PART 1
NoACIC

NICE National Institute for Health and Care Excellence

Prolonged-release potassium bicarbonate and potassium citrate (Sibnayal) for treatment of distal renal tubular acidosis – (ID3787)

Lead team presentation

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Disease overview

- Kidneys filter acids from the blood and removes them from the body in urine, which prevents the build-up of acids in the blood. Distal renal tubular acidosis (dRTA) is a **disorder of impaired acid removal from the blood** → blood becomes too acidic.

- dRTA may be **hereditary** (primary) or **acquired** (secondary) due to other conditions like Sjögren syndrome, sickle cell anaemia, systemic lupus erythematosus, chronic obstructive uropathy, or post-renal transplantation.

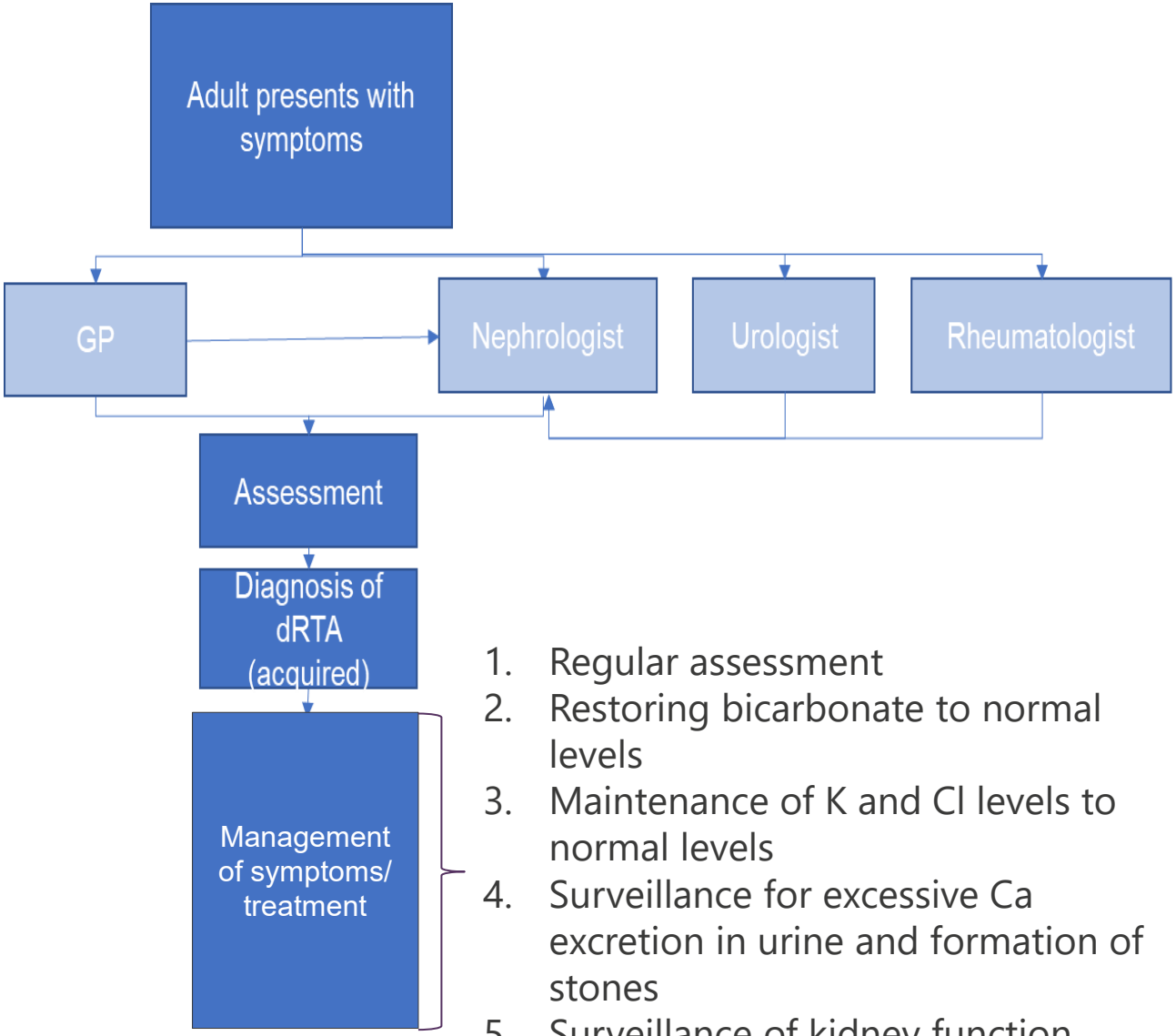
- dRTA has a prevalence in the UK of between **0.46 to 1.6 per 10,000** → between **2,589 and 9,005** people are living with the condition in England. Incidence seems to be unknown.

- Primary dRTA is a highly variable disorder and can affect people differently → some may have slightly elevated acid levels and no accompanying symptoms while others may have **kidney stones, deafness, growth failure, rickets** (bowing of the bones) or **osteoporosis** (thinning of the bones).

