Targeting improved growth in children and bone density & quality of life in adults with dRTA using novel prolonged-release oral alkalizing agent

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Disclosures

- Consultancy and Speaker fees from Avanzanite bioscience

Distal renal tubular acidosis (dRTA)

Distal renal tubular acidosis (dRTA) is characterized by an impaired ability of the distal tubule to excrete acid leading to metabolic acidosis

- **Primary,** rare metabolic disease due to pathogenic variants in genes involved in acid excretion
- **Secondary,** associated with acquired damage to the distal tubule

Primary dRTA

Prevalence <1:100 000

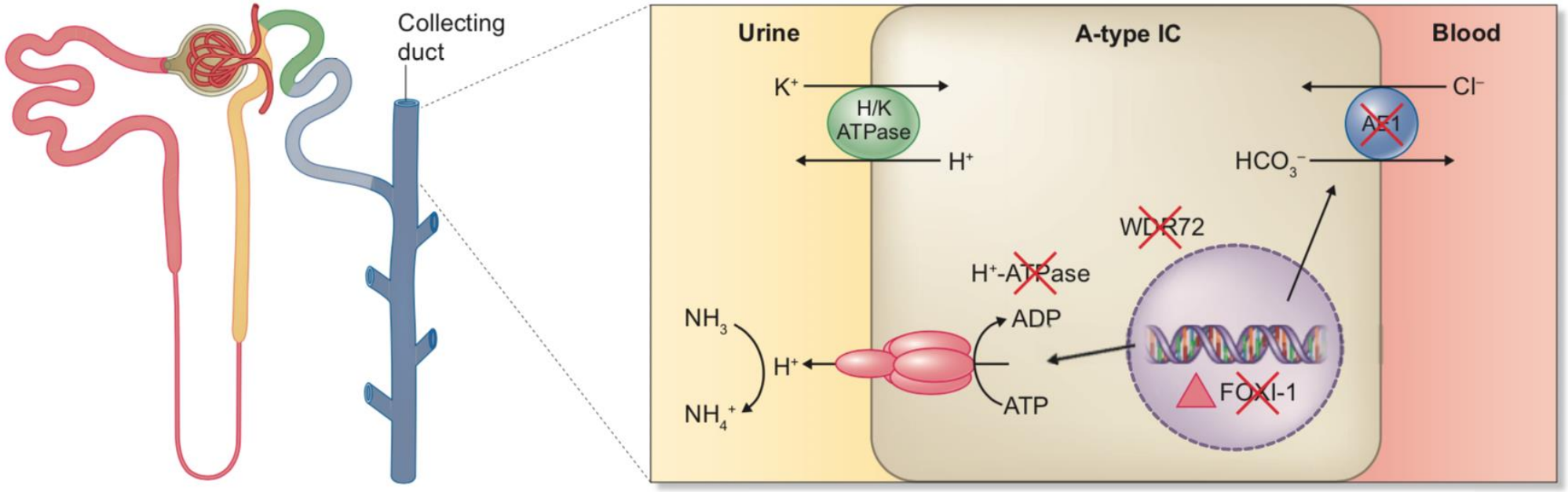

Table 3. Genes associated with dRTA: listed are currently recognized genes associated with dRTA

Gene	Function	Phenotype MIM	Inheritance	Extra-renal features	Reference
SLC4A1	Anion exchanger (AE1)	179800	AD, AR	none	[32]
ATP6V1B1	V-type H^+ ATPase subunit B1	267300	AR	SND	[33]
ATP6V0A4	V-type H^+ ATPase subunit a4	602722	AR	±SND	[34]
FOXI1	Transcription factor FOXI1	N/A	AR	SND	[35]
WDR72	WD repeat-containing protein 72	N/A	AR	AI	[36]

MIM, Mendelian Inheritance in Man; AD, autosomal dominant; AR, autosomal recessive; SND, sensorineural deafness; AI, amelogenesis imperfect; N/A, not available.

Trepiccione F, et al. Nephrol Dial Transplant (2021) 36: 1585–1596

Secondary dRTA -usually diagnosed in adults

- **Autoimmune diseases** (Sjögren syndrome, systemic lupus erythematosus)
- **Drugs** (amphotericin B, lithium, CNI)
- **Nephrocalcinosis/ hypercalciuria**
- **Medullary sponge kidney** (MSK)
- **Kidney transplantion** (rejection)
- **Chronic obstructive uropathy**
- **Hyponatriuric states** (cirrhosis, nephrotic syndrome)
- **Sickle cell anemia**

→ When to suspect dRTA

- An established diagnosis of Sjogren syndrome
- History of kidney stones/muscle weakness/polyuria
- Dipstick showing low specific gravity
- Persistent hypokalaemia, metabolic acidosis (low bicarbonate), hypophosphataemia

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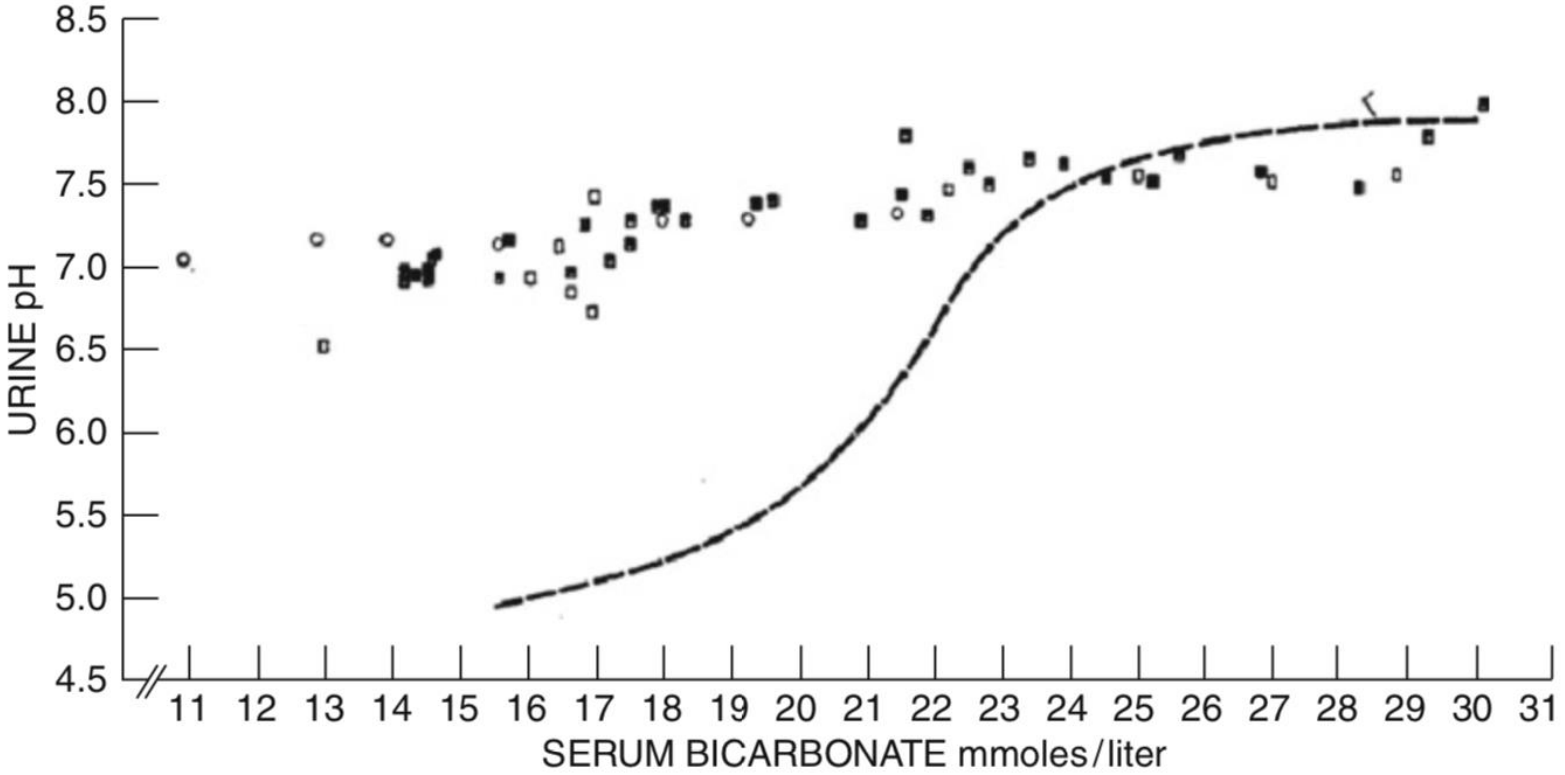
dRTA

Impaired urine acidification

↓

Urine pH > 5.5, despite blood acidosis



Rodriguez-Soriano J, Edelmann Jr CM. Renal tubular acidosis. Annu Rev Med. 1969;20:363–82.

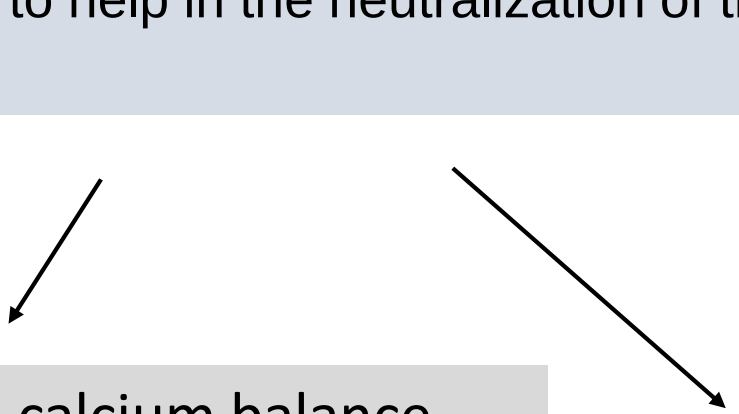
dRTA

- Patients with hereditary forms of dRTA may develop symptoms very early, even during infancy typically **failure to thrive**

dRTA – pathophysiology and clinical features

- Protons that accumulate during metabolic acidosis are buffered by the skeleton, inhibiting osteoblast and promoting osteoclast activity
- Hydroxyapatite can be dissolved to liberate hydroxyl ions to help in the neutralization of the acid

Citrate reabsorption in the proximal tubule will be increased to help provide for base equivalents → hypocitraturia



Negative calcium balance due to the reabsorption of bone- Bone disease

Nephrocalcinosis and nephrolithiasis

Giglio S, et al, J Nephrol. 2021 Dec;34(6):2073-2083.
Trepiccione F, et al. Nephrol Dial Transplant (2021) 36: 1585–1596

dRTA- Clinical characteristics

- **Growth retardation in children**
- **Bone manifestations**, such as rickets or osteomalacia due to buffering of acid by hydroxyapatite in the bone
- Excess calcium dissolved from the bone is excreted in the urine resulting in **nephrocalcinosis and/or urolithiasis**
- Hypokalaemia is another typical manifestation and can be associated with **muscle weakness or even paralysis**
- **Chronic kidney disease** (CKD), especially stages 2 and 3, are more prevalent and occur at an earlier age than in the general population

