base case (probabilistic)							
ADV 7103	-	-	-				
SoC	-	-	-	-	[redacted]	[redacted]	[redacted]

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years
SoC: Standard of Care †Undiscounted (all other values are discounted)

Table 45: ERG's indicative deterministic ICER (adults)

Description	Life years†	QALYs	Costs	Incremental			ICER
				Life years†	QALYs	Costs	
ADV7104	24.16	[redacted]	[redacted]				
SoC	20.26	[redacted]	[redacted]	3.90	[redacted]	[redacted]	[redacted]
Probabilistic	-	-	-	-	[redacted]	[redacted]	[redacted]

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years

SoC: Standard of Care †Undiscounted (all other values are discounted)

Table 46: ERG's indicative deterministic ICER (non-adults)

Description	Life years†	QALYs	Costs	Incremental			ICER
				Life years†	QALYs	Costs	
ADV7104	25.72	[redacted]	[redacted]				
SoC	20.93	[redacted]	[redacted]	4.87	[redacted]	[redacted]	[redacted]
Probabilistic	-	-	-		[redacted]	[redacted]	[redacted]

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years

SoC: Standard of Care †Undiscounted (all other values are discounted)

Table 47: ERG's indicative deterministic ICER assuming that proportion of patients with controlled disease was defined as having bicarbonataemia values equal or above the lower normal range on all of Days 2-4 of Study B21CS

Description	Life years†	QALYs	Costs	Incremental			ICER
				Life years†	QALYs	Costs	
ADV7104	24.93	[redacted]	[redacted]				
SoC	20.54	[redacted]	[redacted]	4.40	[redacted]	[redacted]	[redacted]
Probabilistic	-	-	-		[redacted]	[redacted]	[redacted]

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years

SoC: Standard of Care †Undiscounted (all other values are discounted)

Table 48: ERG's indicative deterministic ICER assuming that the proportion of patients with controlled disease was that inferred from the transition probabilities for disease control in Months 0-6

Description	Life years†	QALYs	Costs	Incremental			ICER
				Life years†	QALYs	Costs	
ADV7104	24.93	[redacted]	[redacted]				
SoC	20.60	[redacted]	[redacted]	4.33	[redacted]	[redacted]	[redacted]
Probabilistic	-	-	-		[redacted]	[redacted]	[redacted]

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years

SoC: Standard of Care †Undiscounted (all other values are discounted)

4.4.3.2 Key changes to the company's base case model that could not be undertaken by the ERG within the timescales of the appraisal

This section concentrates on the three key issues that the ERG considers are most important in potentially changing the ICER that has not been adequately explored. The full list of issues that could not be amended are contained in Sections 4.3.3.1 and 4.3.3.2.

The first key limitation is that there appears to be no targeted literature reviews to identify the most appropriate parameter values, therefore this is a high risk that the selected values may be inaccurate. The model also relies on a considerable amount of clinical opinion which is likely to increase

uncertainty in the results. Formal targeted reviews would be required to reduce the uncertainty in the ICER.

The second key limitation is that disutility associated with SoC was not incorporated into the model. It is likely that patients would value a twice a day treatment considerably more than a treatment with multiple intakes, including nightly doses with supportive evidence provided by the company summarised in Section 4.2.3.7.

The third key limitation is the uncertainty in the efficacy of ADV7103. Neither Study B21CS nor Study B22CS recruited a large number of people (less than 40 in both studies) and Study B22CS was non-comparative. Some comparative efficacy data was generated in B21CS although this used patients as self-controls and was for a short duration (up to 5 days of optimised treatment).

5 END OF LIFE

The company makes no reference to NICE's end of life criteria. The ERG deems this appropriate given the longevity of patients receiving SoC, which is considerably in excess of 2 years.

6 OVERALL CONCLUSIONS

Study B21CS demonstrated the non-inferiority of ADV7103 vs. SoC with a mean difference (SD) in blood bicarbonate levels of 1.4195 (2.647), $p<0.0001$. Within months 3 to 48 of B22CS, the percentage of patients receiving ADV7103 treatment with blood bicarbonate levels in the normal range ranged from 60.9% to 92.3%. There were similar AE rates and types during five days SoC treatment (7/37, 18.9%) and five days of optimised ADV7103 treatment (6/32, 18.8%) in Study B21CS. During B22CS, compliance to ADV7103 was high, with compliance reported as 75% or higher for 79.3% patients at month 24.

The model submitted by the company was subject to a number of conceptual errors, calculation errors and debatable parameter assumptions. For some of these limitations, the ERG could provide exploratory analyses that gave an indication of alternative assumptions on the ICER; however, for the remainder it could not. The changes that could be made by the ERG resulted in a deterministic indicative ICER of [redacted] for a weighted population, with ADV-7103 providing [redacted] more QALYs than SoC at an additional cost of £[redacted]; the probabilistic estimate of the ICER was [redacted]. When subgroups based on age was considered due to potentially different disease types. the indicative ICERs were [redacted] (£[redacted] probabilistic) for adults and £[redacted] probabilistic) for non-adults.

The ERG's ICERs are stated to be indicative due to uncertainties related to: the small number of patients included in BC21S and B22CS; the limited comparative efficacy data of ADV7103; the reliance on clinical opinion for numerous model parameters; the lack of a literature search or clear justification as to why the chosen sources were selected; insufficient details relating to how transition probabilities were derived from the literature; multiple limitations that could not be addressed by the ERG within the timescales of the project; and some parameter values being set to zero in the ERG's indicative base case when the company's values were deemed implausible. A particular advantage of ADV7103 treatment compared with SoC is the more convenient treatment regimen, with these benefits not incorporated within the company's model.

Given the reasons detailed above, the ERG believes that its indicative ICER is likely to be unfavourable to ADV7103, although the extent of this possible bias is unknown. The model has a large number of limitations, and therefore the ERG has provided some bullet points that the Appraisal Committee may find informative:

- ADV7103 is licensed for the treatment of dRTA, whereas the components of SoC are not
- ADV7103 has a much more convenient dosing regimen than SoC, than has not been formally captured in the estimates of QALYs

- that the price premium for ADV7103 compared with SoC in terms of mEq is [redacted]%

The ERG has been informed by NICE that there are Commercial Medicines Unit prices for Shohl's solution, potassium bicarbonate and sodium bicarbonate which are used within SoC. Results incorporating these reduced prices are contained in a confidential appendix.

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Slow-release potassium bicarbonate and potassium citrate for treating distal renal tubular acidosis [ID3787]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 25 February** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 The multiplier for the utility for CKD2 presented by the ERG is incorrect.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
ERG report section 4.3.3.2.3 page 79 states: "For CKD stages, Jesky et al.56 was used by the ERG which reports the EQ-5D score and mean age for patients by CKD stage. For those with CKD stages 1-2, an EQ-5D score of 0.64 was reported for patients with a mean age of 41; comparing with Ara and Brazier,55 this suggests a multiplier of 0.932. For CKD3-4, weighted data from Jesky et al. suggests a utility of 0.76 for patients aged 66; comparing with Ara and Brazier, this suggests a multiplier of 0.951. The ERG considers it implausible that the utility multiplier for CKD3-4 is higher than for CKD2." **The multiplier for the utility for CKD2 presented by the ERG is incorrect.**	**The multiplier for the utility for CKD2 presented by the ERG is incorrect.** If the utility = 0.64 and the multiplier = 0.932, this would suggest the general population utility is 0.687 (=0.64/0.932). The company believe this is incorrect as, at age 41, Ara and Brazier report general population utility = 0.892. Instead, the company believe that, as reported in Table 3 of Jesky et al., the mean utility for patients with CKD1-2 = 0.85. Comparing with Ara and Brazier general population utility at age 41 (0.892), the multiplier for CKD2 = 0.953 (=0.85/0.892).	Correction of incorrect multiplier used by ERG	Apologies there were typos in this paragraph. When the 0.85 was divided through by the expected utility at age 41 (0.895) this is a multiplier of 0.950. We have used the value at 41 years rather than the average between 40 and 45 which explains the difference in utility multiplier estimates.

Issue 2 The company believe that the multiplier for those with CKD3-4 has been incorrectly calculated based on an incorrect calculation of the weighted general population utility.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
ERG report section 4.3.3.2.3 page 79	The table below presents the summary information presented in Jesky et al. and the relevant supplementary appendix. **Stage G3a** | **Stage G3b** | **Stage G4**	It was the ERGs conclusion that it is implausible that the utility multiplier for CKD3-4 is higher	The ERG has taken on board the company's suggestion

To estimate a weighted general population utility for CKD3-4 the ERG use an average age of 66 (weighted average age using Jesky et al. patient numbers) and cross-reference this with Ara and Brazier to get a general population utility of 0.795.

The company believe this is incorrect, and that the weighting should follow the same calculation that was used for the weighted study utilities which is equal to:

= sum of (state utility * count of patients) for CKD3a, 3b and 4 / sum of patients

= ((0.858*45)+(0.818*173)+(0.795*423))/(45+173+423)

= 516.366 / 641

= 0.8056

The multiplier for CKD3-4 can then be calculated as the mean weighted utility for CKD3-4 (0.760) divided by the mean weighted general population utility (0.8056) **to**

n	45	173	423
Age	55	61.5	69

The relevant utilities are presented as follows:

	Stage G3a	**Stage G3b**	**Stage G4**
Utilities reported in Table 3 in Jesky et al.	0.80	0.80	0.74
	CKD3-4		
Utilities presented by the ERG	((0.80*45)+(0.80*173)+(0.74*423))/(45+173+423) 0.760		

The company agrees with the calculation used to estimate the weighed utility for CKD3-4.

