



advicenne

Innovative treatments in nephrology

Euronext: **ADVIC** | Nimes, France

September 2020

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Specialty pharma developing novel therapeutics for rare diseases in nephrology

- Lead asset, ADV7103, with a large market potential for two main sub-indications
 - dRTA:
 - pending EU marketing authorization and orphan drug status in Europe
 - ongoing pivotal Phase III trials in the US and Canada
 - Cystinuria:
 - ongoing pivotal Phase III trials and orphan drug status in Europe

- Well financed, with €17,8 million of cash and equivalents at June 30, 2020*, plus €12.5 remaining million loan facility granted by EIB in July 2019

2020 highlights to date

- Evolution in Company governance
 - Split between Chairman & CEO functions
 - Strengthening of management team with international & marketing profiles
- Strategic focus on nephrology
- Creation of a US subsidiary
- Market approval process ongoing for dRTA in Europe
 - European commercialization preparation
- COVID-19 impact on ongoing studies: ± 12 months initial impact to be reduced
 - Opportunity taken to redesign protocols of phase III studies with aim to catch up totally or partially with these imposed delays
- Ozalin[®] option for commercialization exercised by Primex
 - €33m to be received by Advicenne over the next 5 years
- Financial visibility maintained over the period via non-dilutive financing

Sustained development to prepare the next value creation phases

Seasoned management team



André Ulmann, MD, PhD

Interim CEO

- 30 years in pharma industry
- Previously Director at HRA Pharma



Paul Michalet, MBA, CEFA

Chief Financial Officer

- 30 years in executive management
- Previously worked at Fermentalg



Caroline Roussel-Maupetit, Eng

Co-founder and Director of Operations

- Extensive background in pharmaceutical development
- Previously worked at synt:em



Catherine Guittet, PharmD

Head of Clinical Operations Department

- 30 years in clinical affaires
- Previously worked at MERCK SERONO



Nathalie Lemarié, PharmD

Director of Regulatory Affairs & Qualified Person

- 20 years in regulatory affairs
- Previously worked at



Sarah Delbaere

Financial & Logistics Director

- 15 years in finance in pharma and biotech sectors
- Previously worked at Takeda



Victor Navas, MD, PhD

Chief Medical Officer

- 22 years in pharma industry
- Following 7 years in medical practice, he worked at 4 pharma companies Shire



Robbie Mc Carty

General manager of Advicenne Inc.

- 20 years of pharmaceutical practice
- Deep commercial know-how acquired in pharma & start-up companies Shire

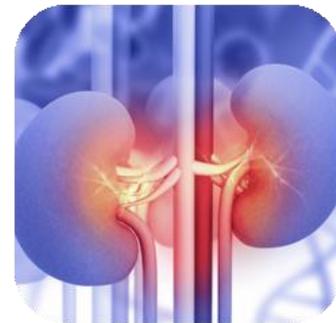
Development based on Company's unique know-how

- Unique knowledge in innovative formulations & excellence in clinical development
- Ozalin®: a deal of up to €40m with Primex Pharmaceuticals
 - A novel oral solution for pediatric sedation
 - The first licensed oral sedative developed by Advicenne and approved in EU
 - Deal signed in 2016:
 - up fronts + milestones + royalties based on sales
 - Market potential: 100 to 300M€*
- Ozalin® option for commercialization exercised by Primex in September 2020
 - €33m to be received by Advicenne over the next 5 years



Targeting unmet needs in nephrology

- Kidney alterations lead to serious disorders or debilitating diseases
- Few approved treatments in Europe and the US
- Few players and large unmet needs