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dRTA symptoms by age

Infants

Failure to thrive and growth retardation

Polyuria/polydipsia
Vomiting
Constipation

Dehydration (sometimes with fever episodes)

Rickets
Hypotonia
Nephrocalcinosis

Haemolytic anaemia (spherocytosis/ovalocytosis)
Sensorineural hearing loss

Children and adolescents

Growth retardation
Polyuria/polydipsia

Rickets
Vomiting
Constipation
Dehydration
Muscle weakness/hypokalaemic paralysis

Haemolytic anaemia (spherocytosis/ovalocytosis)
Sensorineural hearing loss

Nephrocalcinosis and/or urolithiasis

Enamel defects

Adults

Nephrocalcinosis and/or urolithiasis
Osteomalacia (may be misreported as osteoporosis)
Muscle weakness, hypokalaemic paralysis
Bone pain
Fractures
Haemolytic anaemia (spherocytosis/ovalocytosis)
Sensorineural hearing loss
Enamel defects
*In patients with secondary dRTA **symptoms of the primary immune disorder**: SS, systemic lupus erythematosus, Graves disease

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dRTA- Biochemical features

- **Normal anion gap, hyperchloraemic, metabolic acidosis**
- **Absence of advanced CKD** (CKD stage <4)
- **Hypokalaemia** (< 3.5 mmol/l)

- **Inappropriately elevated urine pH (>5.5)** with a **positive urine anion gap**
- **Urine concentration defect**

- **Hypercalciuria, hypocitraturia**
- **Nephrocalcinosis and/or nephrolithiasis**

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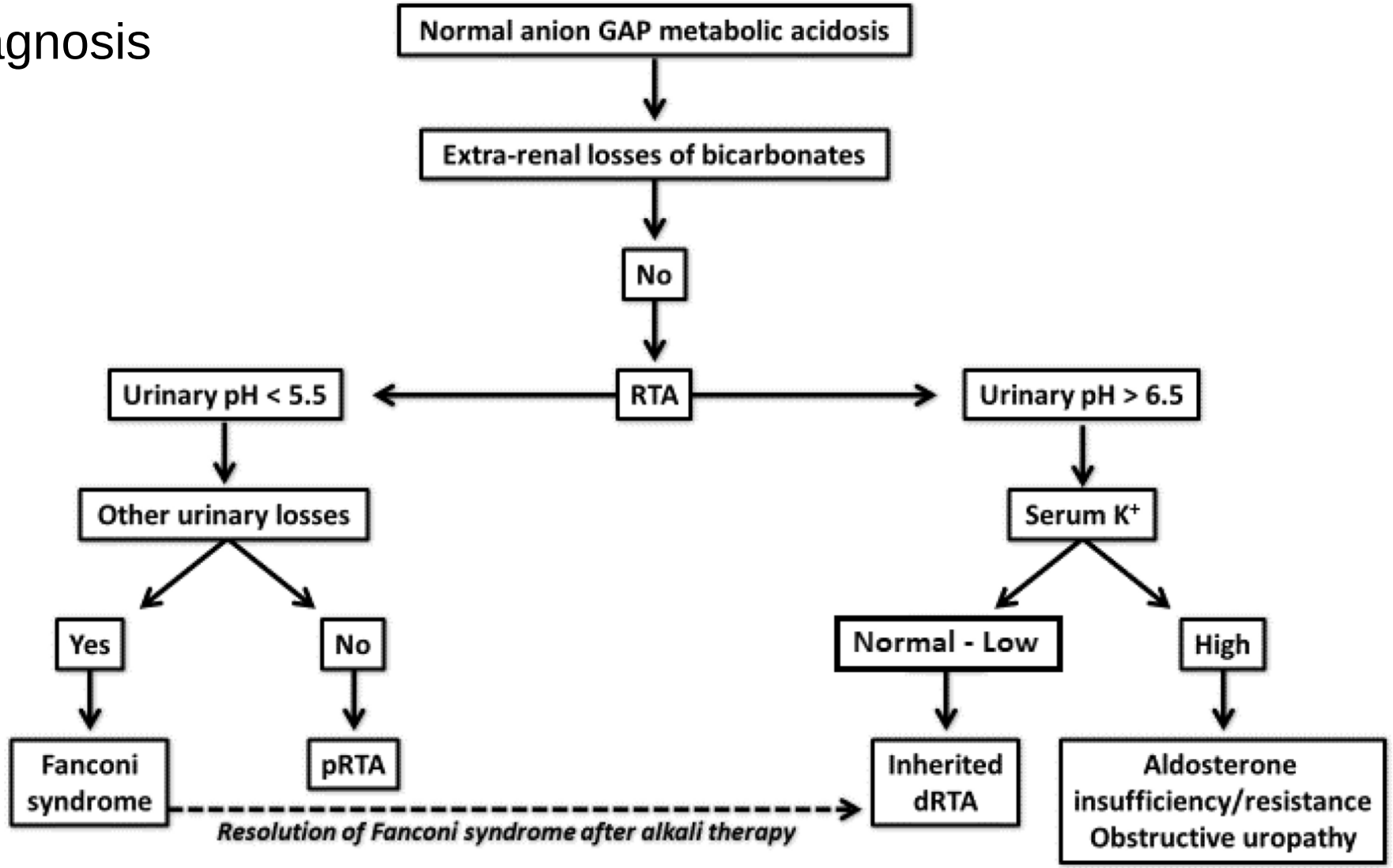
dRTA- diagnosis



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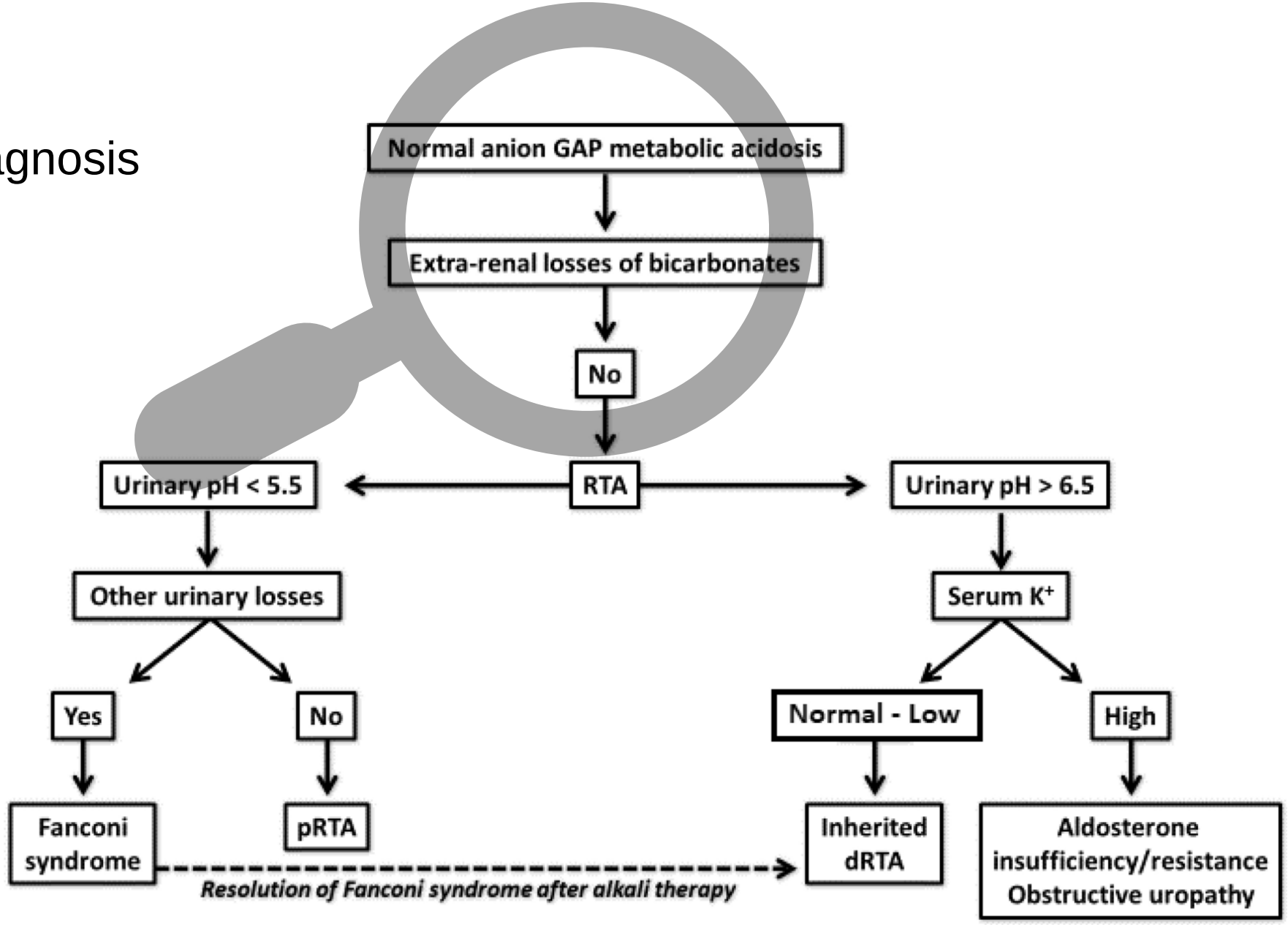
dRTA- diagnosis