Referencing Ara and Brazier, the company believe the relevant general population utilities are as follows:

	Stage G3a	**Stage G3b**	**Stage G4**
Age	55	61.5	69
Relevant band	50 to ≤ 55	60 to ≤ 65	65 to ≤ 70
Ara and Brazier general pop utilities	0.858	0.818	0.795

To estimate a weighted general population utility for CKD3-4 the ERG use an average age of 66 (weighted average age using Jesky et al. patient numbers) and cross-reference this with Ara and Brazier to get a general population utility of 0.795.

than for CKD2. With the suggested correction, the CKD2 multiplier is now 'correctly' higher than the multiplier for CKD3-4.

related to calculating the multiplier, although when the exact ages are used (rather than the midpoint of 5 year bands) the utility multiplier remains at 0.951 (to 3 dp). This is slightly higher than the CKD1-2 multiplier, and so the value for CKD1-2 has still been increased to that of CKD3-4.

give a multiplier for CKD3-4 of 0.943.

The company believe this is incorrect, and that the weighting should follow the same calculation that was used for the weighted study utilities which is equal to:

= sum of (state utility * count of patients) for CKD3a, 3b and 4 / sum of patients
= ((0.858*45)+(0.818*173)+(0.795*423))/(45+173+423)
= 516.366 / 641
= 0.8056

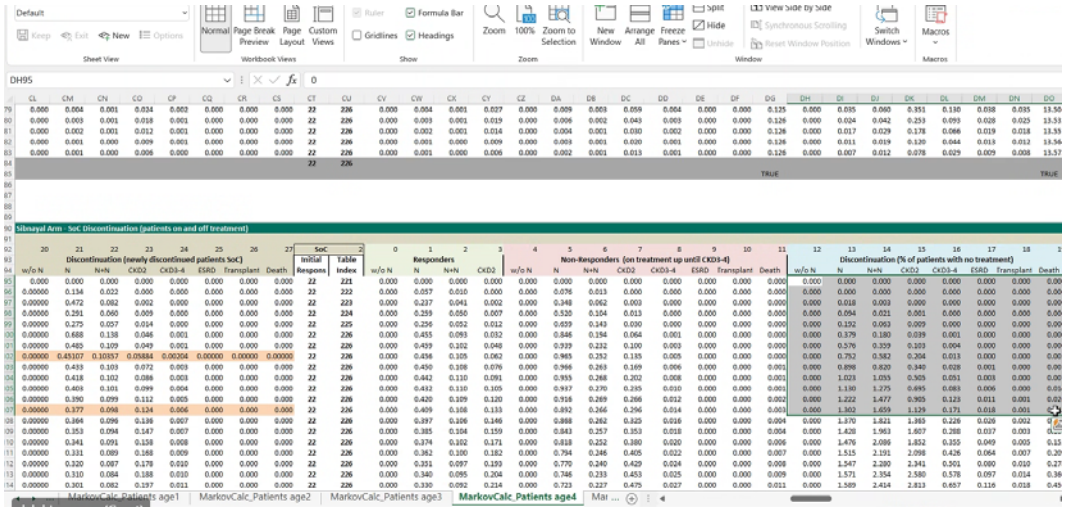
The multiplier for CKD3-4 can then be calculated as the mean weighted utility for CKD3-4 (0.760) divided by the mean weighted general population utility (0.8056) to give a **multiplier for CKD3-4 of 0.943.**

Summary

	ERG reported	**Suggested correction**
CKD2 utility	0.64	0.85
Weighted mean gen pop. utility	n/r	0.892
CKD2 multiplier	0.932	0.953
CKD3-4 utility	0.76	0.76
Weighted mean gen pop. utility	n/r	0.8056
CKD3-4 multiplier	0.951	0.943

It was the ERGs conclusion that it is implausible that the utility multiplier for CKD3-4 is higher than for CKD2. With the suggested correction, the CKD2 multiplier is now 'correctly' higher than the multiplier for CKD3-4.

Issue 3 Patients discontinuing ADV7103 treatment and starting SoC treatment will never discontinue SoC treatment.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 75 4.3.3.1.3 **Patients discontinuing ADV7103 treatment and starting SoC treatment will never discontinue SoC treatment** The ERG state - Within the model patients can discontinue treatment. For patients receiving SoC, this results in the patient receiving no treatment. However, for patients receiving ADV7103, half receive SoC treatment and half receive no treatment. The structure of the model means that patients who receive SoC treatment after ADV7103 treatment will never discontinue SoC, which does not follow the logic for those patients who start on SoC treatment.	Propose to amend report to remove the ERG's observation. Following the model schematic, for the patients who discontinue ADV7103 and then receive SoC, the model uses the transition probabilities of the SoC arm (please refer to the tab 'Table TP'). Therefore, these patients are still at risk of discontinuing, and stopping completely treatment. This can be clearly seen in the tab 'MarkovCalc_Patientsage4' ,for instance, in the columns DH:DO (as highlighted in the print screen below). 	To remove statement that is incorrect.	Apologies for this error. We have removed this criticism from the report and amended the text and tables appropriately. The change has marginally lowered the ICER for ADV7103.

The ERG could not amend the model within the timescales of the appraisal to rectify this limitation. However, exploratory analyses have been undertaken to assess the impact of assuming that all patients that discontinue ADV7103 treatment receive no treatment thus applying consistent assumptions between the two treatment arms." This is incorrect.			

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**	**ERG Response**
Give full details of inaccurate marking - document title and page number	Give details of incorrect confidential marking	Please copy the impacted section here, with your amended marking.	
ID3787 bicarb ERG Report 170222 GK (ACIC) **Page 35, 2nd paragraph**.	From Advicenne. Study B21CS Clinical Study Report. 2019.	(from CSR, difficulty swallowing ADV7103 first intake attempt)[13].	All AIC markings identified in this document have been removed. We had erred on the side of caution where it was not clear if the values were in the public domain

<table>
<tr><td></td><td>Not deemed to be academic in confidence. Mark up not required.</td><td></td><td>and the company had not stated that this could be released.</td></tr>
<tr><td>ID3787 bicarb ERG Report 170222 GK (ACIC)
Page 39 Table 15</td><td>From Advicenne. Advicenne Data on file 2019 CSR B21CS Final QCed FV 06March19 (003). In; 2019.
Not deemed to be academic in confidence. Mark up not required.</td><td>
<table>
<tr><th colspan="3">PP Set</th><th colspan="3">ITT Set</th></tr>
<tr><th>SoC</th><th>ADV7103</th><th>n/N (%)</th><th>SoC</th><th>ADV7103</th><th>n/N (%)</th></tr>
<tr><td>Response</td><td>Response</td><td>13/29 (45%)</td><td>Response</td><td>Response</td><td>13/30 (43%)</td></tr>
<tr><td>Non-response</td><td>Response</td><td>13/29 (45%)</td><td>Non-response</td><td>Response</td><td>14/30 (47%)</td></tr>
<tr><td>Response</td><td>Non-response</td><td>0/29 (0.0%)</td><td>Response</td><td>Non-response</td><td>0/30 (0.0%)</td></tr>
<tr><td>Non-response</td><td>Non-response</td><td>3/29 (10%)</td><td>Non-response</td><td>Non-response</td><td>3/30 (10%)</td></tr>
<tr><td colspan="2">p-value[a]</td><td><0.001</td><td colspan="2">p-value[a]</td><td><0.001</td></tr>
</table>
ITT=intent-to-treat, PP=per protocol, SoC=standard of care
Note: Post-dose samples are excluded from the analysis. [a]exact p-value obtained from a McNemar's test</td><td></td></tr>
<tr><td>ID3787 bicarb ERG Report 170222 GK (ACIC)
Page 42</td><td>From Auelia B-T. Advicenne Data on File Clinical Study Report B22CS 48 Month Data; 2021.
Not deemed to be academic in confidence. Mark up not required</td><td>One child had renal stones only at baseline in B22CS (CS, Section B.2.6). Five patients had nephrolithiasis at baseline, that recurred throughout follow-up. Nine other patients did not have nephrolithiasis at baseline but did during follow-up (of which six patients had one event, and three patients had recurrent events).[15]</td><td></td></tr>
<tr><td>ID3787 bicarb ERG Report 170222 GK (ACIC)
Page 43 HRQoL</td><td>From Auelia B-T. Advicenne Data on File Clinical Study Report B22CS 48 Month Data; 2021.</td><td>HRQoL was measured in Study B22CS, but not Study B21CS. The analysis population in Study B22CS comprised patients who had at least one dose of study drug, and at least one treatment acceptability or HRQoL assessment.[15]</td><td></td></tr>
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<tr><td></td><td>Not deemed to be academic in confidence. Mark up not required</td><td></td><td></td></tr>
<tr><td>ID3787 bicarb ERG Report 170222 GK (ACIC)
Page 44</td><td>From Auelia B-T. Advicenne Data on File Clinical Study Report B22CS 48 Month Data; 2021.
Not deemed to be academic in confidence. Mark up not required</td><td>Study B22CS measured treatment acceptability by VAS 0-100mm, at month 24 (CS, Section B.2.6).[15] Patients and/or parents were asked to score improvement over previous alkalising treatment in terms of: efficacy; safety; formulation; number of daily doses; taste; and other improvements to be specified by patient.[15]</td><td></td></tr>
<tr><td>ID3787 bicarb ERG Report 170222 GK (ACIC)
Page 46</td><td>From Auelia B-T. Advicenne Data on File Clinical Study Report B22CS 48 Month Data; 2021.
Not deemed to be academic in confidence. Mark up not required</td><td>nervous system disorders 6/30 (20.0%); skin and subcutaneous tissue disorders 6/30 (20.0%); general disorders and administration site conditions 2/30 (6.7%) (CS, Section B.2.10).[15]</td><td></td></tr>
<tr><td>ID3787 bicarb ERG Report 170222 GK (ACIC)
Page 83 Table 43</td><td>Not deemed to be academic in confidence. Mark up not required</td><td>Table 1: Disease control for adults and non-adults
<table>
<tr><th></th><th>Adults</th><th>Non-adults</th></tr>
<tr><td colspan="3">Probability of maintaining controlled disease</td></tr>
<tr><td>24 to 36 months</td><td>100%</td><td>86.67%</td></tr>
<tr><td>36 to 48 months</td><td>100%</td><td>78.95%</td></tr>
<tr><td colspan="3">Probability of recovering disease control</td></tr>
<tr><td>24 to 36 months</td><td>0%</td><td>85.71%</td></tr>
<tr><td>36 to 48 months</td><td>0%</td><td>66.67%</td></tr>
</table></td><td></td></tr>
</table>