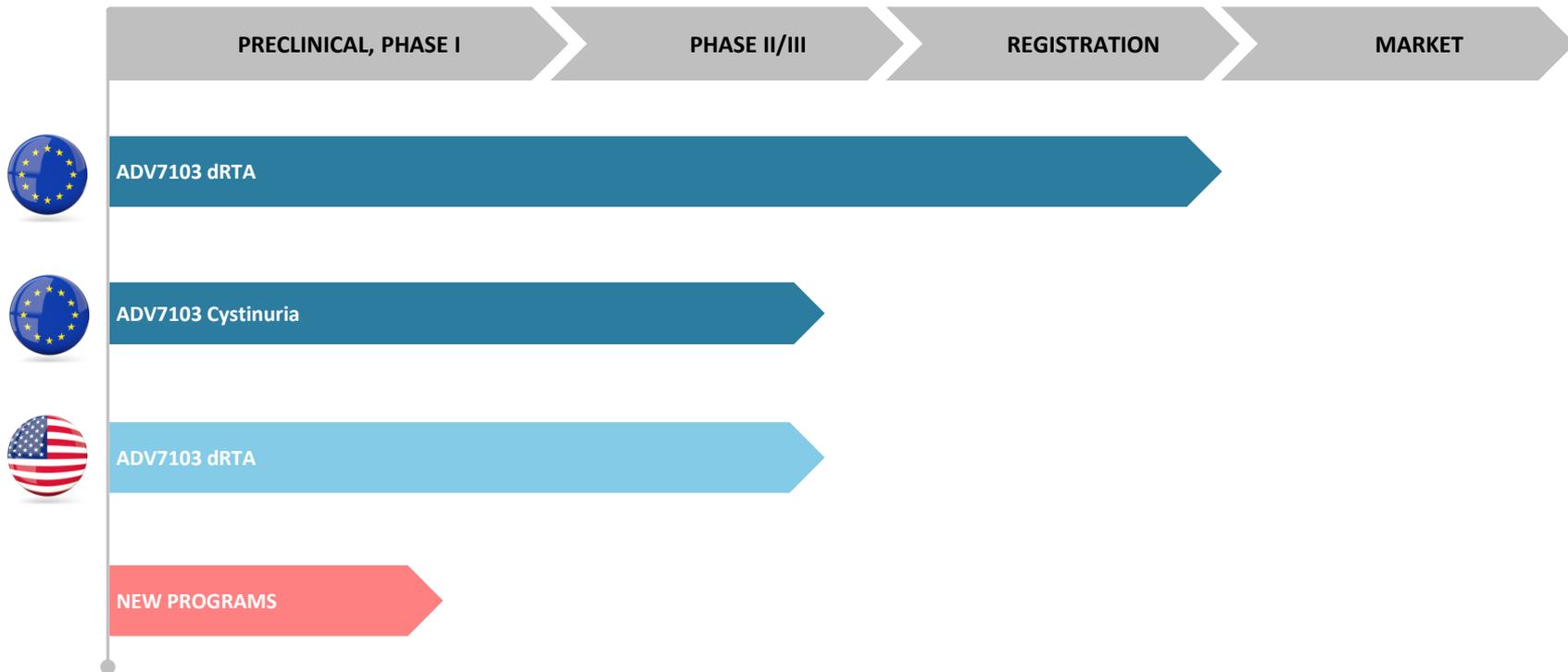


ADV7103 addresses two orphan renal diseases

with severe debilitating consequences and significant unmet medical needs: dRTA and Cystinuria