- Key characteristics of dRTA**:**
  - **Metabolic acidosis with excess of chloride:** inability to acidify urine pH less than 5.5
  - **Hypokalaemia:** deficiency of potassium in the bloodstream
  - **Nephrocalcinosis**: Excess calcium deposits within the kidney.
  - **Nephrolithiasis**: Presence of stones in the kidney due to a decrease in urine volume or excess of stone-forming substances in the urine.
    - **Nephrolithotomy**: surgical removal of kidney stones when they can't pass on their own.

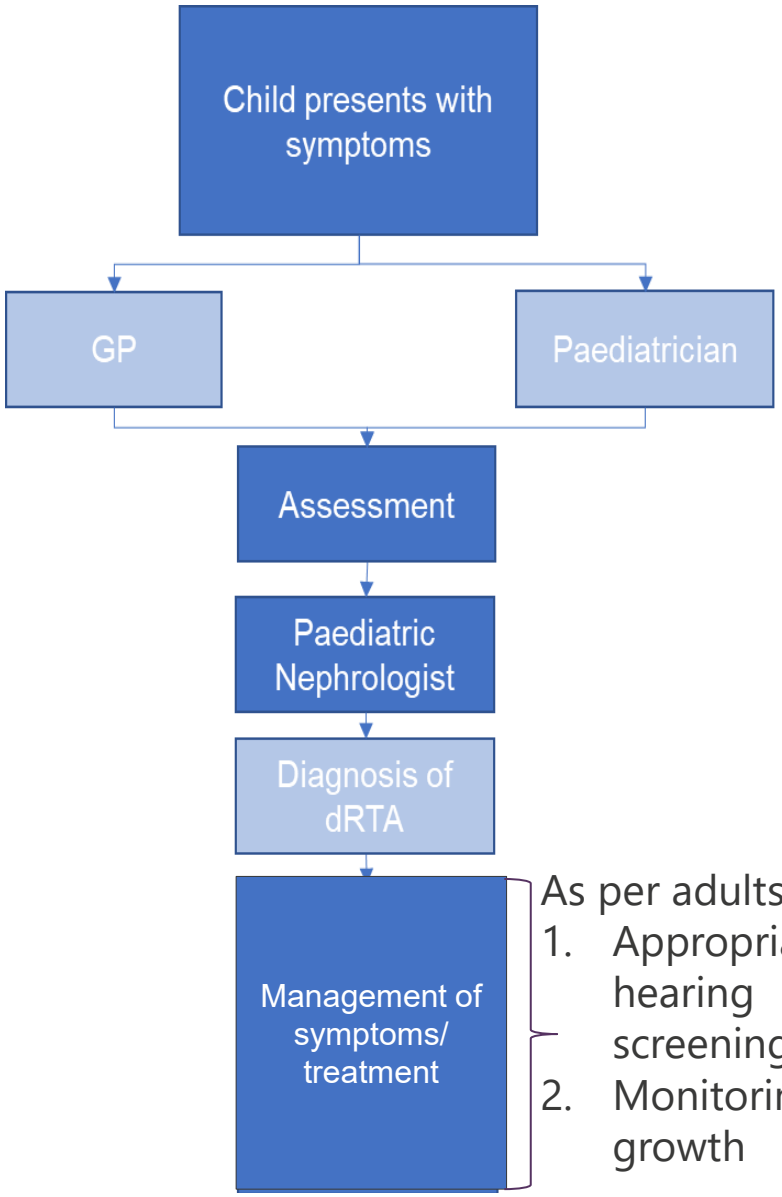
Treatment pathway - dRTA is a multisystem disease

Adults



1. Regular assessment
2. Restoring bicarbonate to normal levels
3. Maintenance of K and Cl levels to normal levels
4. Surveillance for excessive Ca excretion in urine and formation of stones
5. Surveillance of kidney function
6. Monitoring bone health

Children



As per adults with:

1. Appropriate hearing screening
2. Monitoring of growth

dRTA clinical monitoring

Bicarbonate levels in the blood are used as a surrogate outcome of dRTA for long-term complications

Potassium levels, calcium levels in the urine, **citrate level** in the urine, **renal function**, measures of **impaired growth** and **bone mineral density** are also measured in clinical practice.

BMJ best practice for surveillance of patients with diagnosed dRTA

System/ Concern	Evaluation
Renal	Venous blood gas for pH (measure of acidity)
	Serum creatinine, urea, sodium, potassium, chloride, calcium, phosphate, alkaline phosphatase, albumin
	Urinalysis, urine creatinine, Na, K, calcium, citrate
	Renal ultrasound
ENT	Audiometry
Skeletal	Bone densitometry
Constitutional	Measurement of length/height, weight; calculation of body mass index

Source: ERG report, Table 4. Na: sodium, K: potassium.

Patient and carer perspectives

- Being diagnosed with dRTA can be extremely difficult both for patients and their family and friends. It affects patients' mental health and day-to-day activities

- Patients want treatment that will prevent symptoms, such as kidney stones, and give them a good quality of life

- There is an unmet need for people living with dRTA

"The mental side of living with RTA has hit harder as I feel I am not as strong as a normal 29yr old"

"I've recently resigned from my job because of the stress affecting my health"

"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 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"

"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."