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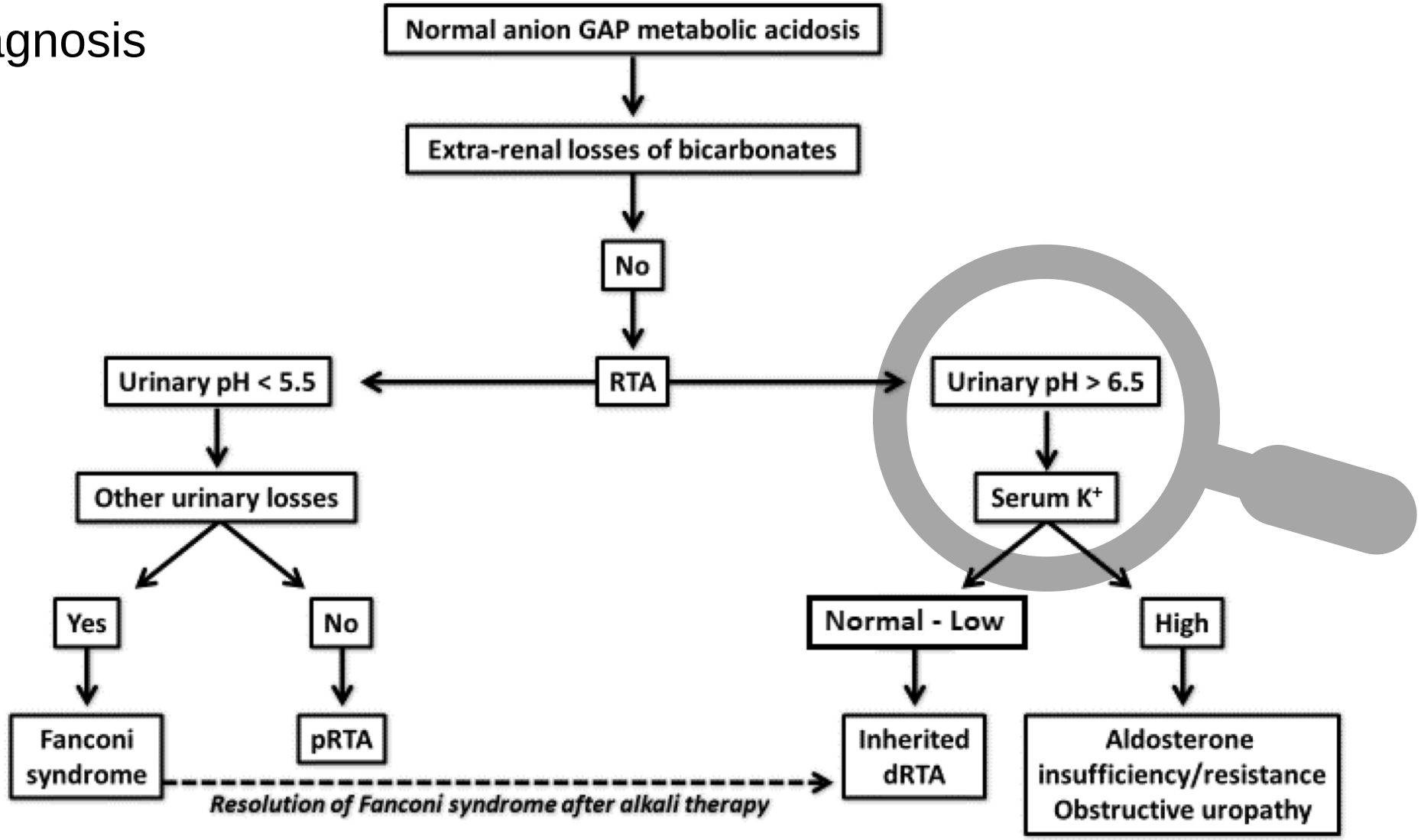
dRTA- diagnosis



Giglio S, et al, J Nephrol. 2021 Dec;34(6):2073-2083.

dRTA - treatment

- dRTA is a **treatable disease**
- Biochemical and clinical abnormalities associated with acidosis can be reversed or halted with adequate alkali supplementation

Treatment target:

Plasma HCO_3, Cl and K, as well as urinary calcium excretion within the age-appropriate normal range

Aiming to:

1. Normalization of growth (in children) and bone mineralization
2. Prevention of progression of nephrocalcinosis

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dRTA - treatment

Forms of alkali supplementation:

- >30 different alkali preparations
- Categorized by the accompanying cation (Na^+ versus K^+, occasionally also Mg) and the alkali (bicarbonate versus citrate), as well as by the formulation (liquid versus tablet versus powder versus granules)
- Selection by local availability, affordability and palatability

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dRTA - treatment

- Several alkalizing products available but **none specific** for dRTA used as Standard of Care (SoC)
- Limitations and constraints of existing products:
  - ☛**Short action duration** requiring several intakes (day & night) per day
  - ☛Formulations
    - **Not** always **adapted** to children
    - Bad **taste**
    - **High quantities** or volumes in younger patients
  - ☛Poor **gastric tolerability**

⇒

- **High burden** for patients/families
- **Low** patient **adherence** to treatment
- **No efficient control** of the disease in **49% of patients**

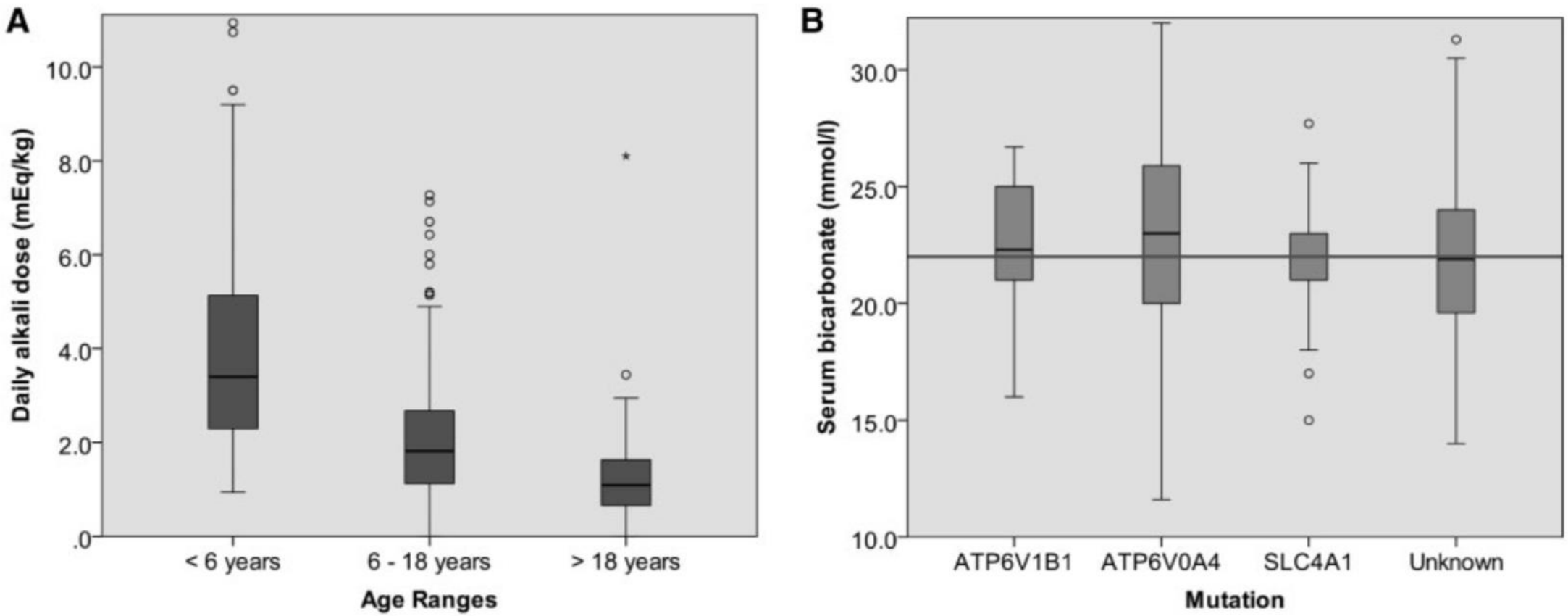
Reddi, 2020; Trepiccione *et al*. 2021; Giglio *et al*. 2021; Lopez-Garcia *et al*., 2019; Guittet *et al*. 2020; Boyer *et al*. 2021

>30 different alkali formulations as SoC

SALTS	COMMERCIAL NAMES	FORMULATION	DOSE	ALKALI MMOLS	ALKALI EQUIVALENTS
Na-Citrate	Bicitra©, Oracit©, Cytra-2©, Shohl's	Oral Solution	1mL	0.33 mmols of Citrate	1 mEq
K-Citrate	Cytra K©	Tablets / sol.	1100mg / 5mL	3.3 mmols of Citrate	10 mEq
	Cytra K©	Crystals	3300mg	10 mmols of Citrate	30 mEq
	CitraK© Forte	Sachets	2g	7.5 mmols of Citrate	22.5 mEq
	Acalka©, Urocit-K©	Tablets	1080mg	3.3 mmols of Citrate	10 mEq
	Uralyt Urate©	Granules	2.5g	6.6 mmols of Citrate	20 mEq
	Kalium-Verla©	Granules	5.4g	6.6 mmols of Citrate	20 mEq
	Urokit©	Sachets	3g	10 mmols of Citrate	30 mEq
	BioKCit©	Sachets	3.5g	5 mmols of Citrate	15 mEq
	BioKCit Forte©	Sachets	4.7g	6.66 mmols of Citrate	20 mEq
Na-Citrate + K-Citrate	Polycitra LC©, Tricitrates©, Cytra-3©	Oral Solution	5 mL (550mg K-Citrate + 500mg Na-Citrate)	3.3 mmols of Citrate	10 mEq
	Uralyt-U©	Granules	2.5g	9 mmols of Citrate	27 mEq
	FONCITRIL 4000©	Sachets	(1.73g K-Citrate + 1.845g Na-Citrate)	5.33 mmols of Citrate	16 mEq
K-Bicarbonate + K-Citrate	ADV7103© 24mEq (also 8mEq)	Sachets	3660mg sachet	16 mmols of Bicarbonate + 2.61 mmols of Citrate	24 mEq
	Kalinor©	Effervescent tablets	1 tablet (2.17g K-Citrate + 2g $KHCO_3$)	6.6 mmols Citrate + 20 mmols of Bicarbonate	40 mEq
K-Bicarbonate + Na-Citrate	Blemaren© N	Effervescent tablets	1 tablet	10 mmols of Bicarbonate + 3.3 mmols of Citrate	20 mEq
K-Citrate + Na-Bicarbonate/Carbonate	Blanel©	Effervescent tablets	1 tablet	5 mmols of Citrate + 15 mmols of HCO_3^{-1} /CO_3^{2-}	30 mEq
K-Citrate + Mg-Citrate	Basica Vital E©	Sachets	5.5g	9.33 mmols of Citrate	28 mEq
	LITHOS© Prevent	PR Tablets	1 tablet (757mg K-Citrate + 358mg Mg-Citrate)	3.5 mmols of Citrate	10.5 mEq
	LITHOS© Dissolve	PR Tablets	1 tablet (1514mg K-Citrate + 581mg Mg-Citrate)	7 mmols of Citrate	21 mEq
	Lithos©	Sachets	4.5g	7 mmols of Citrate	21 mEq
	BioKMag©	Sachets	4.5g	7 mmols of Citrate	21 mEq
Mg-Citrate + Ca-Citrate	Cal-Mag Citrate©	Effervescent powder	5.4g (500mg Ca-Citrate + 200mg Mg-Citrate)	7mmols of Citrate	21 mEq
Mg-Citrate	Magnesium Diasporal 300mg©	Sachets	5g	8.3 mmols of Citrate	25 mEq
	Magnesium Diasporal 100mg©	Tablets		2.66 mmols of Citrate	8 mEq
Mg-Citrate + K-Citrate	Lithoren©	Sachets	1 sachet	10 mmols of Citrate	30 mEq
Na-K-Ca-Mg Citrate	Basica Vital©	Powder	16g	5.5 mmols of Citrate	16.5 mEq
Na-Bicarbonate	Nephrotrans©	Tablets	500mg	6 mmols of Bicarbonate	6 mEq
K-Bicarbonate		Tablets	1 g	10 mmols Bicarbonate	10 mEq