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Technical engagement response form

Slow-release potassium bicarbonate and potassium citrate for treating distal renal tubular acidosis [ID3787]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **11 April 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Advicenne
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**n/a**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1. Limited evidence related to the comparative efficacy of ADV7103 compared to SOC	No	
Issue 2. Limitations in the conceptualisation and functionality of the model	Yes	The ERG model has been updated to include SoC utility decrement to demonstrate chronic utility gain associated with the more convenient dosing regimen of ADV7103 compared to SoC. See also newly published paper on “Lived experiences of patients with distal renal tubular acidosis treated with ADV7103 and of their caregivers: a qualitative study” Acquardo et al March 2022 Orphanet Journal of Rare Disease. (included in Appendix)
Issue 3. Lack of targeted reviews to populate the model and the reliance on clinical opinion	Yes	Refreshed TLR with search criteria and PRISMA included, expanded to include TLR results for additional inputs (mortality, dosing regimen utility, average weight). Methods for the formal targeted review conducted for the company's base case has been included, the outcome of which led to reliance on expert opinion for certain inputs.

Issue 4. Inappropriate population of the model from the sources cited by the company	Yes	ERG model version accepted and used Adjustment to value of Acquired dRTA disutility (not ERG preferred)
Issue 5. Implementation issues within the model	Yes	ERG model version accepted and used

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Issue 2. Issue 3. Issue 4. Issue 5.	Company's base case assumptions and values before technical engagement.	Accepted the ERG preferred assumptions and values. See ERG report for detail.	The reported ERG base case ICER is [redacted] The company believe there is an error in this ICER (explained below). The company estimated revised ERG base case ICER is [redacted].
Issue 2.	No chronic utility gain associated with the more convenient dosing regmin of ADV7103 compared to SoC included in the model	The revised company model now captures the added benefit of ADV7103 dosing regimen via applying a utility decrement to those on SoC. This has been added to the 'Quality of Life' sheet in the company's model. The utility decrement was informed by a targeted literature review and validated by 2 clinicians. The TLR and clinical validation piece have been provided as new evidence.	When applied to the ERG base case (revised), the ICER changes to [redacted]. Additional analyses have been provided below, expanding on the addition of this QALY decrement.

		The value of the disutility is 0.04, applied as a QALY decrement at each cycle to all patients receiving SoC treatment.	
Issue 4.	Patients starting the model as adults are assumed to have acquired dRTA which is associated with a persistent QALY loss (-0.18), per cycle, if patients were non-responders or have discontinued treatment.	The revised company model includes a change to the utility decrement of acquired dRTA. The ERG comment that the B21CS study only had 1 patient with acquired dRTA, which is a considerably lower proportion than that assumed in the original company model. As such, the ERG model sets the utility decrement to 0, effectively assuming that no patients have acquired dRTA in the model. Our revised company model has instead weighted the utility decrement (0.18) by the proportion of adult patients who had acquired dRTA in the B21CS study (1/7). The adjusted disutility value for acquired dRTA is 0.026, applied to adults who are non-responders or have discontinued treatment.	When applied to the ERG base case (revised), the ICER changes to [redacted]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [redacted]	Incremental costs: [redacted]	ICER: [redacted]

Sensitivity analyses around revised base case

Revised base case results

The company's revised base case (following technical engagement) is based on the ERG model with the addition of two modifications. To the ERG model, the company have added:

1. A new input for the disutility associated with treatment with SOC. This disutility, applied as a QALY decrement, has been added in the 'Quality of Life' sheet which can be varied across age groups and can be set to be included at every cycle, or as a one-off applied only to 'new' SOC patients. In the base case, the QALY decrement is 0.04 and is applied at every cycle to all patients receiving SoC treatment.
2. An updated value for the QALY decrement associated with acquired dRTA. This is the original company disutility value of 0.18 multiplied by the proportion of adults in the B21CS study with acquired dRTA (1 out of 7).

As part of their technical report, the ERG noted that a key advantage of ADV7103 treatment compared to SOC is the more convenient treatment regimen, yet this was not incorporated within the original company submission. In response to this, as no direct utility data were captured in the B21CS or B22CS trials, the company conducted a targeted literature review and 2 clinical validation interviews to identify an appropriate proxy utility (or disutility) value that could be used in the revised company model.

The targeted literature review identified 44 records through OVID database searching, with 2 additional records added from reference tracking. Following screening, only 3 studies were included for full review and included in the data validation with clinicians (see Table 1). The targeted literature review report has been included in appendix.

Table 1: TLR proxy disutility values for more convenient treatment regimen

Source	Disutility/year	Disease area and treatment
Matza et al., 2014	<0.00 (SD, 0.01)	Difference between oral regimen of 2 tablets per day vs 3 tablets per day in patients with hepatitis C.
Matza et al., 2021	0.01 (SD, 0.033)	Difference between simple oral treatment and semaglutide oral treatment in patients with type 2 diabetes.
Hadi et al., 2018	0.04	Burden associated with frequent oral medication in patients with Gaucher disease.

Upon full review of the identified studies, the company note the potential limitations associated with the results, and their generalisability and applicability within the company's model:

- All 3 studies adopted a time trade-off (TTO) vignette-based approach to estimate the utility values associated with each health state
- No study looked at the burden of treatment processes in patients with dRTA
- The defined treatment health states may not appropriately reflect the burden associated with treatment with alkali therapies

As part of the clinical validation, the 2 clinical experts were asked 7 questions relating to the burden of daily dosing of alkali therapy for dRTA patients, the B22CS treatment acceptability VAS scores, and the disutility values identified from the targeted literature review (See Table 1). The anonymised and consolidated respondent feedback can be found in the appendix. In summary, the advisors state that twice daily dosing is most manageable long term, with particular burden of three daily doses (SOC current dosing regimen) on children and adolescents. Advisors found it difficult to comment on a potential disutility value to be used in the model, however, 1 advisor believed the value presented by Hadi et al., (2018) (0.04) was the most suitable given that Gaucher disease is a better model for dRTA than hepatitis C or type 2 diabetes.

In further support of the value of ADV7103, the company have attached a qualitative study by Acquadro et al., (2022) on the lived experiences of patients with dRTA treated with ADV7103 and their caregivers. Acquadro et al., (2022) investigated the disease burden and treatment experience of 13 paediatric and 6 adult patients with dRTA, who had been switched from previous SOC treatments to ADV7103 and were followed up for at least 5 years during the B22CS extension study. For 18 patients, gastro-intestinal adverse events and taste problems improved with ADV7103 and better compliance let to milder physical impacts and less need to be hospitalised. For all 13 paediatric patients (and their families), difficulties at school due to burdensome administrative issues and need to explain disease and treatment disappeared. Acquardo et al., (2022) state that simplifying treatment compared to current SOC, through reduction of the number of daily intakes and/or number of products required, as is the case with ADV7103, may result in increased adherence to therapy and improved health outcomes.

The company’s revised base case results are shown in Table 2 below.

Table 2: Revised base case results – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
SoC	[redacted]	20.64	[redacted]				
ADV7103 deterministic	[redacted]	24.94	[redacted]	[redacted]	4.31	[redacted]	[redacted]
ADV7103 probabilistic				[redacted]		[redacted]	[redacted]

Abbreviations: Inc., incremental; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