"The renal team are great, but I feel that there could be more done to help with the prevention on kidney stones……. Or preventing from having to wait for stones to cause issues before treatment."

Current treatments – company summary

- No NICE guidance and **no specific medicine** or ready-to-use licensed product available
- Standard management → **off-label alkalinizing replacement therapy** to correct metabolic acidosis and to maintain serum potassium levels in the normal range. These are **short-acting** so require more frequent dosing
- 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

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

Alkali supplementation for maintenance of serum bicarbonate concentration
Maintenance of plasma **HCO3-, Cl- and K+**, as well as urinary calcium excretion
Additional **K^+-supplementation** in patients with persistent hypokalaemia
Patients informed of the effects of diet on acid load and alkali supplementation
Patients with dRTA are **regularly assessed**, clinically and biochemically
Patients have a renal tract ultrasound at diagnosis and in regular intervals at follow-up
For recessive dRTA linked to ATP6V1B1, ATP6V0A4 or FOXI1, early and developmentally appropriate hearing screening.

ERKNet: European Rare Kidney Disease Reference Network; ESPN: European Society for Paediatric Nephrology; HCO3: bicarbonate; Cl: chlorine; K:potassium

Prolonged-release potassium bicarbonate and potassium citrate (Sibnayal, Advicenne)

Mechanism of action	Sibnayal is a fixed-dose combination of potassium citrate and potassium hydrogen carbonate (also known as potassium bicarbonate) as prolonged release granules. Both act as alkalising agents and buffer the metabolic acidosis. Sibnayal provides a source of potassium to correct hypokalaemia. In addition, citrate acts also as a calcium chelating agent.
Marketing authorisation	Sibnayal is indicated for the treatment of distal renal tubular acidosis (dRTA) in adults, adolescents and children aged one year and older.
Administration	For oral use. Dosing is based on age and weight → total daily dose is administered twice daily, typically twelve hours apart.
Price (list price)	• Price per box: £360.00 per 24mEq, £120.00 per 8mEq • Average cost for an average adult per year: £11,256 • Confidential simple PAS discount approved

mEq: milliequivalent; PAS: Patient Access Scheme.

Decision problem

	NICE scope	Company submission	ERG comment
Population	People with distal renal tubular acidosis aged 1 year and older	As per scope	-
Intervention	Prolonged-release potassium citrate and potassium bicarbonate (Sibnayal)	As per 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 scope	-
Outcomes	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; HRQoL	As per scope	-
Subgroups	None	Sensitivity analysis: by age group: 1-3 years; 4-11 years; 12–17 years; and 18 years and over.	Dosing of sibnayal dependent on age and weight

HRQoL: Health related quality of life

Clinical trial evidence – B21CS

Study design	Multicentre (France, Serbia and Slovakia), open label, sequential, non-inferiority, study with a follow up of up to 40 days
Population	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
Analysis populations	**Intention-to-treat (ITT)/acceptability analysis:** n=37 **Per protocol (PP):** n=30 (2 patients were excluded due to major protocol deviations and five patients due to early study discontinuation)
Intervention	Sibnayal (ADV7103)
Comparator	Unlicensed: alkali therapy, sodium bicarbonate or sodium citrate
Outcomes	**Primary endpoint** • Average blood bicarbonate level (surrogate outcome for long term dRTA complications) **Secondary endpoints** • 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

Source: Company submission, Table 29.