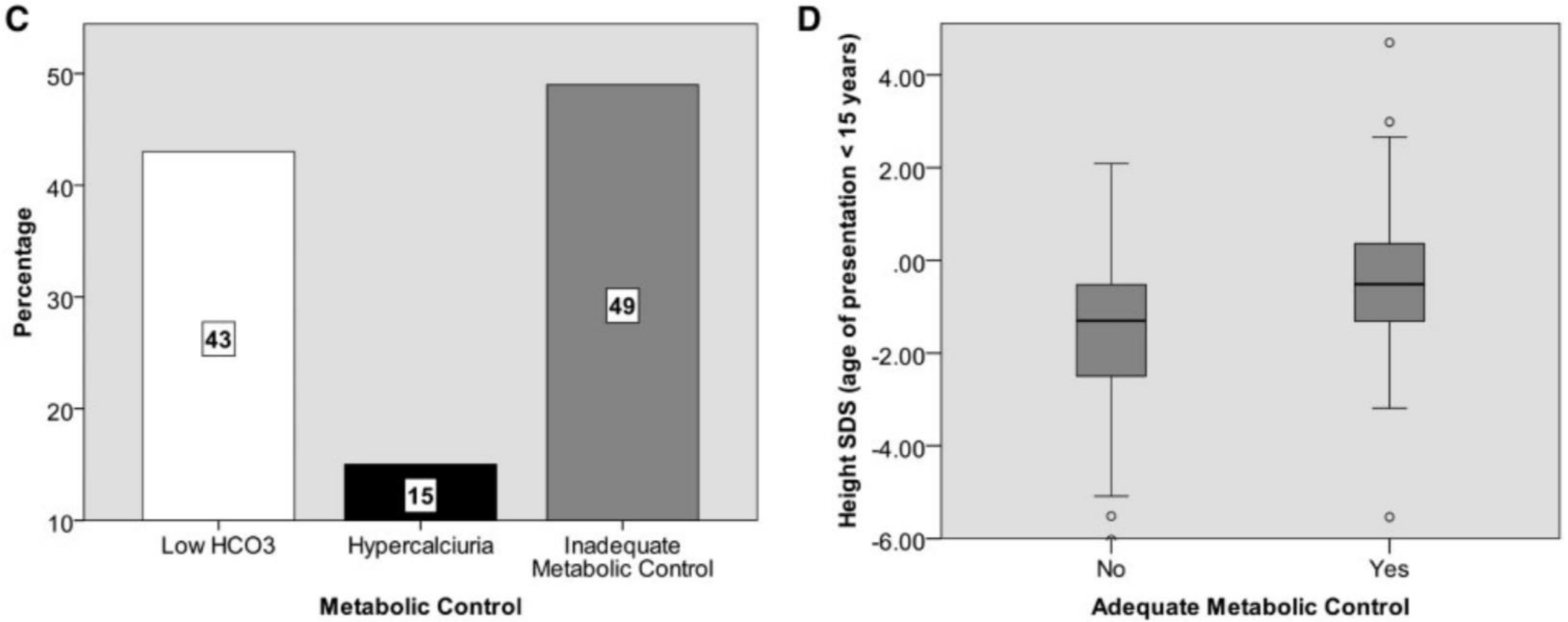
Camilo et al, Nephrol Dial Transplant (2019) 34: 981–991

Alkali dose according to age group and genetic background



Camilo et al, Nephrol Dial Transplant (2019) 34: 981–991

Growth is dependent on metabolic control



Camilo et al, Nephrol Dial Transplant (2019) 34: 981–991

What’s new in dRTA treatment?

Sibnayal (ADV7103)- Prolonged-release oral granules alkali formulation

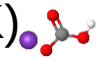
- Sibnayal is the **first drug specifically developed and approved for dRTA** combining potassium citrate/potassium hydrogen carbonate in sustained-release formulation with twice-daily administration

- **Sibnayal is approved by EMA for the treatment of dRTA in adults, adolescents and children aged one year and older**

Sibnayal contains 2 molecules with 3 components in an innovative formulation[1]

Fixed combination of 2 alkalizing agents

- 1/3 potassium citrate (CK)
- 2/3 potassium bicarbonate (BK)

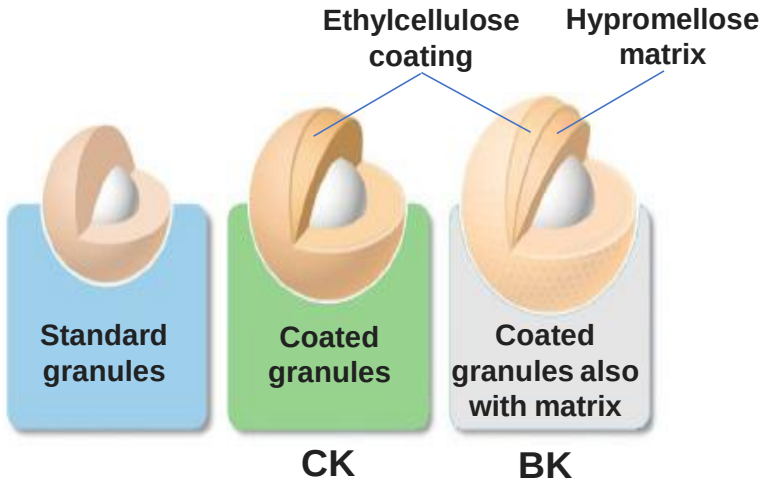


2 mm coated granules

- Designed for all ages
- Tasteless
- Easy to swallow

Innovative patented formulation

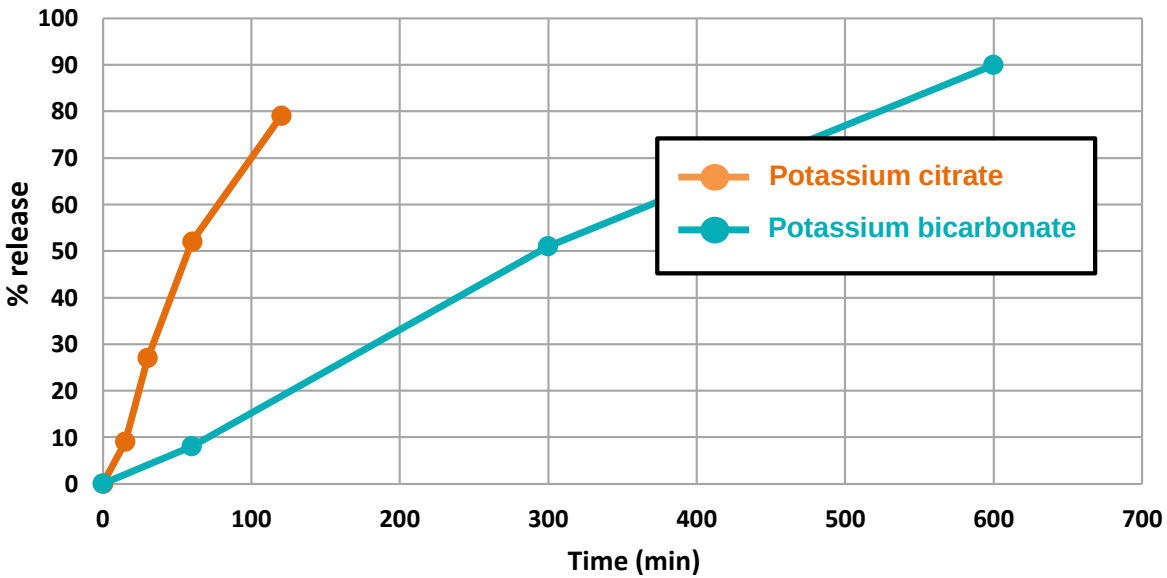
- Sustained release matrix enables absorption throughout the intestinal tract
- Formulation allows twice-daily intake



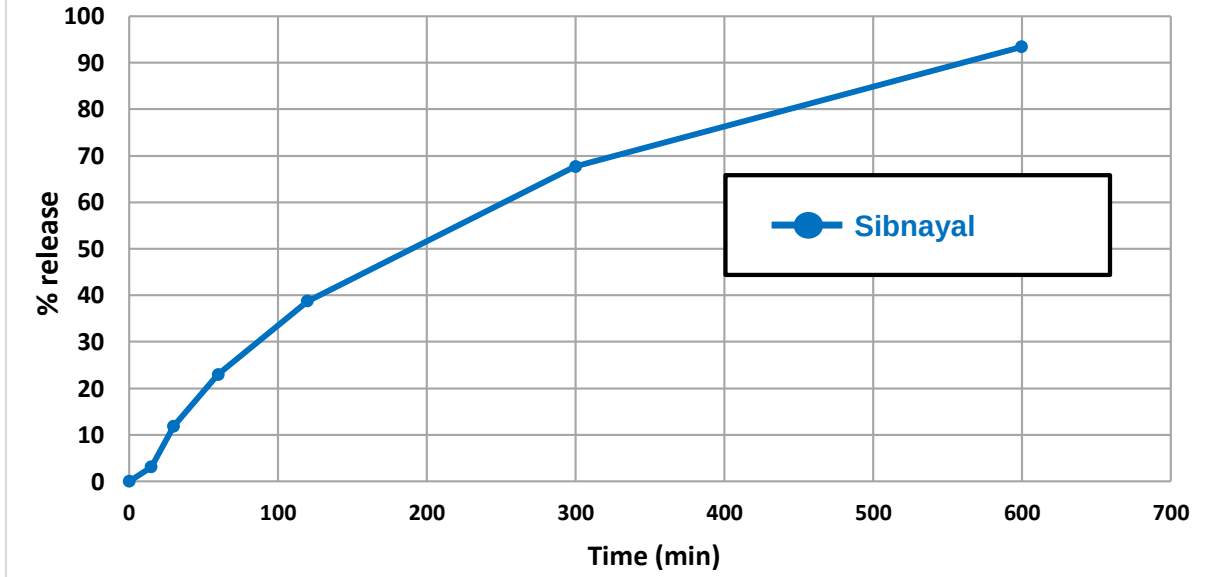
Guittet et al. 2020

Sibnayal allows twice daily dosing giving 24-hour coverage[1,2,3]

In vitro dissolution profiles[3]



Batches of prolonged-release granules of potassium citrate and potassium bicarbonate used in Sibnayal clinical trials.



Sibnayal formulation calculated by combining both release profiles in adequate proportions.