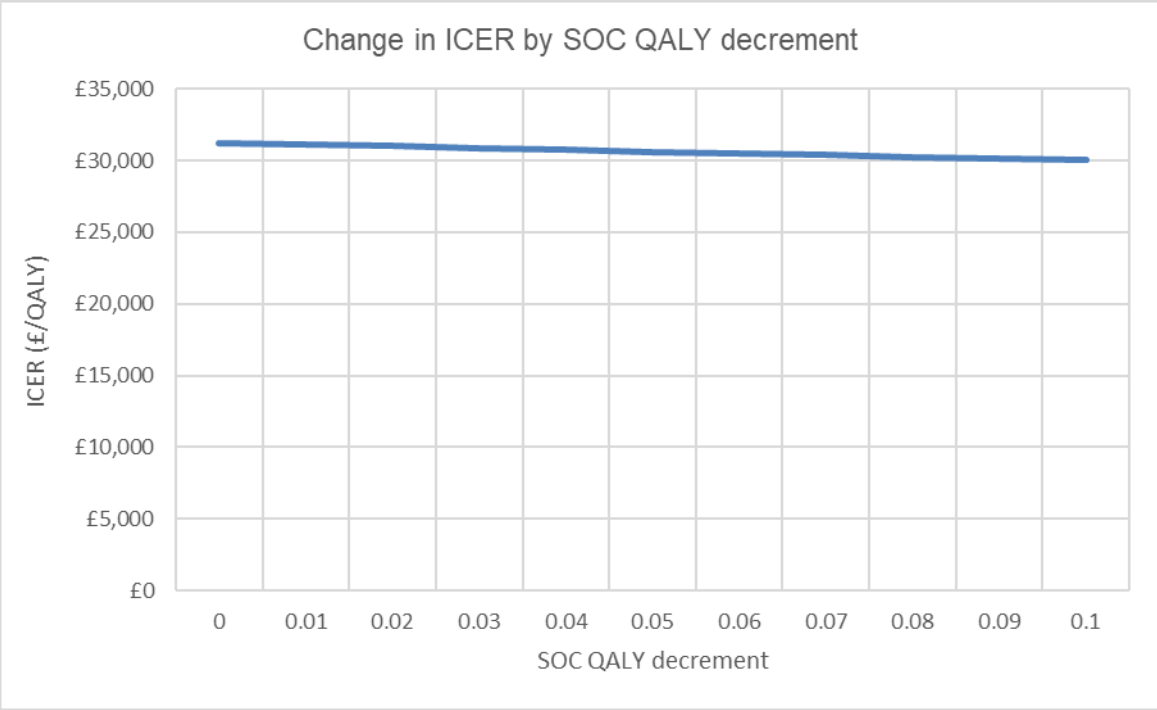
The revised company model was built on the ERG model presented at technical engagement. During the development of the revised model, the company believe that the ERG ICER may have been calculated based on an incorrect solver transition probability. In short, the ERG deterministic ICER presented [redacted] had been calculated using a transition probability for NC to CKD2 (cell G14) and NC+NL to CKD2 (cell G16) equal to 4.13%. When another transition probability in the model is updated, the solver transition probabilities update and equal 3.98%. As a result, re-running the ERG model, gives a new ERG deterministic ICER of [redacted].The revised company model ICERs include this amendment to the transition probability values.

Sensitivity analysis

The company present exploratory analysis on the revised model focusing on the addition of the QALY decrement applied to SOC treatment. The QALY decrement used in the base case was 0.04. Figure 1 presents the results of a one-way sensitivity analysis Technical engagement response form

assessing the impact that changes in the QALY decrement associated with SOC have on the on the ICER. The results present a range of QALY decrements from 0.00 to 0.10.

Figure 1: One-way sensitivity analysis for SOC QALY decrement

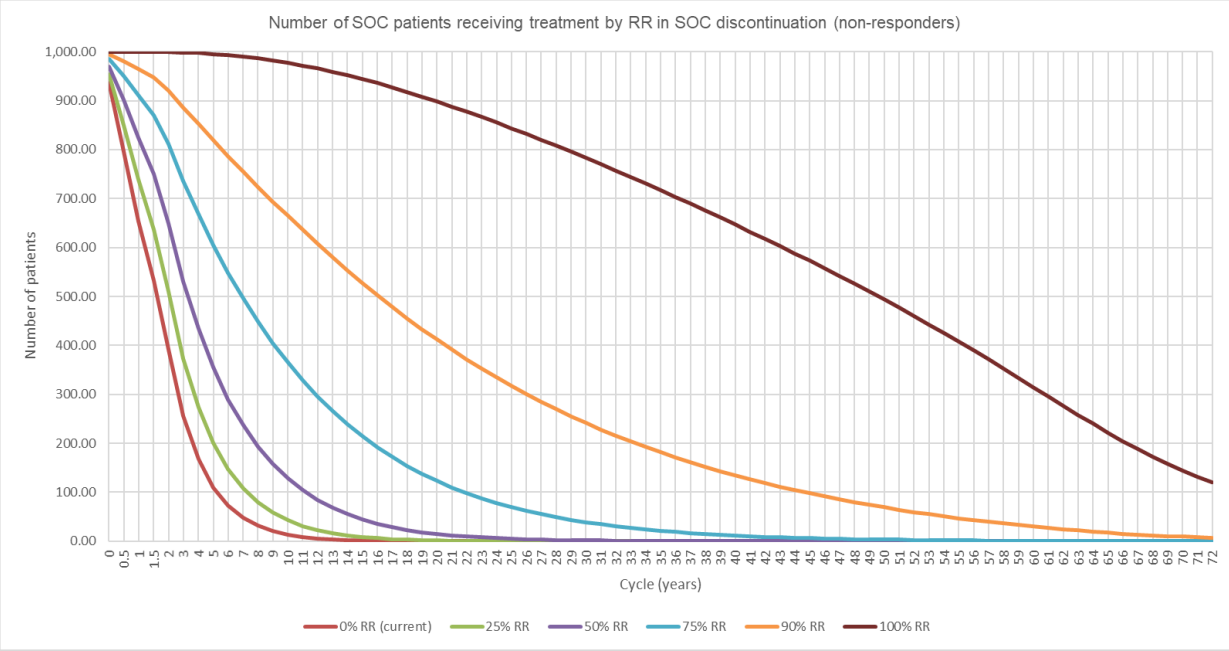


The company note that changes in the QALY decrement have a minimal impact on the ICER. The company believe this is due to lower efficacy and high discontinuation rates applied to non-responders (39.00% for children; 45.00% for adults) at each cycle in the SOC arm.

In the original company submission, and in the revised company model, a proportion of patients who discontinue ADV7103 can receive SOC treatment (as either a responder or non-responder). This proportion is set to 50%. As such, the QALY decrement applied to patients receiving SOC will also have an impact on the total QALYs in the ADV7103 model arm. When setting this proportion to 0%, the impact on the revised company ICER is negligible [redacted].

The number of patients receiving SOC treatment for different discontinuation rates is presented in Figure 2. The company has applied a relative reduction to the discontinuation rate of non-responders receiving SOC treatment (cells G57 and G58 in 'Clinical Efficacy' sheet) to show the impact on the number of patients receiving SOC treatment by the treatment discontinuation rate. A relative reduction of 0% gives the base line discontinuation rates (39.00% for children; 45.00% for adults), and a relative reduction of 100% gives discontinuation rates of 0.00% for both children and adults.

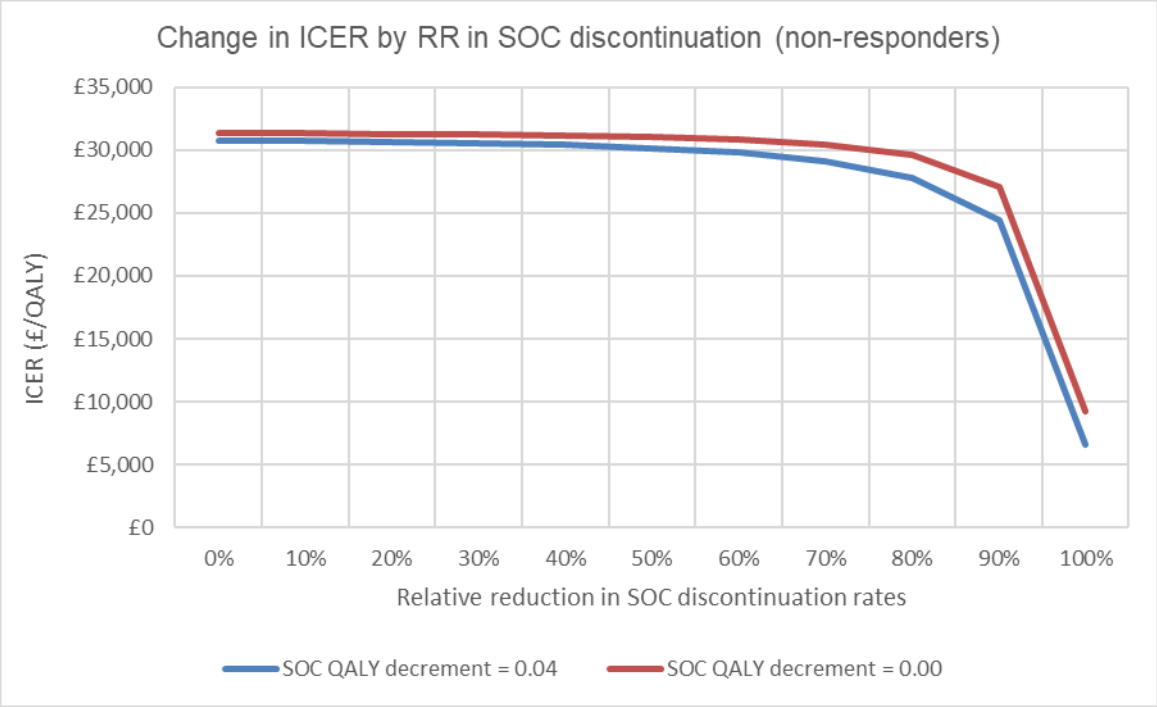
Figure 2: Number of SOC patients receiving treatment



In the base case, by year 2 (cycle 4) the number of SOC patients receiving treatment falls by 50%, with less than 100 SOC patients receiving treatment by year 6 (cycle 8).

Figure 3 presents the results of a one-way sensitivity analysis assessing the impact that changes in the SOC discontinuation rate of non-responders has on the on the ICER.

Figure 3: One-way sensitivity analysis for SOC non-responder discontinuation rates



The non-linearity of the curve in Figure 3, and the exponential growth in the Figure 2 can be explained by the increased risk of mortality associated with the discontinued population.

In line with the ERG's exploratory analysis, ICER results are also presented for the adult population (18+) (Table 3) and the non-adult population (<18) (Table 5). For the adult population only subgroup, ICERs (versus SOC) have also been provided when only

the SOC QALY decrement is applied (the dRTA QALY decrement set to 0) (Table 4). As the dRTA QALY decrement is only applied to the adult population, this scenario is not relevant for the non-adult population results.