Clinical trial evidence – B22CS

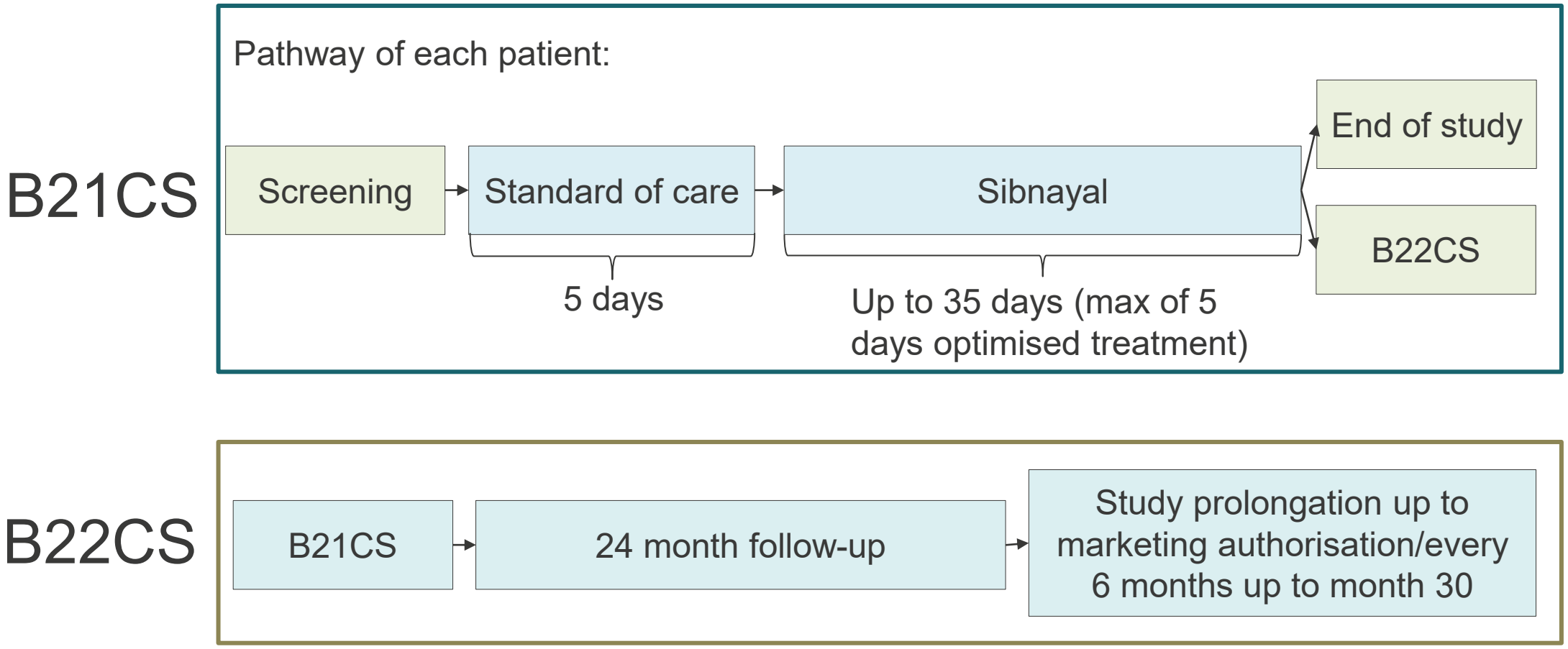
Study design	Multicentre (France, Serbia and Slovakia), open label, 24 month **extension study to B21CS***
Population	Patients with inherited dRTA with satisfactory completion of Study B21CS.
Analysis populations	N=30
Intervention	Sibnayal (ADV7103)
Comparator	None (single arm)
Outcomes	**Primary endpoint** • Number/proportion of subjects presenting adverse events during the course of the study, including the incidence and severity of the adverse events **Secondary endpoints** Long-term efficacy of Sibnayal on: • correcting metabolic acidosis as measured by bicarbonataemia Long-term effects of Sibnayal on: • hypocitraturia • hypercalciuria • crystalluria

*originally planned for 24 months but extended in France until market authorisation and availability of Sibnayal and extended for six additional months (30 months in total) in Slovakia and Serbia, until approval of the import licence for Sibnayal

Source: Company submission, Table 29.

B21CS and B22CS study design

B21CS ITT population = 37 patients; B22CS = 30 patients



Source: Company submission, Figures 14 and 15.

B21CS study results

B21CS non-inferiority and superiority (blood bicarbonate levels)	PP set		ITT set	
	SoC	Sibnayal	SoC	Sibnayal
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	
Mean blood bicarbonate levels in mmol/L (SD)	21.7 (3.06)	23.1 (1.62)	21.2 (3.11)	23.0 (1.62)

B21CS

- Normalisation of blood potassium achieved with Sibnayal and SoC → however, PP and ITT sets, mean (SD) blood potassium levels were higher with Sibnayal than with SoC at each time point
- 1 (3.6% PP set; 3.3% ITT set) patient had hypercalciuria with SoC but did not experience hypercalciuria when on Sibnayal
- All patients had hypocitraturia either after SoC, or Sibnayal or both treatments. However, most patients had hypocitraturia after SoC
- Compliance was high for both SoC (91.9%) and optimised Sibnayal treatment (96.9%) across the five days of treatment
- Adverse events were similar between SoC and Sibnayal

NICE Source: Company submission (Table 33)

CI: confidence interval; LS: least square; SoC: standard of care, PP: per protocol, ITT: intention to treat

B22CS study results

B22CS

- Within months 3 to 48, percentage of patients with blood bicarbonate levels in normal range was from 60.9% to 92.3%
- Study compliance to Sibnayal was reported as ≥75 % for n=28/30 (93.3%) at month 3, and n=23/29 (79.3%) at month 24
- Adverse events were experienced by 90% of people – most were mild or moderate intensity

Bicarbonataemia Status by Visit – Blood Tests Done Before Drug Intake

	Analysis Visit	n	Bicarbonataemia status		
			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: Company submission (Table 44)

Issues resolved after technical engagement

Summary	Company responses	ERG response
Issue 2: Limitations in the conceptualisation and functionality of the model • Patients start the model in different health states dependent on initial treatment	Base case updated	Resolved
Issue 4: Uncertain values used in the model from the sources cited by the company • 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 • Assumption that all patients with nephrolithiasis would have 1 percutaneous nephrolithotomy each year • Estimation of risk of death associated with fracture or with hypokalaemia • The assumed dosages for Sibnayal	Base case updated	Largely resolved - some uncertainty remains
Issue 5: Implementation issues within the model	Resolved	Resolved