1. SmPC; 2. Bertholet-Thomas et al. 2021; 3. Guittet et al. 2020

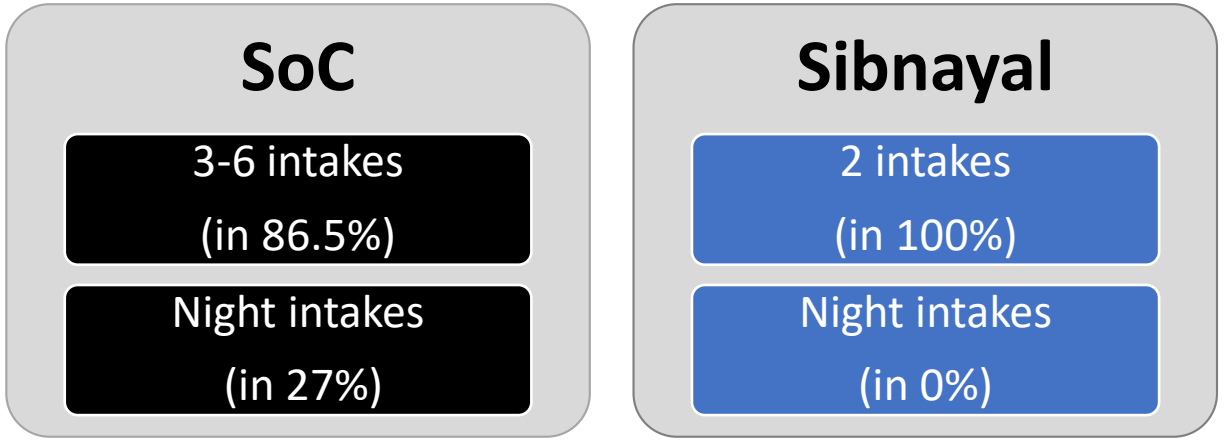
Sibnayal provides 24-hour coverage with twice-daily dosing[1,2]

Sibnayal formulation design features[3]

- Coating thickness selected to:
  - Avoid absorption peaks (dose dumping)
  - Provide continuous efficacy over 12 hours
  - Allow twice-daily administration
- Coating ensures taste masking and good palatability
- Small granules (2mm diameter) suitable for young children/ infants
- Reduced risk of GI adverse events

Prolonged release formulation designed to improve compliance with long-term treatment[3]

Only 2 daily intakes of Sibnayal were required to control plasma bicarbonate levels compared with multiple daily intakes of SoC[2]



The average number of daily intakes for SoC and following switch to Sibnayal were compared in 37 patients with dRTA[2]

Mean ± SD alkali doses prescribed with SoC were 1.99 ± 1.54, 2.20 ± 1.41, 2.70 ± 1.23, and 5.27 ± 2.54 mEq/kg/day, in adults, adolescents, children, and infants/ toddlers, respectively.

Mean ± SD alkali doses prescribed with Sibnayal were 1.74 ± 1.05, 2.79 ± 1.74, 3.80 ± 1.15, and 6.11 ± 2.26mEq/kg/day, in adults, adolescents, children, and infants/toddlers), respectively.

1. SmPC; 2. Bertholet-Thomas et al. 2021; 3. Guittet et al. 2020

Sibnayal clinical studies

- **Phase I:** B03CS[1]

Randomized, double-blinded, placebo-controlled, two-period study, adaptive design, **healthy adult subjects**

Primary objective:
Pharmacodynamic effect on urine pH of 6 oral doses of ADV7103 *versus* placebo after 4-5 days of treatment

- **Phase II/III:** B21CS – dRTA[2]

Multicenter, open-label, non-randomized, non-inferiority study, switch from SoC to ADV7103

6 months – 55 years old, with **acquired or inherited dRTA**

Primary objective:
Efficacy on metabolic acidosis (plasma bicarbonate) in comparison to SoC

- **Phase III:** B22CS – dRTA[3]

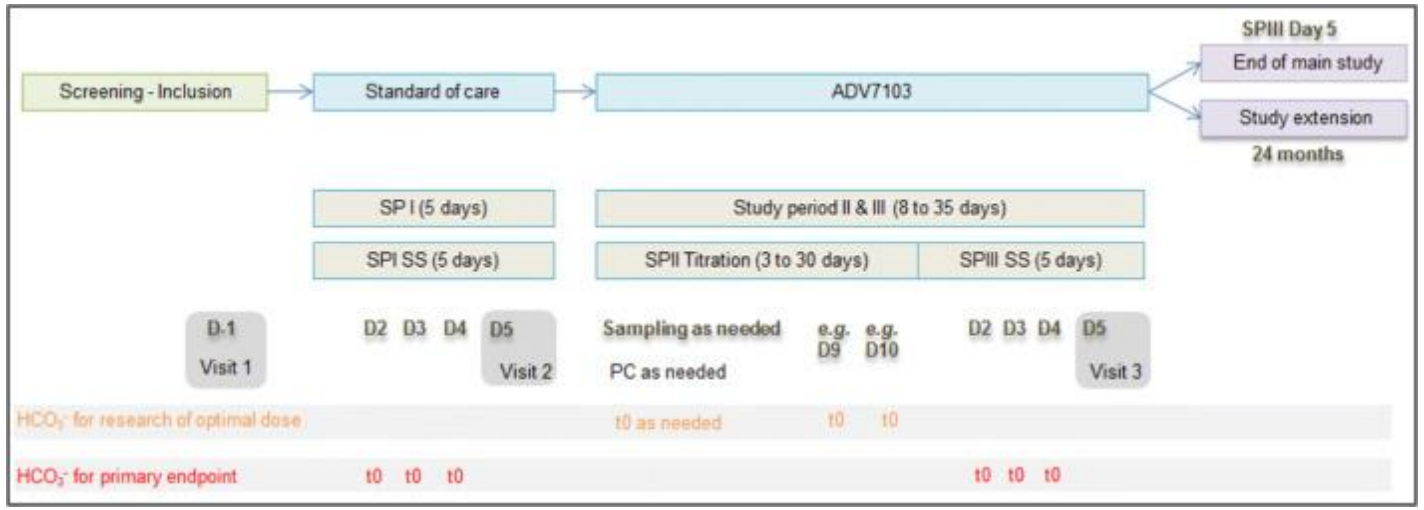
Multicenter, single arm, open-label, **extension or follow-up study**

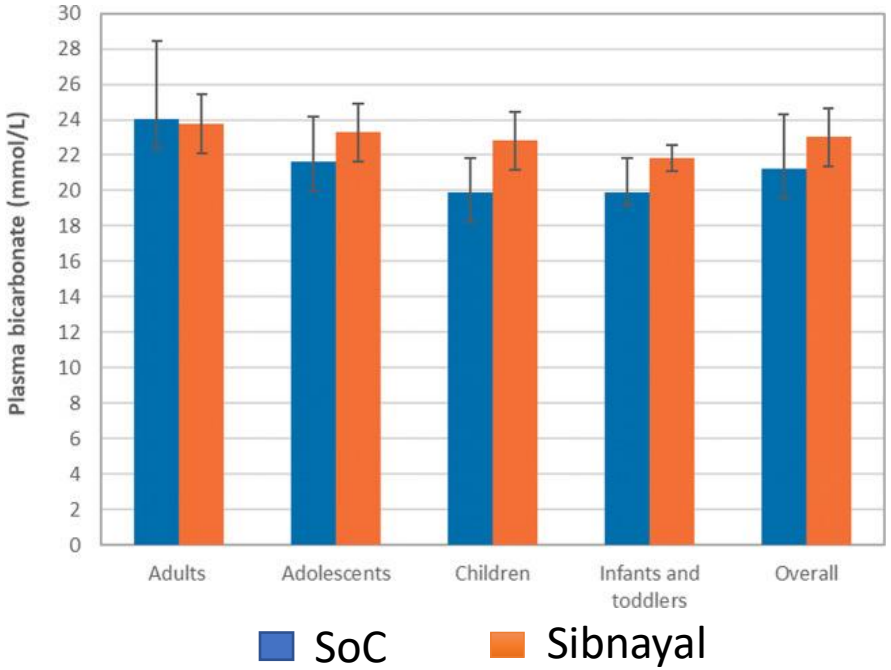
Primary objective:
Long-term safety & tolerability

1:Guittet *et al.*, 2020 – 2: Bertholet-Thomas *et al*., 2021 3: Bertholet-Thomas *et al.* (24 months), 2021

B21CS - Clinical Study

ADV7103 = Sibnayal®





Patients: 37 Overall

7 Adults, 10 Adolescents, 15 Children, 5 Infants

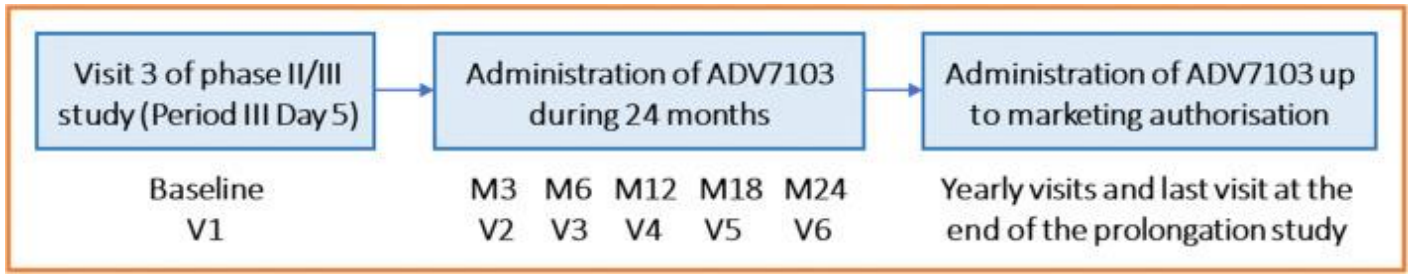
dRTA type

- **Inherited** : 36
- **Acquired**: 1 concomitant to Sjögren syndrome

90% of the dRTA patients treated with ADV7103 (Sibnayal®) reach normal plasma bicarbonate level *vs.* 43.3% with SoC