The ICERs for the subgroups based on age are [redacted] ([redacted] probabilistic) for adults and [redacted] ([redacted] probabilistic) for non-adults.

Table 3: Revised base case results (adults) – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
SoC	[redacted]	20.34	[redacted]				
ADV7103 base case deterministic	[redacted]	24.17	[redacted]	[redacted]	3.83	[redacted]	[redacted]
ADV7103 base case probabilistic				[redacted]		[redacted]	[redacted]
Abbreviations: Inc., incremental; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 4: Revised scenario results (adults) – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
SoC	[redacted]	20.34	[redacted]				
ADV7103 SOC decrement only deterministic	[redacted]	24.17	[redacted]	[redacted]	3.83	[redacted]	[redacted]
ADV7103 SOC decrement only probabilistic				[redacted]		[redacted]	[redacted]
Abbreviations: Inc., incremental; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 5: Revised base case results (non-adults) – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
SoC	[redacted]	20.94	[redacted]				
ADV7103 base case deterministic	[redacted]	25.77	[redacted]	[redacted]	4.83	[redacted]	[redacted]
ADV7103 base case probabilistic				[redacted]		[redacted]	[redacted]
Abbreviations: Inc., incremental; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

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Slow-release potassium bicarbonate and potassium citrate for treating distal renal tubular acidosis [ID3787]. A Single Technology Appraisal. Addendum: ERG comments on company's technical engagement response

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK Emma Simpson, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Geoff Holmes, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Andrew Rawdin, Research Assistant, ScHARR, University of Sheffield, Sheffield, UK Ruth Wong, Information Specialist, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
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1 Introduction

In April 2022, the company submitted its technical engagement (TE) response for the appraisal of slow-release potassium bicarbonate and potassium citrate (ADV7103) for treating distal renal tubular acidosis.[1] The company's response was structured around the five key issues raised within the Evidence Review Group (ERG) report. The company's TE response includes a written technical engagement response document, together with updated version of the executable model. The company accepted the amendments made by the ERG to the company's model in the ERG report, and made one further structural change, as recommended by the ERG, to allow for a utility decrement to be applied to the standard of care (SoC) arm to take the inconvenient dosing regimen of SoC (often nightly doses are required) into consideration.

This document provides a commentary on the company's TE response and should be read in conjunction with the ERG report.[2] Section 2 provides a description of the company's response to each issue and the ERG's critique of these points. Section 3 presents the results of the company's updated base case and scenario analyses and additional analyses undertaken by the ERG. Overall conclusions are presented in Section 4.

All results presented in this document include the Patient Access Scheme (PAS) discount for ADV7103. The ERG has been informed by NICE that there are Commercial Medicines Unit (CMU) prices for Shohl's solution, potassium bicarbonate and sodium bicarbonate which are used within SoC. Results incorporating these reduced prices are contained in a confidential appendix.

2 The company's TE response and the ERG critique of these points

This ERG addendum is structured around the five key issues in the initial ERG report which are detailed in Sections 2.1 to 2.5. Each section summarises the issue as reported by the ERG, new data presented by the company (if any), the view put forward by the company, and any new incremental cost-effectiveness ratios (ICERs), expressed in terms of cost per quality-adjusted life year (QALY) gained, generated when using the company's preferred assumptions. Each section also includes the ERG's opinion on the new data / assumptions; the impact of these assumptions on the ICER is presented in Section 3 alongside the company's preferred ICER and the indicative ICERs preferred by the ERG. The company identified an implementation error in the ERG's preferred assumptions; this is detailed in Section 2.6.

2.1 Key Issue 1: Limited evidence related to the comparative efficacy of ADV7103 compared to SOC

The ERG commented that there is little long-term comparative efficacy data for ADV7103. The B21CS study used patients as their self-controls, but had a short duration (a maximum of 5 days of optimised treatment) and Study B22CS was single-armed. Both studies involved less than 40 patients. Understandably, the company could not address this issue within technical engagement, and this issue remains unresolved.

2.2 Key Issue 2: Limitations in the conceptualisation and functionality of the model

This issue covers several of sub-issues. Full details are provided in Section 4.3.3.1.1 of the ERG report. Headers for each issue are provided here. The following sub-issues have not been changed in the company's model and remain unresolved with an unknown impact on the ICER:

- Patients responding to treatment cannot progress beyond chronic kidney disease stage 2
- Patients not responding, but remaining on treatment, cannot progress to end-stage kidney disease
- Patients discontinuing treatment will never restart that treatment
- Patients who lose disease control or regain disease control remain in the same health state
- Conditions that are chronic in nature have been modelled as transitory health states.

For the following sub-issue, the company has revised its base case to incorporate the exploratory analyses performed by the ERG:

- Patients start the model in different health states dependent on initial treatment
  - The ERG exploratory analysis adds 5 days of ADV7103 costs to the intervention arm to approximate the costs associated with starting people in different health states.

For the following sub-issue, the company has amended the model such that the assumed disutility associated with acquired dRTA (0.18) was applied only to 1 in 7 adults, as this was the proportion of adult patients in the B21CS study that had acquired dRTA.

- The assumption that the disutility associated with those with acquired dRTA is not incurred when patients have controlled disease

The ERG comments that the change made by the company has multiple limitations (see Sections 4.3.3.1.7 and 4.3.3.1.8 of the ERG report for more details). These are as follows:

- No additional evidence has been provided to show that the disutility associated with patients with acquired dRTA is not incurred when dRTA is controlled
- That the value of 0.180 may not be generalisable to English patients with dRTA as it has been generated from patients receiving renal replacement therapy for acute renal failure at a tertiary centre in Finland
- that the patient with acquired dRTA in the B21CS study did not continue into the B22CS study
- that if patients with acquired dRTA form a distinct sub-group, then these should be analysed separately, with ICERs produced for the acquired dRTA group and the inherited dRTA group individually rather than reporting a blended ICER.

Given the limitations associated with the modelling of acquired dRTA, the ERG has chosen to provide ICERs for patients with inherited dRTA only, and noting the uncertainty in the cost-effectiveness of ADV7103 for patients with acquired dRTA.

For the following sub-issue, the company has amended the model structure:

- No chronic utility gain associated with the more convenient dosing regimen of ADV7103 compared to SoC

The model now allows a disutility associated with taking SoC. The disutility was informed by a targeted literature review (TLR) and through discussions with 2 clinicians. The TLR had the aim of identifying utility or disutility values associated with different treatment regimens and is described in detail in an appendix submitted in the company's TE response. Forty-four records were identified in the search, with two additional records identified from reference tracking and grey literature searching. Following screening, five full text articles were assessed for eligibility with three papers containing useable utility values.[3-5] None of these papers related to patients with dRTA.

Matza *et al*.[3] used time trade off (TTO) methods to estimate the burden of treatment regimens for hepatitis C. This allowed a comparison of seven tablets a day versus one tablet a day, and the comparison of seven tablets a day alongside a weekly injection versus 18 tablets a day alongside a

weekly injection. Assuming a TTO horizon of 10 years, in the all-oral regimen, the difference in utility was estimated to be 0.01 (standard deviation (SD) 0.03) in favour of one tablet a day (no comment was made on statistical significance). For oral regimens in combination with a weekly injection, the difference in utility was estimated to be 0.07 (SD 0.16) in favour of seven tablets a day which was reported to be statistically significant (p-value<0.001).

Hadi *et al*.[4] used a TTO approach to assess the burden of treatment regimens for patients with Gaucher disease, in terms of intravenous vs oral administration and frequency of treatment. For oral treatments two alternative scenarios were developed, alternative 1 which was reported to have a reduced frequency of intake (one capsule a day) and reduced side effects (temporary diarrhoea, headache and tiredness) compared with the standard scenario (one capsule one to three times a day and temporary diarrhoea), and alternative 2 which had an increased frequency of intake (three capsules a day) and increased side effects (temporary diarrhoea, flatulence, abdominal pain, weight loss and tremors) compared with the standard scenario. There appears to be a contradiction in that alternative 1 is reported to have less side effects, but the reported side effect profile appears worse. This may impact on the face validity of the results, as alternative 1 was assumed to have a lower utility than the standard scenario despite being described as having a reduced frequency of intake and reduced side effects. These results appear to be driven by one respondent providing a TTO value of -0.85 for alternative 1, which lacks face validity. Comparing alternatives 1 and 2, the difference in utility was estimated to be 0.04 in favour of reduced intake and reduced side effects, although it was not reported whether this difference was statistically significant. It also does not appear possible to disentangle the impacts of reduced intake from the impact of reduced side effects.

Matza *et al*.[5] used TTO methods to assess the utility difference in people treated for type 2 diabetes between an oral treatment without administration requirements and oral semaglutide, which has administration requirements. Administration requirements for semaglutide include taking the tablet "on an empty stomach when you first wake up," "with a sip of plain water," and "wait at least 30 minutes after taking this tablet before eating, drinking, or taking other oral medications." The difference in utility between simple oral tablets and semaglutide was 0.01 (SD 0.033) which was statistically significant (adjusted p-value 0.0002).