Outstanding issues after technical engagement

Key issues	Impact on ICER	Slides
NICE issue: a) Standard of care breakdown		19
NICE issue: b) Utility multiplier for end stage kidney disease		20
1. Limited comparative evidence of Sibnayal compared with SOC		21
2. Limitations in the conceptualisation and functionality of the model		
a) Patients responding to treatment cannot progress beyond CKD2 b) Patients not-responding, but on treatment, cannot progress to end-stage kidney disease c) Patients discontinuing treatment will never restart treatment d) Patients who lose disease control or regain disease control remain in the same health state e) Conditions that are chronic in nature have been modelled as transitory health states		22 - 23
f) No acquired dRTA disutility applied when patients have controlled disease g) No chronic utility gain associated with the more convenient dosing regimen of Sibnayal compared with SoC		24 - 26

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Key: Model driver; Unknown impact; Small/moderate impact;

Outstanding issues after technical engagement (2)

Key issues	Impact on ICER	Slides
3. Lack of targeted reviews to populate the model and the reliance on clinical opinion		27
4. Uncertain values used in the model from the sources cited by the company		
a) Assumption of equal disease control for patients regardless of age b) Uncertainty in the proportion of patients with acquired dRTA		28 - 29
c) Estimation of the proportions of patients with disease control at the start of the model (ERG scenario analyses)		30

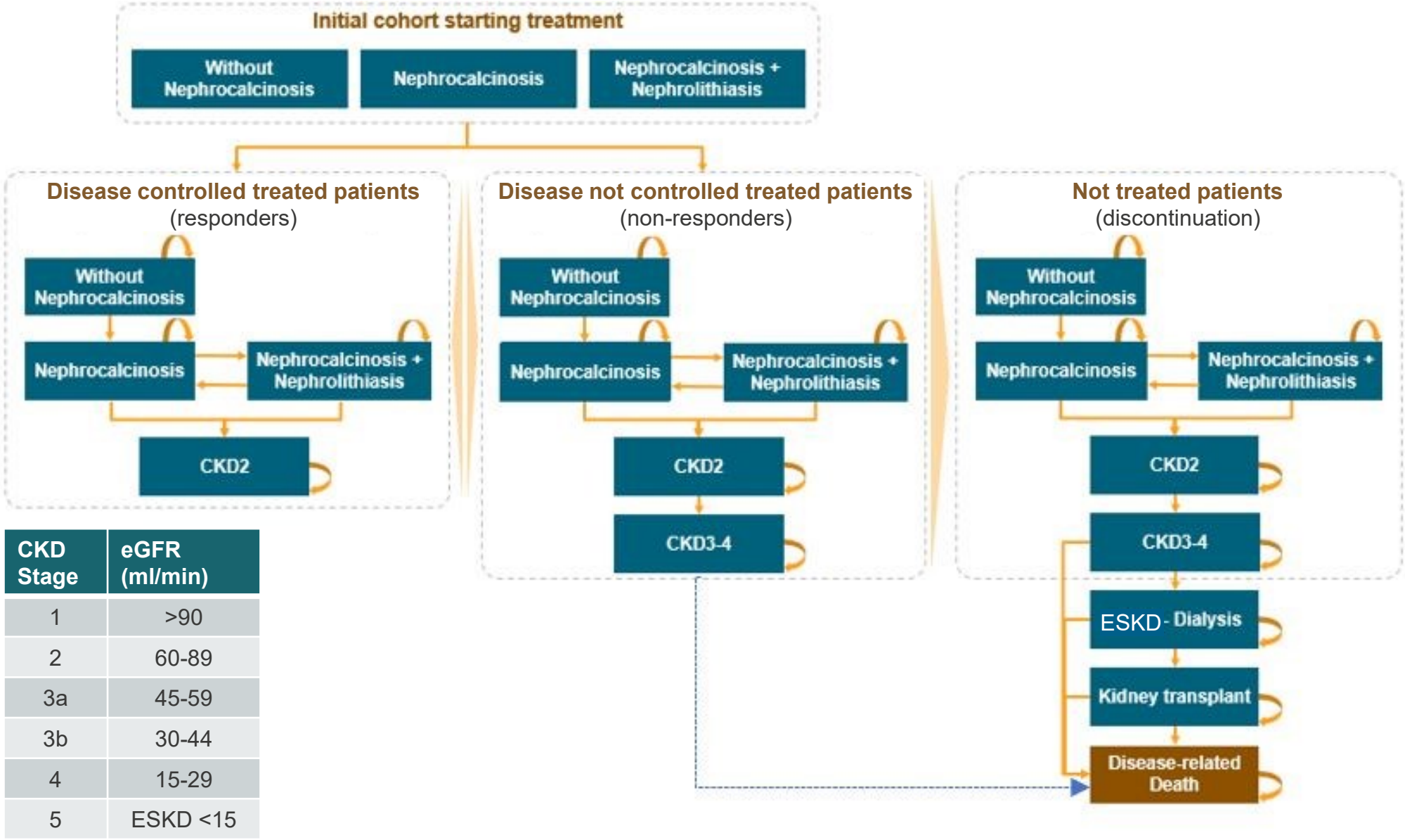
Key: Model driver; Unknown impact; Small/moderate impact;