Mature pipeline in nephrology

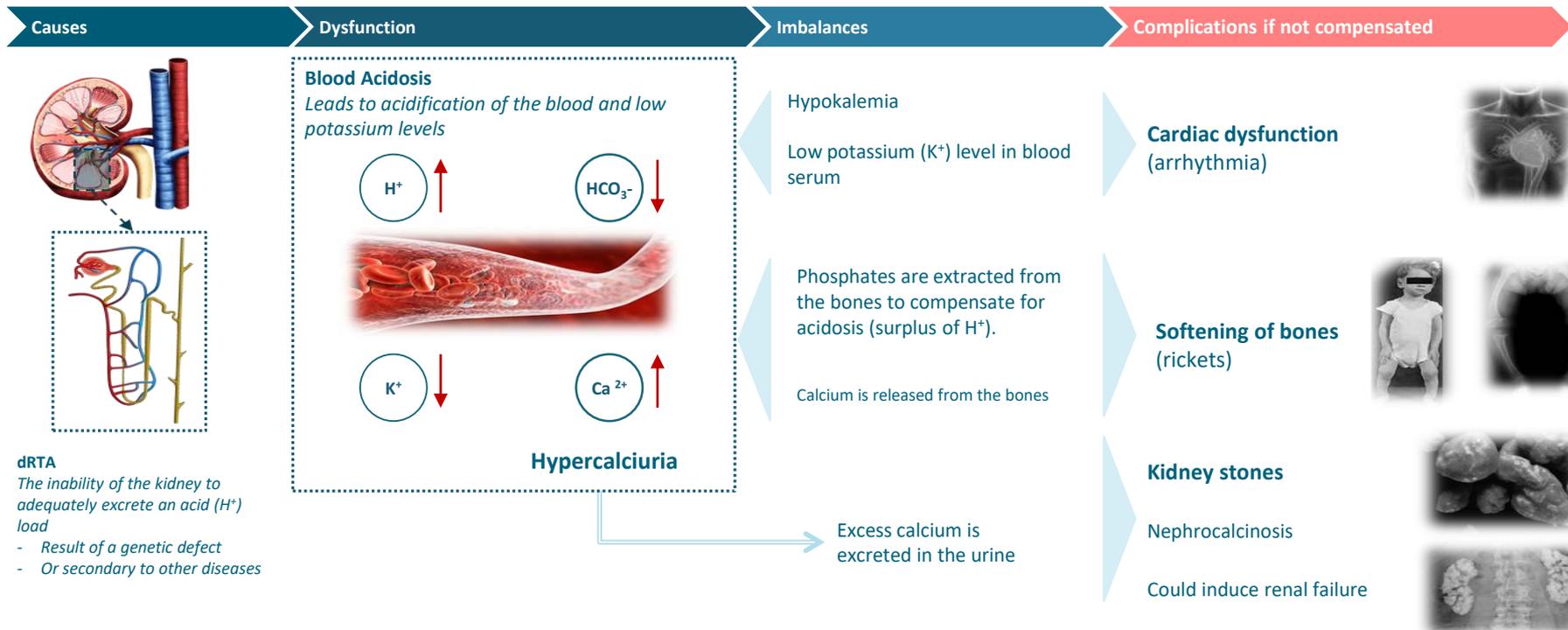


ADV7103

Global Development for dRTA

EU & US

Consequences of distal renal tubular acidosis (dRTA)



Source: Advicenne, Rodriguez-Soriano et al 1982, Domrongkitchaiporn et al. 2002a, Domrongkitchaiporn et al. 2002b, MacSherry et al. 1978, Caldas et al. 1992

dRTA: a severe debilitating orphan renal disease

In literature, of the largest dRTA Cohort (89 patients) genetically studied :

- Nephrocalcinosis was found in up to 93.6% of patients
- Failure to thrive (FTT) was present up to 74.2%
- Chronic kidney disease (CKD) is present in 31.3% of patients

Table 5 | Clinical features of patients included in the study

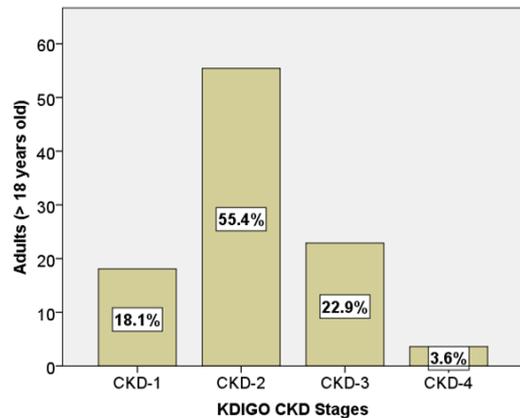
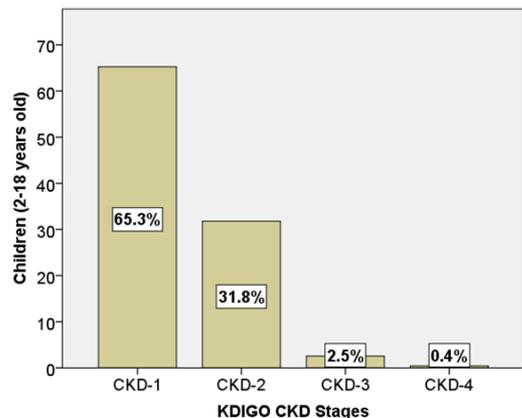
	<i>SLC4A1</i>	<i>ATP6V1B1</i>	<i>ATP6V0A4</i>	Variants of unknown clinical significance	Negative	Mutated
M/F, no. (%)	4/9 (44.4)	13/25 (52)	14/30 (46.6)	5/7 (71.4)	7/18 (38.9)	31/64 (48.4)
Age at onset of dRTA, mo	153.2	13.9	28.6	47.6	131.1	65.2
SNHL, no. (%)	1/8 (12.5)	23/25 (92)	17/30 (56.7)	3/7 (42.9)	3/18 (16.7)	41/63 (65)
Age at onset of SNHL, mo	240	41.8	183.5	168	198.7	155.1
Nephrocalcinosis, no. (%)	8/8 (100)	24/25 (96)	27/30 (90)	4/7 (57.1)	12/18 (66.6)	59/63 (93.6)
FTT, no. (%)	4/8(50)	19/24 (79.1)	23/30 (76.6)	5/6 (83.3)	2/21 (9.5)	46/62(74.2)
Hypokalemia, no. (%)	3/9 (33.3)	15/25 (60)	15/25 (60)	3/6(50)	3/17(17.6)	33/59 (55.9)
CKD		16/51 (31.3)		2/7 (28.6)	5/14 (35.7)	16/51 (31.3)

CKD, chronic kidney disease (defined as estimated glomerular filtration rate <90 ml/min per 1.73 m²), dRTA, distal renal tubular acidosis; FTT, failure to thrive; M/F, male/female; SNHL, sensorineural hearing loss.