The clinical advisors consulted by the company found it difficult to comment on the potential disutility value that should be used in the model, although one advisor believed the Hadi *et al*.[4] value was most suitable given that Gaucher disease is a better model for dRTA than either hepatitis C or type 2 diabetes. The company also provide supporting evidence from Acquardo *et al*.[6] which reported findings from semi-structured, one-hour interviews with six adults and 13 paediatric patients with confirmed dRTA. The mean satisfaction score with ADV7103 treatment compared to SoC was 9 out of 10 (1 = not

satisfied and 10 – very satisfied, with 14 of the 17 patients that commented on whether ADV7103 treatment had met or exceeded their expectations expressing this positive view. The authors comment that changing from SoC to ADV7103 treatment was '*perceived as life-changing for patients / parents.*'

The ERG comments that none of the identified studies reporting utility values are ideal as it appears that none explicitly evaluate the impact of doses taken during the night as required by SoC for treating dRTA. In addition: Matza *et al*.[3] show that the difference in utility associated with more pills per day is strongly dependent on whether there is a weekly injection (0.07 with and 0.01 without) which may not have face validity; in Hadi *et al*.[4] the utility benefit estimated from reduced number of capsules (0.04) also includes the impact of reduced side effects, and there appears to be a potential face validity error in the results; and Matza *et al*.[5] did not evaluate the impact of a change in dosing frequency but evaluated the impact of administrative requirements (0.01). The data most relevant to dRTA patients is provided by Acquardo *et al*.[6] although no preference-based measure of utility was collected. However, patients commented that they were very satisfied with ADV7103 treatment compared with SoC. Considering all of the evidence presented by the company, the ERG believes that the 0.04 disutility associated with SoC used in the company's base case is a reasonable estimate, although this value is uncertain.

2.3 Key Issue 3: Lack of targeted reviews to populate the model and the reliance on clinical opinion

In Section 4.1 of the ERG report, the ERG highlighted that the search strategies used by the company in its TLRs were not provided. Following TE, the company updated its search strategy (March 2022) and provided search strategies to two TLRs A (six searches) and B (one search).

TLR A:

1. Utility/dis-utility values/HRQoL of the health states (5 searches): dRTA and nephrocalcinosis nephrolithiasis/CKD/ERSD/transplantation
2. Utility/dis-utility values of the transitory events (6 searches): dRTA and osteomalacia /facture/failure to thrive/one deformities/gastro-intestinal events/hypokalemia
3. Loss of QoL in acquired dRTA -decrement associated with underlying condition
4. Discontinuation/compliance to treatment
5. Disease and event related mortality – annual probabilities of CDK3-4, ESRD, transplant, Hypokalaemia, CKD, no CKD, fracture
6. Average weight by age

TLR B:

7. Utility/disutility value of treatment regimen difference

Searches were carried out simultaneously across 11 databases in Ovid (including MEDLINE, Embase, NHS EED and EconLit). Highly focused terms for dRTA and a precise filter for utility and disutility was consistently applied across searches 1-3 above. Given the number of records retrieved in searches 2 (gastro-intestinal events) and 5, the company has restricted the searches to title field only.

The ERG recognises that the searches for the two TLRs are systematic, pragmatic and transparent. However, the ERG would have wanted to see text explicitly justifying the reasons for choosing the source used to populate the base case model.

2.4 Key Issue 4: Inappropriate population of the model from the sources cited by the company

In the ERG report, the ERG conducted exploratory analyses to address limitations related to the population of the company's model. The company accepted the following changes made by the ERG, and these have been largely resolved, although some uncertainty remains:

- Inappropriate utilities used for the general population (see Section 4.3.3.2.2 of the ERG report and ERG EA4)
- Inappropriate calculations of utility multipliers related to health states (see Section 4.3.3.2.3 of the ERG report and ERG EA4)
- Potentially inappropriate QALY losses associated with transitory health states (see Section 4.3.3.2.4 of the ERG report and ERG EA5)
- The assumption that all patients with nephrolithiasis would have 1 percutaneous nephrolithotomy each year (see Section 4.3.3.2.9 of the ERG report and ERG EA2)
- Estimation of risk of death associated with fracture or with hypokalaemia (see Section 4.3.3.2.12 of the ERG report and ERG EA12)
- Estimation of the proportions of patients with disease control at the start of the model (see Section 4.3.3.2.13 of the ERG report and ERG EA13)
- The assumed dosages for ADV7103 (see Section 4.3.3.2.14 of the ERG report and ERG EA14)

The ERG identified uncertainty related to the assumption of equal disease control due to ADV7103 treatment regardless of age (see Section 4.3.3.2.15 of the ERG report) and that no continuity correction had been performed due to small patient numbers (see Section 4.3.3.2.17 of the ERG report). The ERG did not perform exploratory analyses on these issues, which remain additional sources of uncertainty.

The ERG also noted the uncertainty in the proportion of patients with acquired dRTA (see Section

4.3.3.2.6 of the ERG report). However, the ERG has not modelled patients with acquired dRTA; see Section 2.2 of this report for the rationale for this decision.

2.5 Key Issue 5: Implementation issues within the model

The ERG identified multiple implementation issues within the company's model. The company has accepted the ERG's amendments to the company's model.

2.6 Additional Issue: Error in the implementation of the ERG's preferred assumptions

The company identified an implementation issue when the ERG amended the company's model. This related to the fact that the company's model had been calibrated such that the proportion of patients who are non-responders that move from nephrocalcinosis to CKD2 or to CKD3-4 matched the value reported for 11-year-old patients in Lopez-Garcia *et al*.[7] When the ERG amended transition probabilities in the company's model, the SOLVER add-in within Excel should have been re-run. The ERG accepts the company's position on this matter.

However, when this correction is made, the ICER is marginally different in the company's model to that reported in the company's response to TE [redacted] compared with [redacted]). The ERG suspects that the value in the report is a typographical error as the ERG can replicate the remaining ICERs cited by the company.

3 Additional analyses undertaken by the company and the ERG

3.1 Results of the analyses presented by the company

This section presents the central estimates of costs effectiveness using the deterministic version of the updated version of the company's model submitted at the TE response.

Table 1 presents the deterministic estimates of cost-effectiveness reported by the company, with the exception of the suspected typographical error in the corrected base case.

Table 1: Company's updated deterministic results (weighted population)

Analysis	Life years†	QALYs	Costs	Incremental			ICER
				Life years†	QALYs	Costs	
ERG's indicative base case							
ADV7103	24.94	[redacted]	[redacted]	4.39	[redacted]	[redacted]	[redacted]
SoC	20.55						
1) ERG's corrected indicative base case (having run SOLVER after changing transition probabilities)*							
ADV7103	24.94	[redacted]	[redacted]	4.31	[redacted]	[redacted]	[redacted]
SoC	20.64						
2) 1) + assuming disutility associated with SOC treatment on 0.04							
ADV7103	24.94	[redacted]	[redacted]	4.31	[redacted]	[redacted]	[redacted]
SoC	20.64						
3) 1) + assuming 1 in 7 adults have acquired dRTA and have a utility loss of 0.18 when disease is not controlled							
ADV7103	24.94	[redacted]	[redacted]	4.31	[redacted]	[redacted]	[redacted]
SoC	20.64						
Company's revised base case (1 + assuming disutility associated with SOC treatment on 0.04 and assuming 1 in 7 adults have acquired dRTA and have a utility loss of 0.18 when disease is not controlled							
ADV7103	24.94	[redacted]	[redacted]	4.31	[redacted]	[redacted]	[redacted]
SoC	20.64						

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years
*SoC: Standard of Care †Undiscounted (all other values are discounted) * calculated by the ERG*

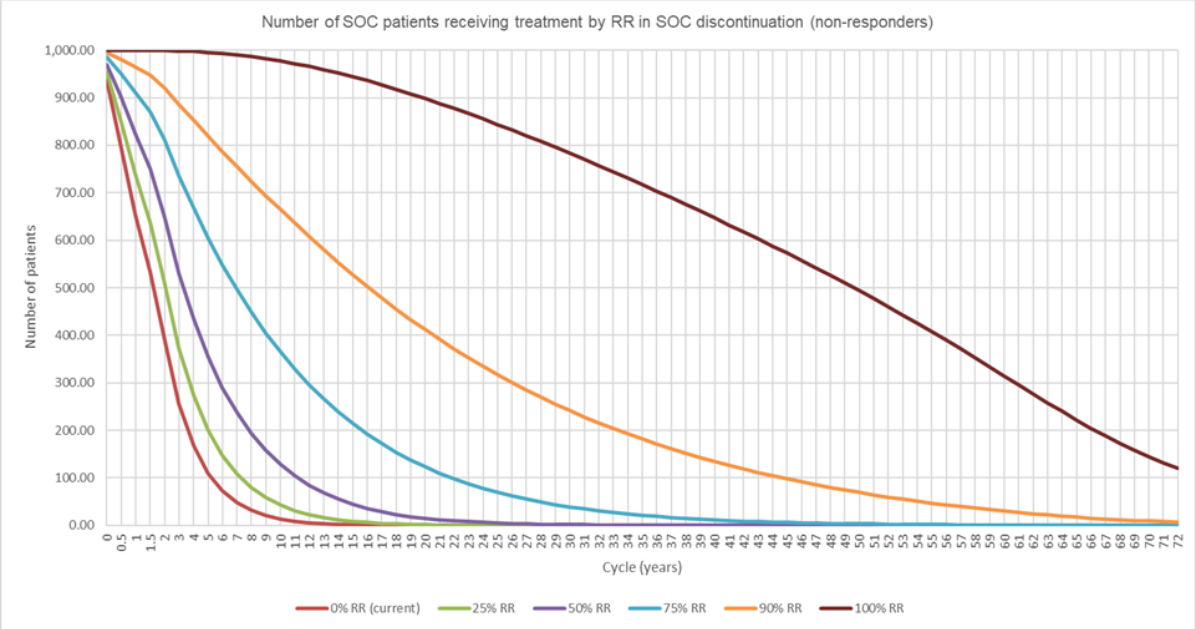
The company presented the ICER from the probabilistic version of its revised base case, which was lower [redacted]; incremental costs [redacted] and incremental QALYs [redacted]). However, the ERG notes that the model was not recalibrated between probabilistic sensitivity analyses iterations which may introduce inaccuracies within the generated results which should thus be treated with caution.