Company's model

Model type	Cohort Markov Model (state transition model)
Population	Weighted population with acquired and inherited dRTA (infants from 1 year to 3 years old, children from 4 to 11 years old, adolescents from 12 to 17 years old and adults [18+])
Intervention	Sibnayal
Comparators	Alkali therapy
Time horizon	75 years (lifetime)
Model cycle	First 2 years: 6 months; After 2 years: 1 year
Treatment waning	No
Utility values	Literature (health utilities were not collected during the trial)
Costs	Literature and National Cost Collection (Resources used were not collected during the trial)

Source: Company submission

dRTA model schematic



CKD Stage	eGFR (ml/min)
1	>90
2	60-89
3a	45-59
3b	30-44
4	15-29
5	ESKD <15

Source: ERG report, Figure 4.

CKD: chronic kidney disease; ESKD: end stage kidney disease; eGFR: estimated glomerular filtration rate.

NICE issue (a): Standard of care used in the company's model

Range and percentage of alkali products used by the company to define standard of care treatment in the model is derived from the B21CS trial as below

Number of products	Company SoC breakdown	Percentage of users (n=37)
1 product		**51.4%**
	potassium bicarbonate	8.1%
	potassium citrate	21.7%
	modified Shohl's solution	2.7%
	sodium bicarbonate	18.9%
2 products		**48.6%**
	potassium bicarbonate+ potassium citrate	8.1%
	potassium bicarbonate+ sodium bicarbonate	13.5%
	potassium citrate+ sodium bicarbonate	24.3%
	modified Shohl's solution + sodium bicarbonate	2.7%

- Is the company's standard of care breakdown reflective of clinical practice?

Source: Company submission, Table 83. Shohl's solution: Citric Acid and Hydrous Sodium Citrate.

NICE issue (b): Utility multiplier for ESKD

Utility multipliers are used for the underlying health States. QALY decrements are used for transitory events (including having acquired dRTA) except for fractures (which uses a utility multiplier)

Health state	Original company utility multiplier	ERG/company post-TE utility multiplier
Without nephrocalcinosis	1.000[1]	1.000
Nephrocalcinosis	0.907[†]	0.976[††]
Nephrolithiasis	0.880[3]	0.976[6]
Chronic kidney disease stage 2	0.907[2]	0.950[2]
Chronic kidney disease stages 3-4	0.822[2]	0.951[2]
End stage kidney disease (ESKD)	0.541[4]	0.809[2]
Kidney transplant - year of transplant	0.736[5]	0.619[4]
Kidney transplant - each subsequent year	0.736[5]	0.619[4]

Potential face validity error in utility multiplier applied to ESKD because 0.809 higher than for patients with liver transplant (0.619) → ERG conducted scenario using 0.541 multiplier for ESKD

- Which utility multiplier for ESKD is most appropriate?

Source: ERG report (Table 27 and 42). [†]Company assumed equal to chronic kidney disease stage 2. [††] assumed the same as nephrolithiasis. Multipliers are mid-point multipliers. Utility multipliers are multiplied by general population health

Issue 1: Limited evidence related to the comparative efficacy of Sibnayal compared with SOC

ERG

- No long-term comparative efficacy data for Sibnayal
- B21CS study used patients as their self-control, but had a short duration (a maximum of 5 days of optimised treatment)
- Study B22CS was single-armed and had a duration of up to 48 months
- Both studies involved less than 40 patients
- These limitations mean there is considerable uncertainty in true efficacy of Sibnayal
- ERG understand the company could not resolve this at technical engagement

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- Data from B21CS is extrapolated up to 75 years in the model

Company

- No response after Technical Engagement

- Is there enough evidence to compare Sibnayal to standard of care?
- If so, how robust is the evidence?

Issue 2 (a-c): Limitations in the conceptualisation and functionality of the model