Bertholet-Thomas *et al.*, 2021

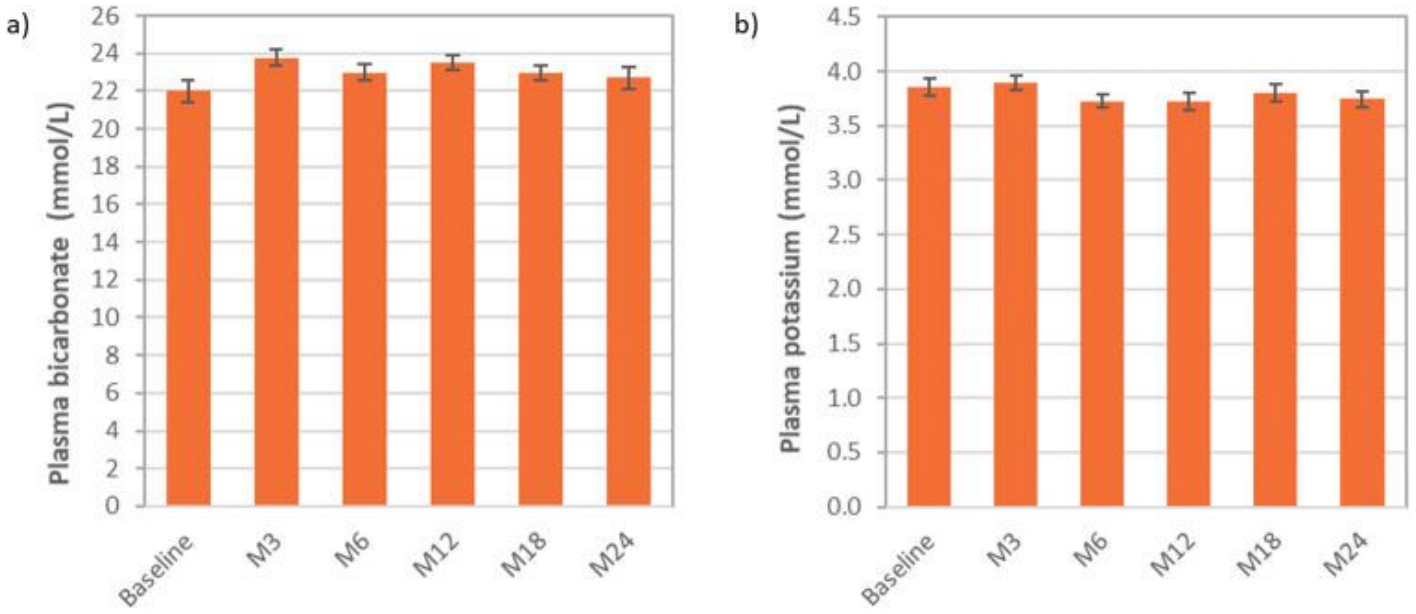
B22CS - Clinical Study



Patients:

- 6 Adults
- 24 < 18 years old ➔ 8 Adolescents, 13 Children, 3 Infants

Enrolled in 12 centers in France, Serbia, and Slovakia



Bertholet-Thomas *et al.*, 2021

Conclusions from pivotal study and 24-month extension study

Pediatric and adult patients with dRTA

PIVOTAL STUDY[1] Short-term switch trial from SoC to Sibnayal	
Plasma bicarbonate levels (superiority p = 0.0008)	↑
Bicarbonate in normal range (p < 0.001)	↑
Plasma potassium levels	↔
Risk of stone formation (p = 0.021)	↓
Palatability (d = 25 mm in VAS)	↑
Number of daily intakes	↓
GI tolerability problems (d = -14.2 mm in VAS)	↓

When switching from SoC to Sibnayal, management of plasma bicarbonate levels and risk of stone formation, as well as palatability and gastrointestinal safety, were significantly improved.

37 patients were enrolled: ≥18 years (n=7); 12-17 years (n=10); 4-11 years (n=15); 0.5-3 years (n=5)

0	Death
1	Drop out unrelated to safety/ efficay
4	Serious AEs , all unrelated to treatment
9	AEs in 5 (17%) patients related to treatment (all GI)
104	AEs in 27 (90%) patients in total

from Extension Study

Pediatric and adult patients with dRTA having completed the pivotal study

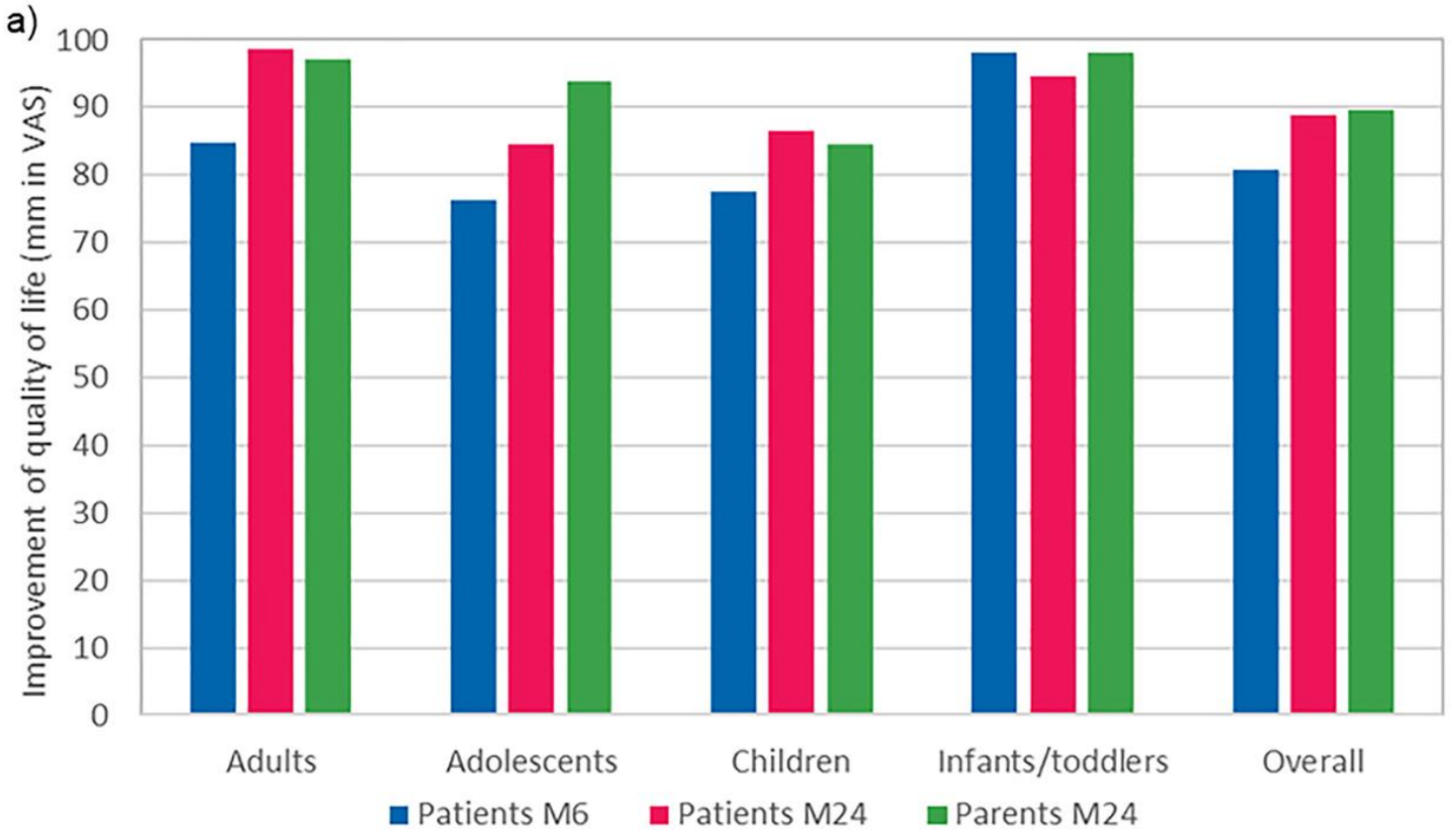
EXTENSION STUDY[2] Long-term trial evaluating Sibnayal for 24 months	
Normal plasma bicarbonate in 69-86% patients	↔
Normal potassium levels in 83-93% patients	↔
Low risk of lithogenesis: 48-63% patients	↔
Growth z-scores restored within ±2SD range	↑
BMD improved in 4 patients (worse in 1)	↑
Acceptability score improvements: 69-91% patients	↑
Adherence rates ≥75%: 79% patients	↔
Quality of life improvement: 89% patients	↑

The good safety profile of Sibnayal was confirmed. Metabolic management remained adequate and clinical signs were improved in some patients. Adherence remained stable over time and quality of life and acceptability were improved with respect to previous treatments.

30 patients were enrolled: ≥18 years (n=6); 12-17 years (n=8); 4-11 years (n=13); 0.5-3 years (n=3)

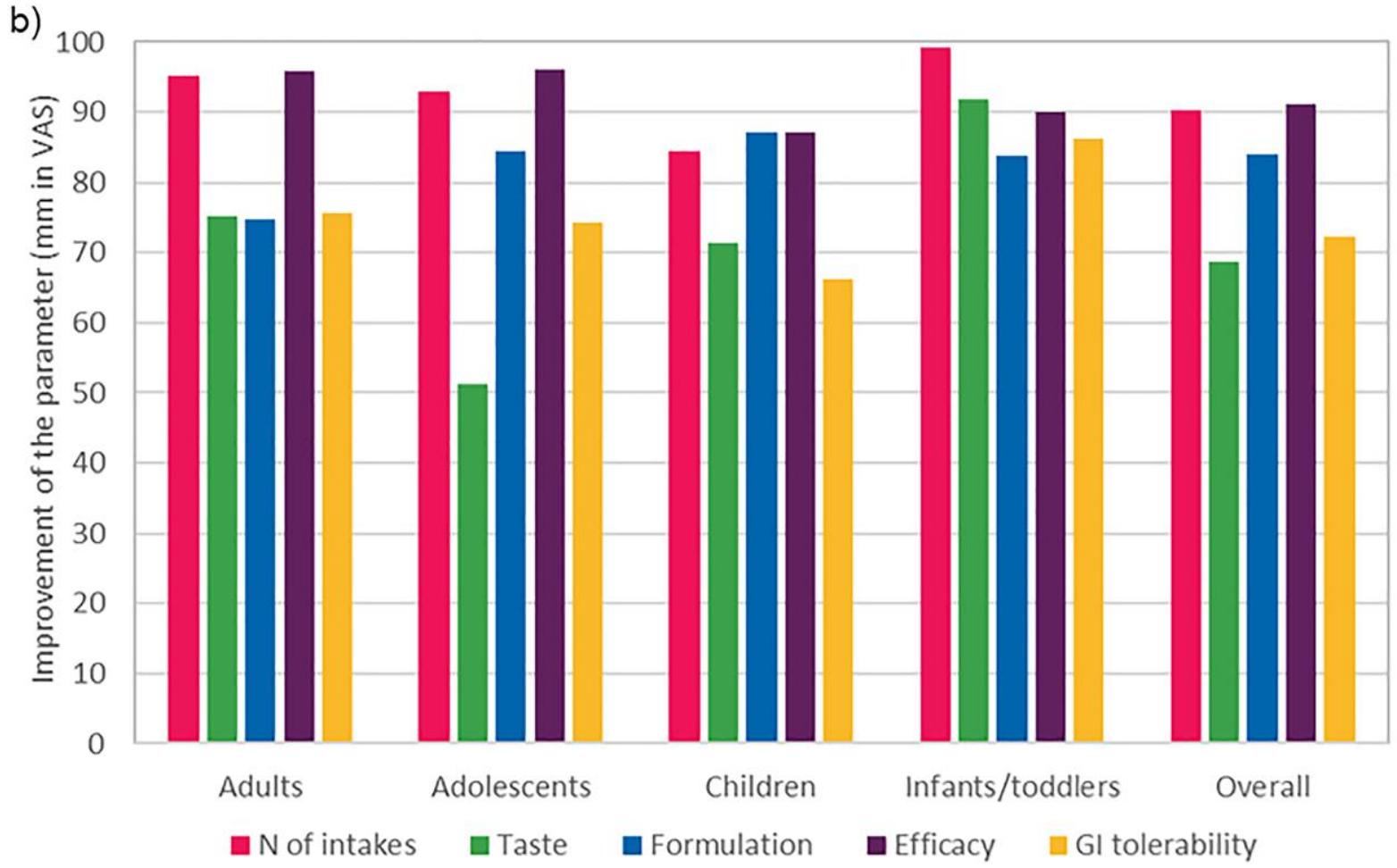
1. Bertholet-Thomas et al. *Pediatr Nephrol.* 2021; 36(1): 83–91. 2. Bertholet-Thomas et al. *Pediatr Nephrol.* 2021; 36(7): 1765–1774.