The company provided results from a sensitivity analysis where the disutility associated with SoC ranged from 0 to 0.1, which was shown to only have a small impact on the ICER (see Figure 1 of the company's response to TE). However, the ERG believes that these results used an assumption that no patient on ADV7103 would receive SoC on discontinuation, whereas the company's base case model assumes that 50% of people discontinuing ADV7103 would receive SoC. Changing the disutility

associated with SoC to 0.04 to 0.10 in the company's revised base case reduced the ICER from [redacted] to [redacted], which remains a small impact.

The company reported the estimated number of patients remaining on SoC treatment over time in its base case and when changing assumptions related to discontinuation on SoC. The discontinuation rates per year in the base case for people not responding to SoC treatment was 39% for non-adults and 45% for adults; these values were based on clinical opinion. An assumption in the company's model is that once people have discontinued SoC they do not resume SoC ever again. Analyses were performed using a relative reduction (RR) in the discontinuation rates, where a RR of 0% gives the base case discontinuation rates and a RR of 100% gives discontinuation rates of 0% for both non-adults and adults. Figure 2 of the company's response to TE is reproduced in Figure 1. In the base case (RR = 0), approximately 90% of patients have discontinued SoC treatment at 5 years. Reducing the discontinuation rate for non-responders on SoC by 75% (RR = 0.75) results in approximately 40% of patients remaining on SoC treatment at 5 years.

Figure 1: Estimation of number of people remaining on SoC treatment over time, assuming different discontinuation rates for non-responders

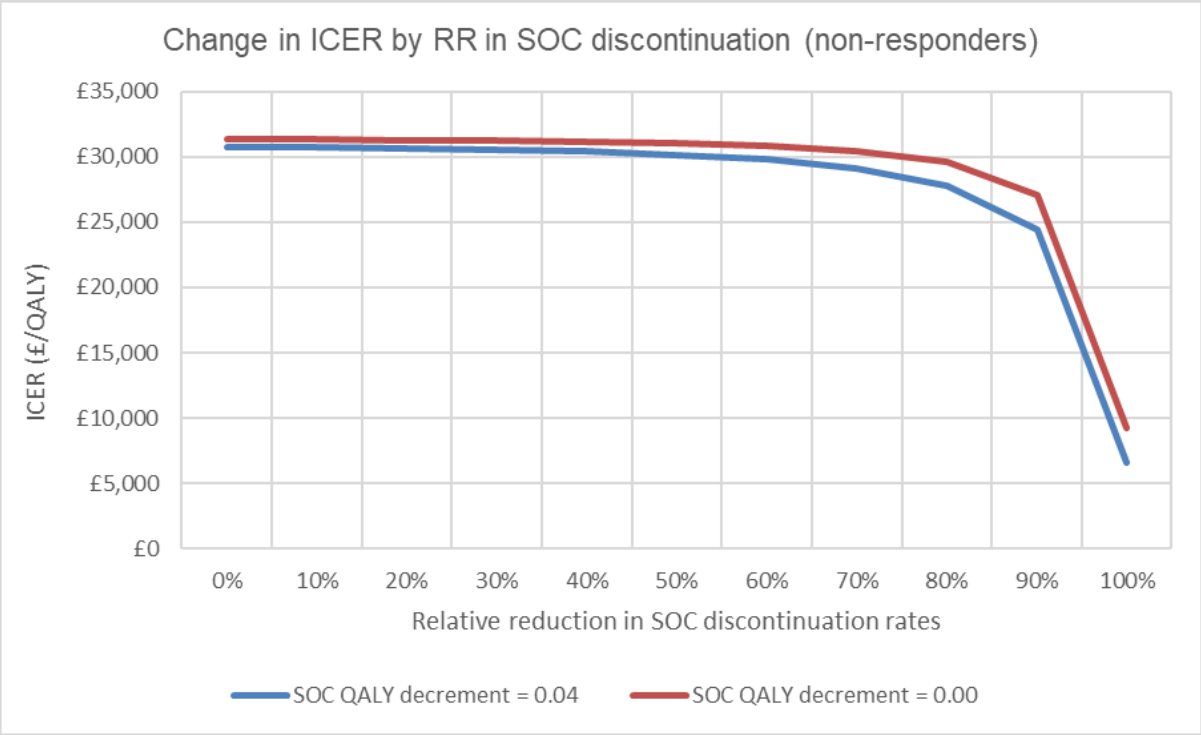


The company additionally presented a one-way sensitivity analysis exploring how the discontinuation rates amongst non-responders to SoC impacted on the ICER. The company's analysis, reproduced in Figure 2, shows that there is a sharp decrease in the ICER when the discontinuation rate is much lower than assumed in the base case. The ERG could not replicate the values provided by the company in Figure 2, but generated similar conclusions, with the company's base ICER falling from [redacted] to

[redacted] when discontinuation rates in non-responders were 3.9% for non-adults and 4.5% for adults (a RR of 0.9) and to [redacted] when discontinuation was not assumed.

The ERG does not know the relative impacts on the ICER made by the debatable assumptions within the company's model that patients on treatment (even if not responding) cannot progress to end-stage kidney disease and that patients will never resume SoC treatment once they have discontinued SoC. However, the ERG believes that a lower discontinuation rate for non-responders on SoC treatment would be more favourable to ADV7103 treatment, although significant changes in the ICER may only occur when there is a very low rate of discontinuation.

Figure 2: Company's exploration of the impact of reduced discontinuation probabilities for patients not responding to SoC



3.2 Description of additional exploratory analyses undertaken by the ERG

In all exploratory and additional sensitivity analyses, the ERG has used the company's updated version of the model. The ERG ran one exploratory analysis which was to remove the disutility associated with acquired dRTA (See Section 2.2 for further discussion). The ERG's indicative ICER is thus the same as for Scenario 2) in Table 1.

The ERG performed three additional sensitivity analyses, the first two of which were also presented in the ERG report. These were:

- ERG additional analysis 1 - using the definition of disease control where patients had to have bicarbonataemia values at least as high as the lower normal range, as defined by local laboratories on all of Days 2, 3 and 4 rather than the mean across the three days being greater than the threshold, resulting in an initial disease control of 76.67% for ADV7103 and 36.67% for SoC (rather than 90.00% and 43.33% respectively);
- ERG additional analysis 2 - using the values of disease control implied by the transition probabilities for maintaining disease control and regaining disease control in Months 0 to 6. This resulted in an initial disease control of 63.33% for ADV7103 (rather than 90.00%), the assumed disease control for SoC was maintained at 43.33%;
- ERG additional analysis 3 – calculating ICERs for each age group to allow exploration of the impact on the ICER if all new confirmed cases of inherited dRTA were in infants or children, and to also allow an assessment of the sensitivity of the weighted population ICER to changes in the assumed proportions of adults, adolescents, children and infants.

Probabilistic analyses were not undertaken by the ERG due to the problem relating to the lack of calibration performed for each iteration. However, the ERG notes that the probabilistic estimates generated by the company, and by the ERG in the ERG report produced lower ICERs (typically by [redacted] to [redacted]) than the deterministic runs.

3.3 Results of exploratory analyses undertaken by the ERG

The results when removing the disutility associated with acquired dRTA is shown in Table 2. This increases the ICER compared with the company's revised base case.

Table 2: ERG's indicative deterministic ICER (weighted population)

Description	Life years†	QALYs	Costs	Incremental			ICER
				Life years†	QALYs	Costs	
ADV7103	24.94	[redacted]	[redacted]	4.31	[redacted]	[redacted]	[redacted]
SoC	20.64	[redacted]	[redacted]				

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years

SoC: Standard of Care †Undiscounted (all other values are discounted)

The results for ERG additional analysis 1 are shown in Table 3 and the results for ERG additional analysis 2 are shown in Table 4. Note that although the disease control value for SoC does not change in ERG additional analysis 2, the results for SoC change from the base case as the model estimates the outcomes for SoC based on the relative efficacy between SoC and ADV7103, which has changed. The two additional analyses had only a small impact on the ICER.

Table 3: ERG's indicative deterministic ICER assuming that proportion of patients with controlled disease was defined as having bicarbonataemia values equal or above the lower normal range on all of Days 2-4 of Study B21CS (weighted population)

Description	Life years†	QALYs	Costs	Incremental			ICER
				Life years†	QALYs	Costs	
ADV7103	24.94	[redacted]	[redacted]	4.32	[redacted]	[redacted]	[redacted]
SoC	20.62	[redacted]	[redacted]				

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years

SoC: Standard of Care †Undiscounted (all other values are discounted)

Table 4: ERG's indicative deterministic ICER assuming that the proportion of patients with controlled disease was that inferred from the transition probabilities for disease control in Months 0-6 (weighted population)

Description	Life years†	QALYs	Costs	Incremental			ICER
				Life years†	QALYs	Costs	
ADV7103	24.94	[redacted]	[redacted]	4.26	[redacted]	[redacted]	[redacted]
SoC	20.68	[redacted]	[redacted]				

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years

SoC: Standard of Care †Undiscounted (all other values are discounted)

Table 5 to Table 8 show the ICERs for infants, children, adolescents and adults respectively. It is noted that the ICERs increase noticeably as the patients age increases.