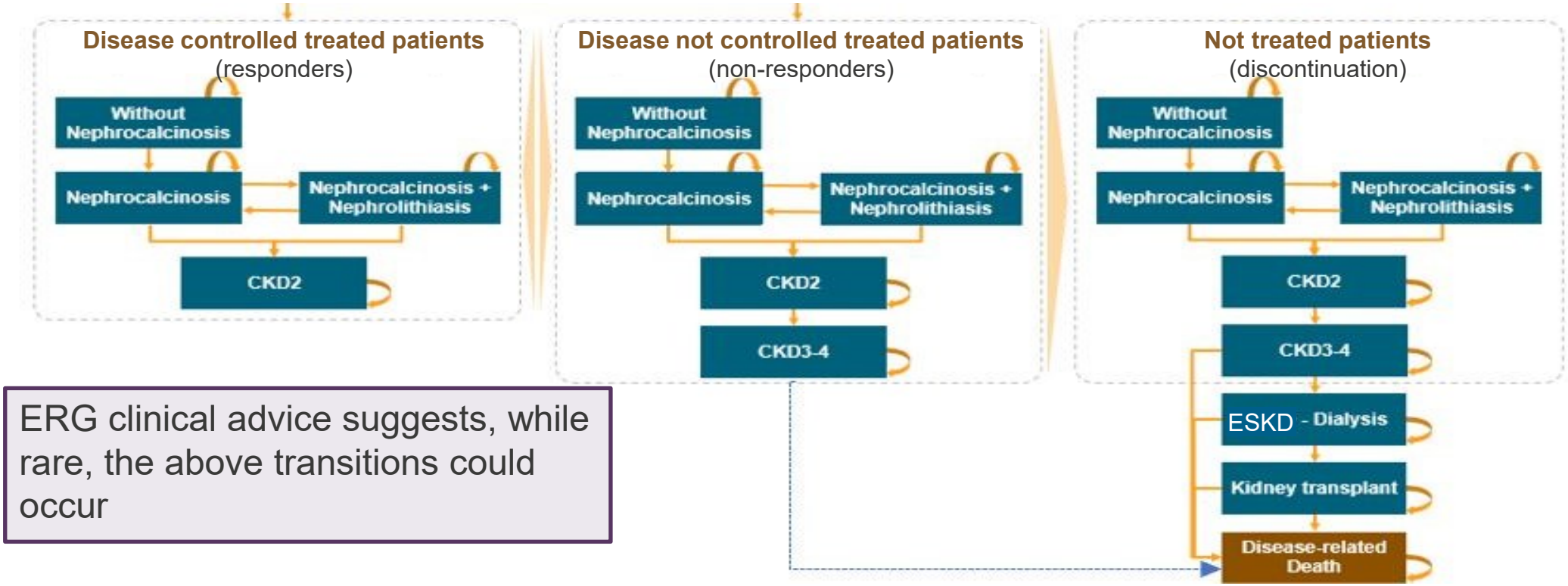
ERG

Identified **several limitations** that the **ERG could not amend**:

a) Patients responding to treatment (either Sibnayal or SoC) cannot progress beyond CKD2

b) Patients not-responding, but on treatment (either Sibnayal or SoC), cannot progress to end-stage kidney disease

c) Patients discontinuing treatment in the model will never restart treatment (with either Sibnayal or SoC) later on in life



ERG clinical advice suggests, while rare, the above transitions could occur

- How much uncertainty do these limitations contribute?

CKD: chronic kidney disease; ESKD: end stage kidney disease; QALY: quality adjusted life year; SoC: standard of care.

Issue 2 (d-e): Limitations in the conceptualisation and functionality of the model

ERG
Limitation that the **ERG could not amend**:
d) Patients who lose disease control or regain disease control remain in the same health state over a cycle → two events occur in the same health state
    - In this situation you can't account for differences in health or costs between controlled and uncontrolled diseases

ERG
Limitation that the **ERG could not amend**:
e) Conditions, such as osteomalacia/rickets, that are chronic in nature have been modelled as transitory health states and the assumed QALY loss taken from patients with severe, chronic disease
    - If persistent, model structure with osteomalacia/rickets defined as health states would have been preferable
    - ERG assumed no QALY loss for osteomalacia/rickets

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- How much uncertainty do these limitations contribute?

CKD: chronic kidney disease; ESKD: end stage kidney disease; QALY: quality adjusted life year; SoC: standard of care.

Issue 2 (f): Disutility associated with those with acquired dRTA is not incurred when patients have controlled disease

Company

- Acquired forms of the disease are usually associated with autoimmune diseases, such as Sjögren's syndrome, systemic lupus erythematosus or autoimmune chronic liver disease
- Therefore, 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 → not applied if patients have controlled disease
- Disagree with assumption of 0 people have acquired dRTA in model

ERG

- Assumption has multiple limitations:
  - No additional evidence to show why these diseases would have no impact on patients who have controlled disease
  - 0.18 value not generalisable to English patients (sourced from study renal replacement therapy for acute renal failure at a Finnish tertiary centre)
  - One patient in B21CS with acquired dRTA did not continue to B22CS
  - If acquired dRTA is distinct subgroup, should be analysed separately
- Given limitations, ERG provide ICERs for inherited dRTA only → note the uncertainty in cost-effectiveness of acquired dRTA

- Should acquired dRTA be considered in the cost-effectiveness results?
- If so, would this disutility be applied to those with controlled acquired dRTA?

Dosing of SoC and Sibnayal

	Sibnayal	SoC
Daily doses	2 doses 12 hours apart	3-6 doses (86.5% of people)
Sleep disturbance	None	27% of people

B22CS collected VAS scores to assess the long-term treatment acceptability of Sibnayal versus standard of care

Number (Percentage) of Patients with Treatment Acceptability by VAS Score Level

Treatment acceptability VAS score vs. SoC n(%)	Adults >=18Y (N=6)	Adolescents [12-18Y] (N=8)	Children [4-12Y] (N=13)	Infants [0.5-4Y] (N=3)	Overall (N=30)
More appropriate formulation: score ≥50%	3 (60.0)	7 (87.5)	13 (100.0)	3 (100.0)	26 (89.7)
More convenient number of daily dose intake: score ≥50%	5 (100.0)	8 (100.0)	11 (84.6)	3 (100.0)	27 (93.1)
Better taste: score ≥50%	4 (80.0)	4 (50.0)	10 (76.9)	3 (100.0)	21 (72.4)

Source: Company submission, Table 65. VAS: visual analogue scale.