Quality of life of ADV7103 (Sibnayal®) after switch from SoC



Bertholet-Thomas A et al. Pediatr Nephrol. 2021 Jul;36(7):1765-1774

Treatment acceptability of ADV7103 (Sibnayal®) after switch from SoC



Bertholet-Thomas A et al. Pediatr Nephrol. 2021 Jul;36(7):1765-1774

Qualitative study explores QoL linked to dRTA

Impressions of patients with this rare disease (and caregivers) after 60 months of ADV7103 (Sibnayal®) treatment

- **Difficulties at school** due to burdensome administrative issues and need to explain disease and treatment affecting all families of paediatric patients (n = 13) disappeared, facilitating parents who had stopped working (to deal with their child's treatment) to return to work
- **Family functioning** was improved (n = 18), as travel and holidays became easier to organise and patients/parents stopped thinking about managing treatment daily/nightly, reducing tension in the family or couple
- The **emotional burden of disease** perceived was relieved (n=12) in the absence of treatment-related invasive questions from others
- **Gastro-intestinal adverse events and taste problems** improved with ADV7103 (n=18) and **better compliance** led to milder physical impacts and less need to be hospitalised

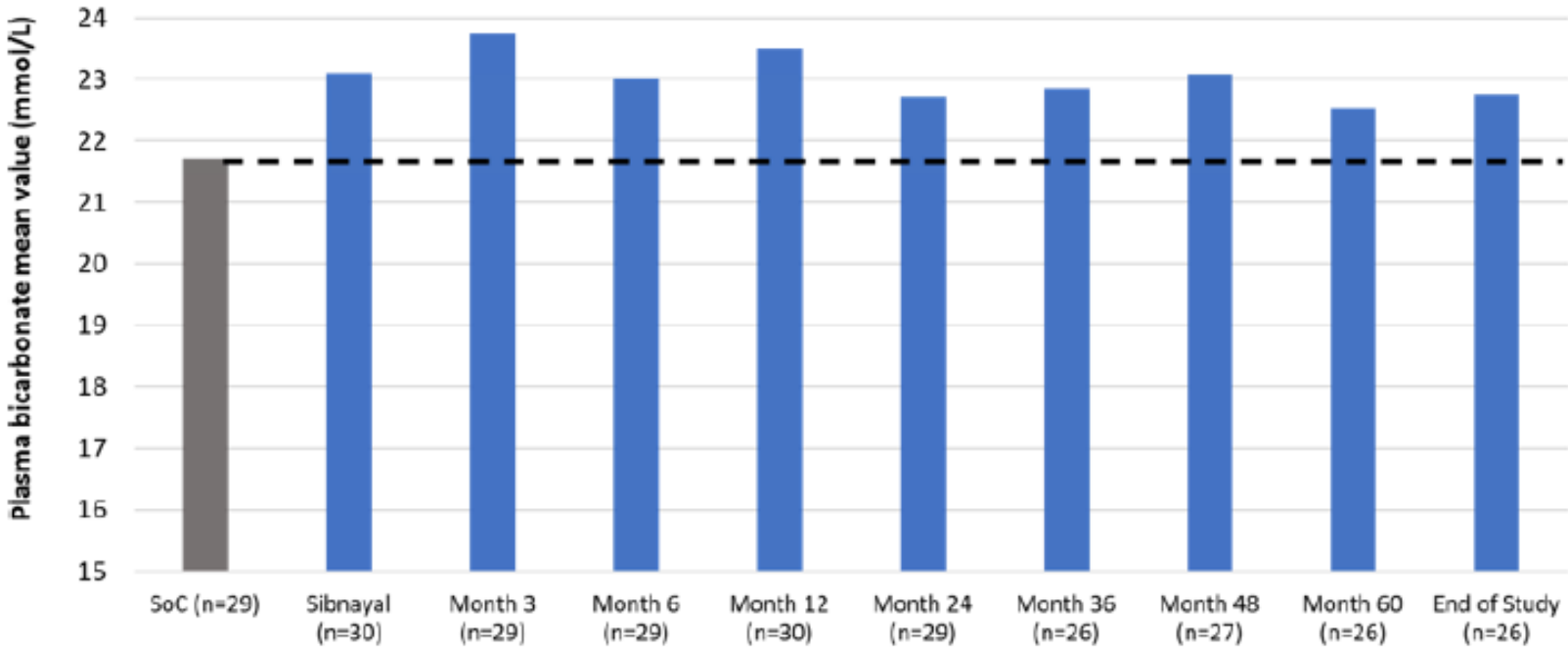
Acquadro M, et al. Lived experiences of patients with distal renal tubular acidosis treated with ADV7103 and of their caregivers: a qualitative study. Orphanet J Rare Dis. 2022 Mar 28;17(1):141.

Significant clinical improvement of pediatric and adult patients with dRTA after 6 years of treatment with Sibnayal

Long-term efficacy

30 patients enrolled in the short-term B21CS study

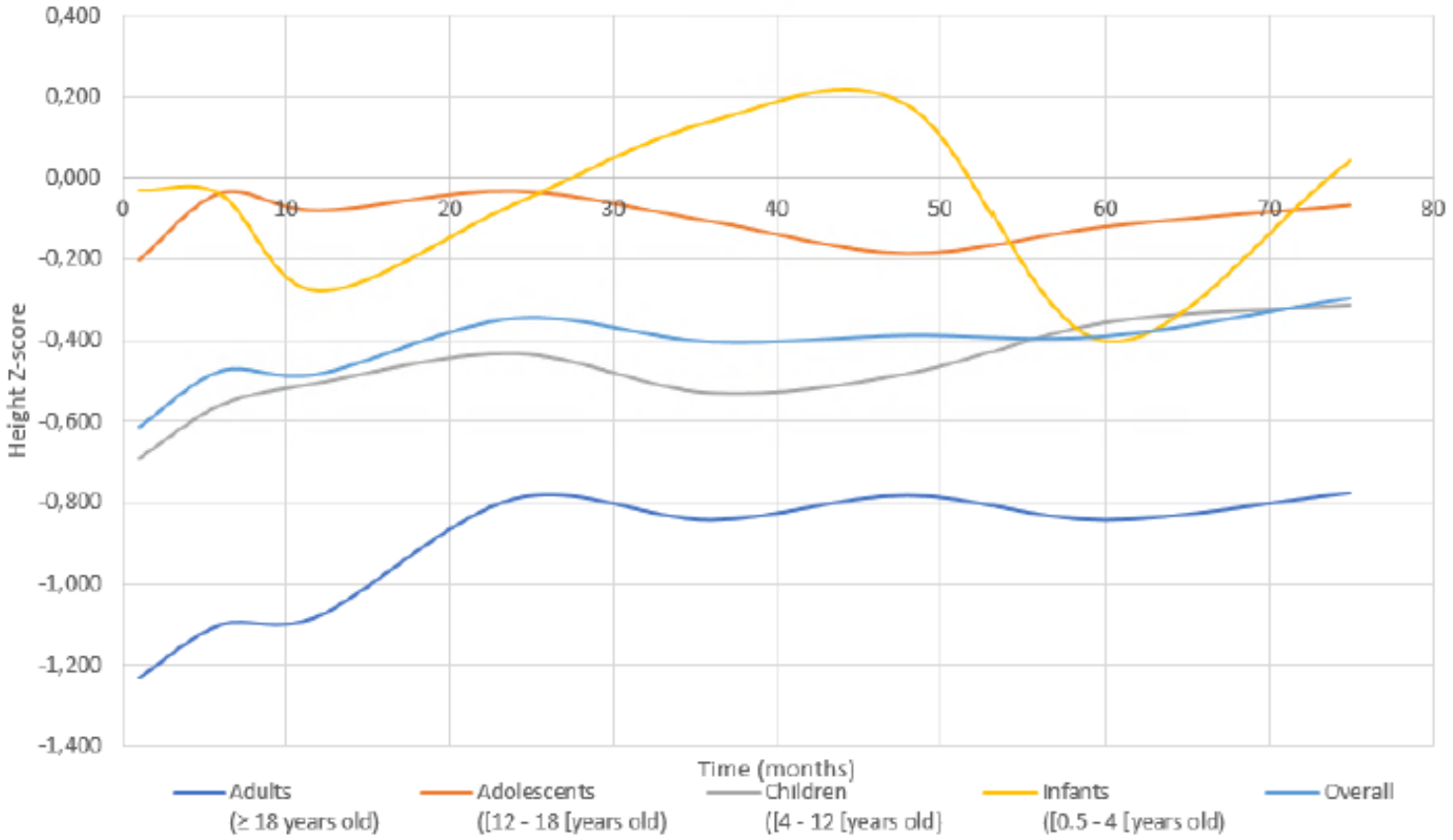
Normalization of bicarbonatemia was maintained



Bertholet-Thomas A et al. *Nephrol. Dial. Transplant. 38* (Suppl 1, 2023; Abstract #6649). Presented at 60th ERA Congress, Milan, June 15-18 2023

Significant clinical improvement of pediatric and adult patients with dRTA after 6 years of treatment with Sibnayal