Table 5: ERG's indicative deterministic ICER (infants)

Description	Life years†	QALYs	Costs	Incremental			ICER
				Life years†	QALYs	Costs	
ADV7103	26.17	[redacted]	[redacted]	5.13	[redacted]	[redacted]	[redacted]
SoC	21.04	[redacted]	[redacted]				

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years

SoC: Standard of Care †Undiscounted (all other values are discounted)

Table 6: ERG's indicative deterministic ICER (children)

Description	Life years†	QALYs	Costs	Incremental			ICER
				Life years†	QALYs	Costs	
ADV7103	25.90	[redacted]	[redacted]	4.91	[redacted]	[redacted]	[redacted]
SoC	20.98	[redacted]	[redacted]				

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years

SoC: Standard of Care †Undiscounted (all other values are discounted)

Table 7: ERG's indicative deterministic ICER (adolescents)

Description	Life years†	QALYs	Costs	Incremental			ICER
				Life years†	QALYs	Costs	
ADV7103	25.25	[redacted]	[redacted]	4.45	[redacted]	[redacted]	[redacted]
SoC	20.79	[redacted]	[redacted]				

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years

SoC: Standard of Care †Undiscounted (all other values are discounted)

Table 8: ERG's indicative deterministic ICER (adults)

Description	Life years†	QALYs	Costs	Incremental			ICER
				Life years†	QALYs	Costs	
ADV7103	24.17	[redacted]	[redacted]	3.83	[redacted]	[redacted]	[redacted]
SoC	20.34	[redacted]	[redacted]				

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years

SoC: Standard of Care †Undiscounted (all other values are discounted)

4 Overall conclusions

The model submitted by the company at TE was implemented to a good standard, although the ERG preferred an alternative assumption relating to the disutility of patients with acquired dRTA to that used by the company. Incorporating this change increased the deterministic ICER of from [redacted] to [redacted].

Additional sensitivity analyses conducted by the ERG suggests that the deterministic ICER is dependent on the age group of the patients with an ICER of [redacted] in infants, rising to [redacted] in adults. This may be of importance if the split between age groups is uncertain (8.8% infants, 23.5% children, 17.6% adolescents and 50.0% adults was assumed in the company's base case) or if newly diagnosed patients with dRTA were infants or children.

The remains considerable uncertainty in the ICER due to the small number of patients included in the BC21S and B22CS studies, the limited comparative efficacy data of ADV7103, and the reliance on clinical opinion for numerous model parameters.

The ERG has been informed by NICE that there are CMU prices for Shohl's solution, potassium bicarbonate and sodium bicarbonate which are used within SoC. Results incorporating these reduced prices are contained in a confidential appendix.

5 References

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4. Hadi M, Swinburn P, Nalysnyk L, Hamed A, Mehta A. A health state utility valuation study to assess the impact of treatment mode of administration in Gaucher disease. *Orphanet Journal of Rare Diseases* 2018;13:159.
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Slow-release potassium bicarbonate and potassium citrate for treating distal renal tubular acidosis [ID3787]. A Single Technology Appraisal – Addendum changing the utility multiplier associated with end stage renal disease

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK Andrew Rawdin, Research Assistant, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
Date completed	24th May 2022

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During the lead team discussion with the ERG, it was commented that there was potentially a face validity error in the utility multiplier applied to the end stage renal disease (ESRD) as this, 0.809, was higher than for patients with liver transplant (0.619). Additional results have been run using a utility multiplier of 0.541 as originally assumed by the company to inform the committee.

Tables 1 to 8 in the ERG addendum following technical engagement are replicated in this document as Table 1 to Table 8 using the lower utility multiplier for ESRD. The ERG's base case before the correction of the transition probabilities by running SOLVER has been omitted for brevity.

Table 1: Company's updated deterministic results (weighted population)

Analysis	Life years†	QALYs	Costs	Incremental			ICER
				Life years†	QALYs	Costs	
1) ERG's corrected indicative base case (having run SOLVER after changing transition probabilities)*							
ADV7103	24.94	[redacted]	[redacted]	4.31	[redacted]	[redacted]	[redacted]
SoC	20.64	[redacted]	[redacted]				
2) 1) + assuming disutility associated with SOC treatment on 0.04							
ADV7103	24.94	[redacted]	[redacted]	4.31	[redacted]	[redacted]	[redacted]
SoC	20.64	[redacted]	[redacted]				
3) 1) + assuming 1 in 7 adults have acquired dRTA and have a utility loss of 0.18 when disease is not controlled							
ADV7103	24.94	[redacted]	[redacted]	4.31	[redacted]	[redacted]	[redacted]
SoC	20.64	[redacted]	[redacted]				
Company's revised base case (1 + assuming disutility associated with SOC treatment on 0.04 and assuming 1 in 7 adults have acquired dRTA and have a utility loss of 0.18 when disease is not controlled							
ADV7103	24.94	[redacted]	[redacted]	4.31	[redacted]	[redacted]	[redacted]
SoC	20.64	[redacted]	[redacted]				

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years
*SoC: Standard of Care †Undiscounted (all other values are discounted) * calculated by the ERG*

Table 2: ERG's indicative deterministic ICER (weighted population)

Description	Life years†	QALYs	Costs	Incremental			ICER
				Life years†	QALYs	Costs	
ADV7103	24.94	[redacted]	[redacted]	4.31	[redacted]	[redacted]	[redacted]
SoC	20.64	[redacted]	[redacted]				

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years

SoC: Standard of Care †Undiscounted (all other values are discounted)

Table 3: ERG's indicative deterministic ICER assuming that proportion of patients with controlled disease was defined as having bicarbonataemia values equal or above the lower normal range on all of Days 2-4 of Study B21CS (weighted population)

Description	Life years†	QALYs	Costs	Incremental			ICER
				Life years†	QALYs	Costs	
ADV7103	24.94	[redacted]	[redacted]	4.32	[redacted]	[redacted]	[redacted]
SoC	20.62	[redacted]	[redacted]				

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years

SoC: Standard of Care †Undiscounted (all other values are discounted)

Table 4: ERG's indicative deterministic ICER assuming that the proportion of patients with controlled disease was that inferred from the transition probabilities for disease control in Months 0-6 (weighted population)

Description	Life years†	QALYs	Costs	Incremental			ICER
				Life years†	QALYs	Costs	
ADV7103	24.94	[redacted]	[redacted]	4.26	[redacted]	[redacted]	[redacted]
SoC	20.68	[redacted]	[redacted]				

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years

SoC: Standard of Care †Undiscounted (all other values are discounted)

Table 5: ERG's indicative deterministic ICER (infants)

Description	Life years†	QALYs	Costs	Incremental			ICER
				Life years†	QALYs	Costs	
ADV7103	26.17	[redacted]	[redacted]	5.13	[redacted]	[redacted]	[redacted]
SoC	21.04	[redacted]	[redacted]				

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years

SoC: Standard of Care †Undiscounted (all other values are discounted)

Table 6: ERG's indicative deterministic ICER (children)

Description	Life years†	QALYs	Costs	Incremental			ICER
				Life years†	QALYs	Costs	
ADV7103	25.90	[redacted]	[redacted]	4.91	[redacted]	[redacted]	[redacted]
SoC	20.98	[redacted]	[redacted]				

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years

SoC: Standard of Care †Undiscounted (all other values are discounted)

Table 7: ERG's indicative deterministic ICER (adolescents)

Description	Life years†	QALYs	Costs	Incremental			ICER
				Life years†	QALYs	Costs	
ADV7103	25.25	[redacted]	[redacted]	4.45	[redacted]	[redacted]	[redacted]
SoC	20.79	[redacted]	[redacted]				

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years

SoC: Standard of Care †Undiscounted (all other values are discounted)

Table 8: ERG's indicative deterministic ICER (adults)

Description	Life years†	QALYs	Costs	Incremental			ICER
				Life years†	QALYs	Costs	
ADV7103	24.17	[redacted]	[redacted]	3.83	[redacted]	[redacted]	[redacted]
SoC	20.34	[redacted]	[redacted]				

ICER: Incremental cost-effectiveness ratio QALYs: Quality-adjusted life years

SoC: Standard of Care †Undiscounted (all other values are discounted)

Conclusion

Reducing the utility multiplier associated with the ESRD health state from 0.809 to 0.541 the ICER is associated with a reduction in the ICER of around [redacted] when the list prices for Shohl's solution, potassium bicarbonate and sodium bicarbonate are used. The ERG's preferred indicative ICER has reduced from [redacted] to [redacted]

NICE National Institute for Health and Care Excellence

Patient expert statement

Slow-release potassium bicarbonate and potassium citrate for treating distal renal tubular acidosis [ID3787]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Nicola MacArthur**

2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	N/A
4. Did your nominating organisation submit a submission?	☐ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	As I've got older I've become more aware of how I need to make changes to maintain the condition, which in turn has made things harder. The thing I struggle with is taking sodium bicarbonate everyday, 3 times a day. Time and time over we have changed the dosage, the type of pill and timings of the days of when to take them. Now it is keeping up with the right diet. What is low in sodium, oxalates and animal protein, but has enough calcium to help my osteoporosis, but then also has enough iron. To keep my energy levels up. As a young adult I just want to enjoy my food and be able to keep active. 3 times a year I often end up at the Royal free, be it a kidney stone, or low electrolytes, that I can't use my muscles. Ive undergone a cystoscopy at least twice a year, been infused with bags of liquids and Have had so many CT scans I've lost count.

	I've recently resigned from my job because of the stress affecting my health. The mental side of living with RTA has hit harder as I feel I am not as strong as a normal 29yr old and can not maintain a job where I would want to climb the career ladder due to being Ill a lot of the times in the year. And thinking of the future and starting a family I worry I will not be able to have a normal pregnancy, let alone do not want to pass this condition onto my children. The Royal Free have always treated my condition immediately when needed. The renal team are great, but I feel that there could be more done to help with the prevention on kidney stones, such as providing a specialist dietitian. Or preventing from having to wait for stones to cause issues before treatment. On the whole there could be more detailed check ups and specific advice given to patients.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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