Issue 2 (g): Utility gain associated with more convenient Sibnayal dosing

Company

- Include SoC utility decrement to demonstrate chronic utility gain associated with the more convenient dosing regimen of Sibnayal compared with SoC
  - No direct utility data captured in B21CS or B22CS trials so conducted targeted literature review and 2 clinical validation interviews to identify appropriate proxy utility/disutility
  - QALY decrement of 0.04 and applied at every cycle to all patients receiving SoC treatment

Targeted literature review: 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.

ERG

- None of identified studies are ideal → 0.04 is reasonable but uncertain
- Studies don't explicitly evaluate impact of doses taken during the night as required by SoC for treating dRTA, some lack face validity, some do not evaluate change in dosing frequency and some do not use preference based measure to elicit utility values

- Is a utility decrement of 0.04 for SoC dosing regimen reasonable?

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Source: Company response to TE, Table 1

QALY: quality-adjusted life year; SD: standard deviation; SoC: standard of care.

Issue 3: Lack of targeted literature reviews to populate the model and the reliance on clinical opinion

Company

- Refreshed targeted literature review in response to ERG commenting that few, if any, systematic literature reviews had been undertaken → expanded to include targeted literature review results for additional inputs (mortality, dosing regimen utility, average weight)
- Outcome of formal targeted review led to reliance on expert opinion for certain inputs

ERG

- Model relies substantially on expert clinical opinion and it is not clear to what extent the sources selected or clinical estimates used to populate the model may influence results of model
- Key parameters relying on clinical opinion are transition probabilities and discontinuation rates
- Recognises searches for two targeted literature reviews are systematic, pragmatic and transparent but wanted to see text explicitly justifying reasons for choosing source used to populate the base case model

- Is reliance on clinical opinion appropriate?

Issue 4 (a): Assumption of equal disease control for patients regardless of age

ERG

Limitation that the **ERG could not amend**:

- Company's model assumes probability of maintaining or recovering disease control is independent of age
- Assumption was supported by clinical advice received by the ERG, but data for patients receiving Sibnayal in B22CS (see table) suggest a difference could be plausible, although the sample size is small
- ERG has maintained the company's assumption but highlights that this assumption is subject to uncertainty

	Over 18	Under 18
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%

- How much uncertainty does this limitation contribute to the overall cost effectiveness?

Source: ERG report (Table 43)

Issue 4 (b): Uncertainty in the proportion of patients with acquired dRTA

ERG

- Linked to issue 2
- All patients over 18 years old have acquired dRTA in the model
- No patients in B22CS had acquired dRTA and 1 person in B21CS had acquired dRTA
- ERG assumed no people have acquired dRTA in model

Company

- Disagree with assumption of 0 people have acquired dRTA in model

- If acquired dRTA is included in the model, what proportion of patients have acquired dRTA? And should they be modelled as a separate subgroup?

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ERG: evidence review group.

Issue 4 (c): Estimation of the proportions of patients with disease control at the start of the model

ERG

- Company choice of definition of disease control not justified but definition is used in ERG preferred indicative ICERs
- ERG provide scenario with two alternative definitions of disease control based on B21CS and transition probability calculations
  - Transition probabilities imply a different proportion of responders than the company model → appears incompatible with B21CS

Definition of disease control	Proportion on Sibnayal	Proportion on SoC
Company model: mean bicarbonataemia levels normal across days 2 to 4	90%	43.33%
B21CS trial: Normal bicarbonataemia on all of days 2 to 4	76.67%	36.67%
Transition probability: Initial disease control based on the patient numbers used to calculate the probabilities of maintaining and regaining disease control	63.33%	44.33%

- Which definition of controlled disease is most reflective of controlled disease in current practice?

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Key assumptions in company and ERG analyses after TE

Parameter	Base case	
	Company	ERG
Number of patients with acquired dRTA	**1 in 7**	**None**
Cost of Sibnayal added to first 5 days of model	Yes	Yes
Costs of nephrolithiasis health state	Equal to nephrocalcinosis health state	Equal to nephrocalcinosis health state
General population utility values	Ara and Brazier general population utilities	Ara and Brazier general population utilities
Utility decrement for acquired dRTA non-responders or treatment discontinuation	0.18	Not applicable
Utility decrement associated with acquired dRTA	0	Not applicable
Utility decrement for inconvenience of SoC dosing regimen	0.04	0.04
Utility decrement for hypokalaemia	0.03	0.03
Utility decrement for osteomalacia/rickets	0	0
Errors identified at technical engagement corrected	Yes	Yes

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All utility decrements are QALYs

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential discounts

Innovation and Equality

Innovation

- Fixed-dose combination of potassium bicarbonate and potassium citrate, formulated as prolonged-release granules developed to control metabolic acidosis and any hypokalaemia in dRTA patients
- Safe and simplified twice daily dosing regimen compared with the current SoCs, which require more frequent administrations including administrations during the night

Equality issues – none identified by the company

dRTA: distal renal tubular acidosis; SoC: standard of care.