Long-term efficacy - Effect on growth



- A positive effect on growth was demonstrated in all patient age groups

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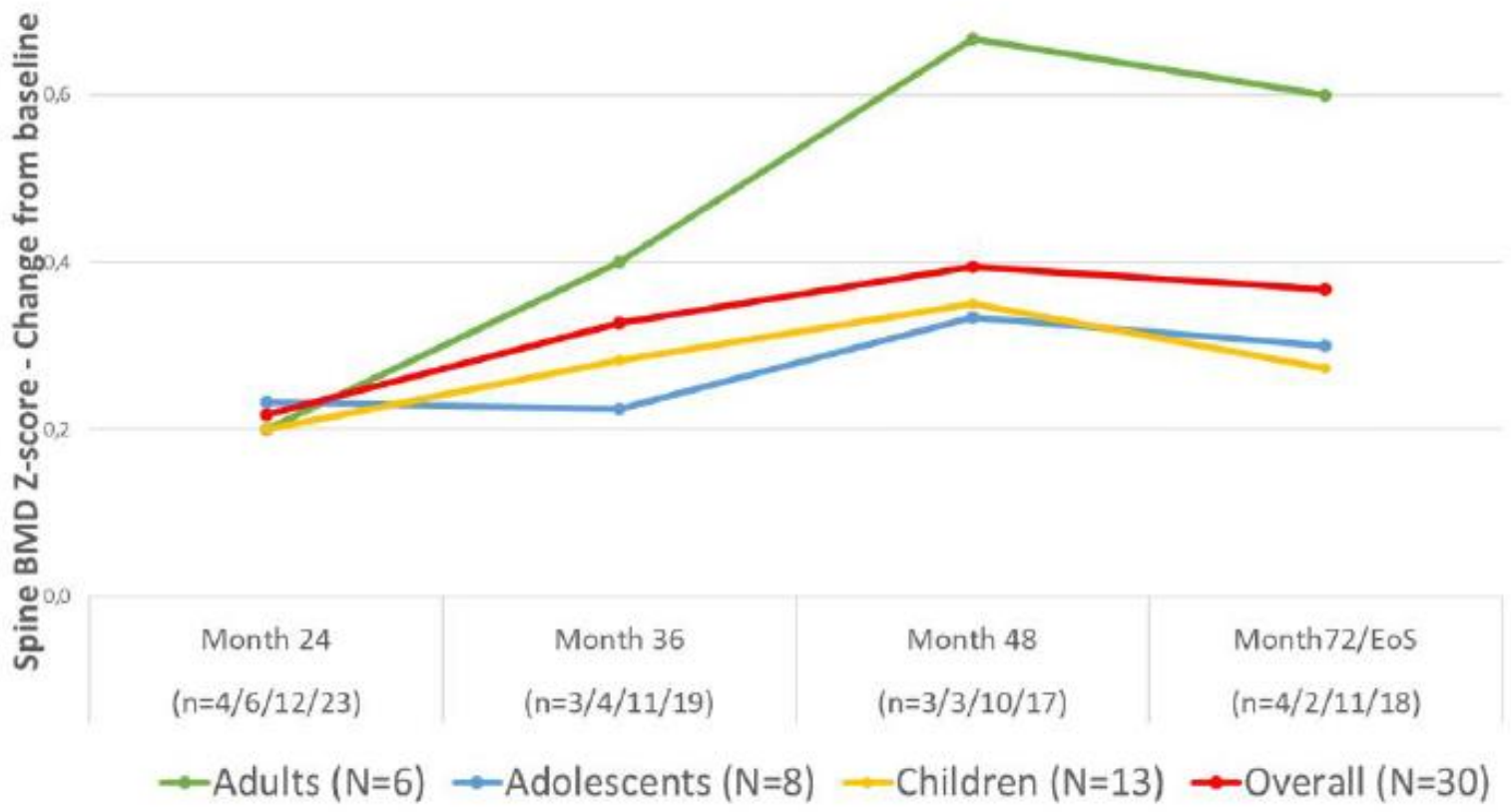
Significant clinical improvement of pediatric and adult patients with dRTA after 6 years of treatment with Sibnayal

- Spine BMD was improved during the course of study

Long-term efficacy - Effect on spine BMD



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Significant clinical improvement of pediatric and adult patients with dRTA after 6 years of treatment with Sibnayal

Long-term efficacy

Kidney function was stabilized

	Baseline	End of study (>72 M)
eGFR, mL/min/1.73m^2 ±SD	121.27 ±23.83	120.94 ±21.22

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Significant clinical improvement of pediatric and adult patients with dRTA after 6 years of treatment with Sibnayal

Long-term safety

- ≥ 1 TEAE occurred in 96.7% (n=29) patients; severity was mild in 93.3% (n=28) patients
  - ≥ 1 Sibnayal related TEAE occurred in 20% (n=6) patients, with GI disorders being the most frequent events
- No TEAE led to study withdrawal or death
- 43.3% (n=13) patients experienced at least one serious TEAE, none of which was related to Sibnayal

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Journal of Nephrology
https://doi.org/10.1007/s40620-022-01306-z

LESSONS FOR THE CLINICAL NEPHROLOGIST

Improved growth of a child with primary distal renal tubular acidosis after switching from a conventional alkalizing treatment to a new prolonged-release formulation containing potassium citrate and potassium bicarbonate: lessons for the clinical nephrologist

A 4.5-year old girl was enrolled in Advicenne's B21CS phase 2/3 clinical study and continued throughout the B22CS follow-up study

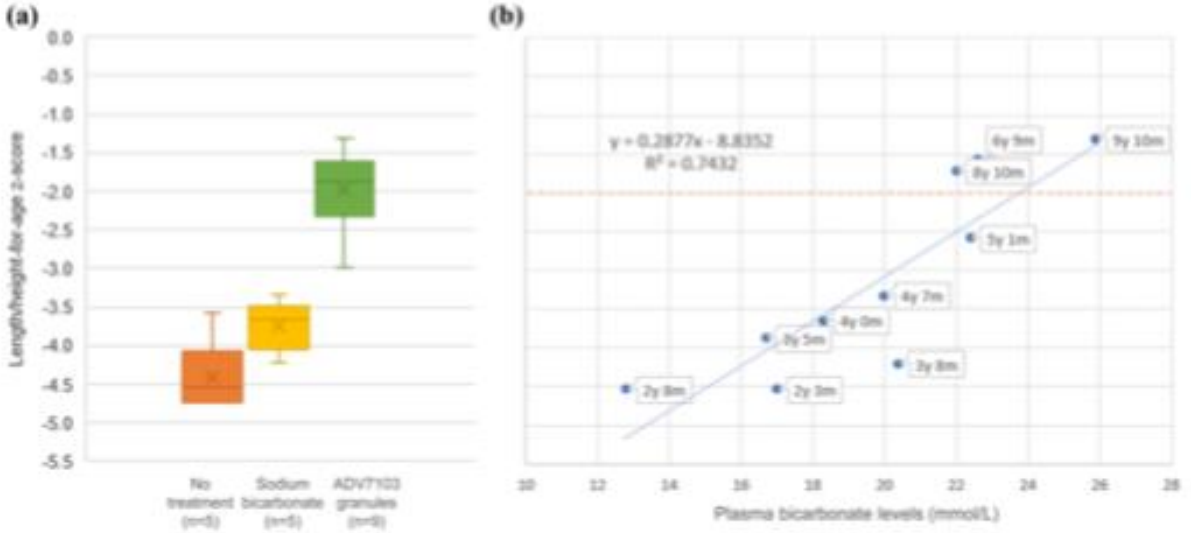


Fig. 1 Boxplots representing mean ± SD (squares) and ranges (bars) for length/height-for-age *z*-scores at different periods of the patient's life (**a**) and correlation between length/height-for-age *z*-scores and plasma bicarbonate levels (**b**)

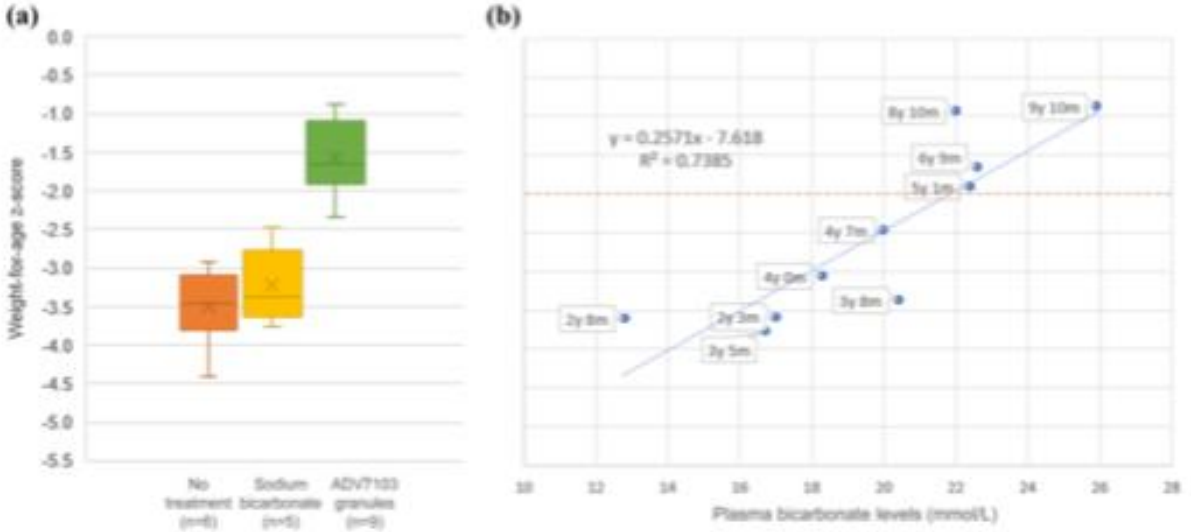


Fig. 2 Boxplots representing mean ± SD (squares) and ranges (bars) for weight-for-age *z*-scores at different periods of the patient's life (**a**) and correlation between weight-for-age *z*-scores and plasma bicarbonate levels (**b**)

Our experience is just started...**5 years old boy with diagnosis of dRTA**

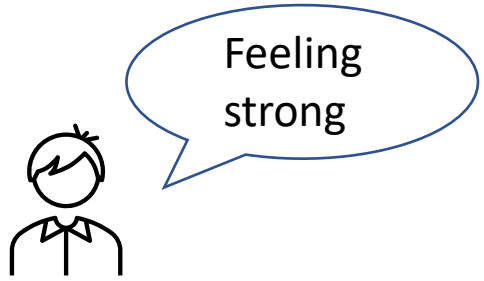
On sodium bicarbonate (SoC) since birth

- **Plasma bicarbonate**, frequently < 18 mmol/L, (range 16–21 mmol/L)
- **Height low *z*-score ➔** < - 1.9
- **Weight low** *z*-score **➔** < - 2

ADV7103 (Sibnayal®)

24 mEq b.i.d mEq since 3 months

- **Plasma bicarbonate** 21–23 mmol/L and normal plasma potassium level
- **Height *z*-score ➔** = - 1.5
- **Weight *z*-score ➔** = - 1.6



Conclusions

- Sibnayal is the first and only label-approved treatment for dRTA
- Patients treated with Sibnayal achieved normal plasma bicarbonate levels
- Sustained 24-hour coverage was achieved with simple twice-daily dosing
- Palatability and GI tolerability were significantly improved
- Switching from standard of care treatments to Sibnayal led to major improvements in patient QoL in the 24-month open-label extension study

Conclusions

72-month data showed sustained effect of Sibnayal

- ☛ Control of metabolic acidosis
- ☛ Improvement of QoL and adherence
- ☛ Prevention of long-term complications, CKD and bone parameters
- ☛ Positive impact on growth