Source: Palazzo, *Giglio Kidney Int.* 2017 May;91(5):1243-1255

dRTA: a long-term and significant medical need

- Chronic Kidney Disease (CKD) is frequent in patients with long-term follow-up
 - Increased prevalence of CKD stage ≥ 2 in children (35%) and adults (82%)

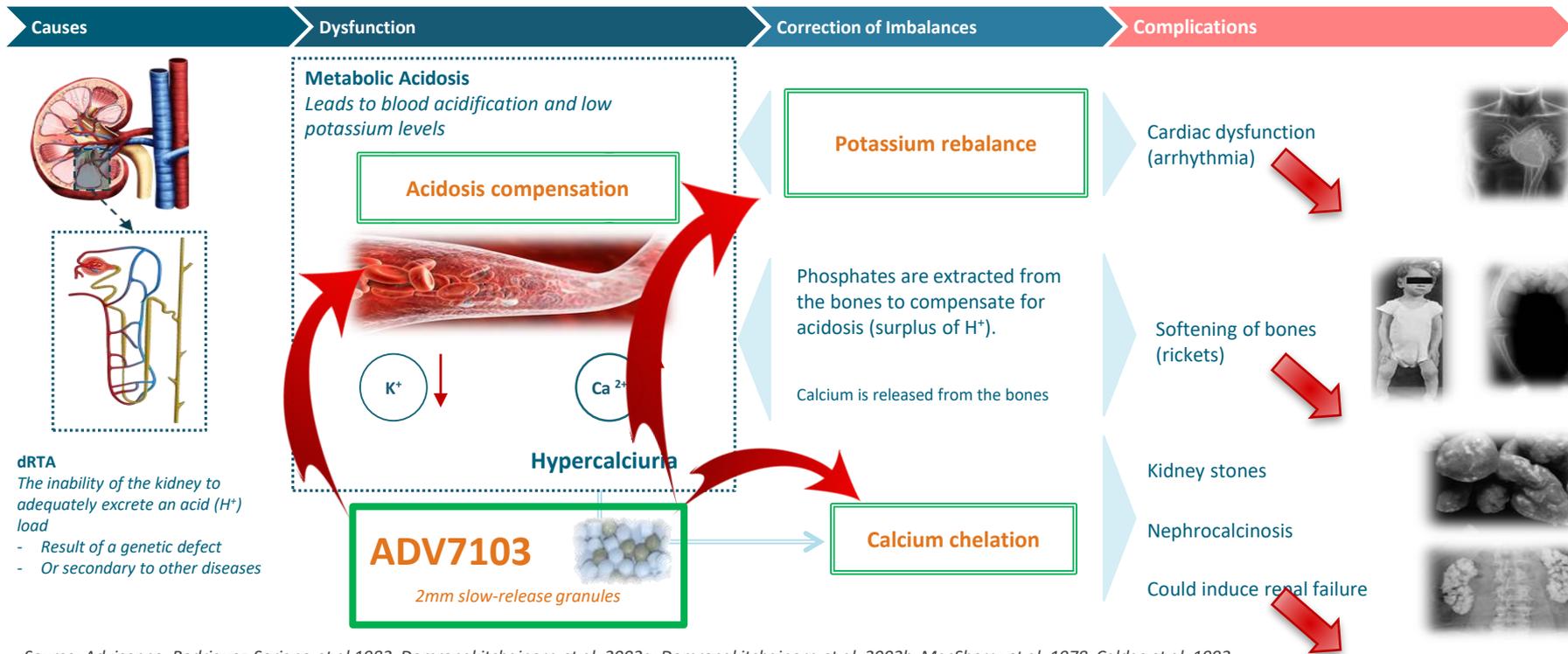


The need for an efficient treatment is obvious with an early treatment initiation to prevent long-term complications

Source: Lopez-Garcia et al. Treatment of long-term outcome in primary distal renal tubular acidosis. *Nephrol Dial transplant* (2019) 1-11.

KIDGO : Kidney Disease: Improving Global Outcomes (CKD severity classification)

What can we expect when treating dRTA with ADV7103 ?



dRTA
 The inability of the kidney to adequately excrete an acid (H⁺) load
 - Result of a genetic defect
 - Or secondary to other diseases

Source: Advicenne, Rodriguez-Soriano et al 1982, Domrongkitchaiporn et al. 2002a, Domrongkitchaiporn et al. 2002b, MacSherry et al. 1978, Caldas et al. 1992

ADV7103 offers indisputable advantages

ADV7103



“Standard” of Care (SoC)



Improved efficacy (HCO ₃ ⁻)	✓	1	✗	Sub-optimal efficacy
Only two doses a day (12h) enabling full night coverage	✓	2	✗	Requires 3-6 treatments a day (<4h) with difficult night coverage
Normalized plasma potassium	✓	3	✗	Potassium supplementation requirement
Improved gastrointestinal tolerance	✓	4	✗	Frequent gastrointestinal intolerance
Tasteless and adapted to pediatric patients	✓	5	✗	Bad taste and not adapted to pediatric patients
Improved acceptability and compliance	✓	6	✗	Poor acceptability and compliance

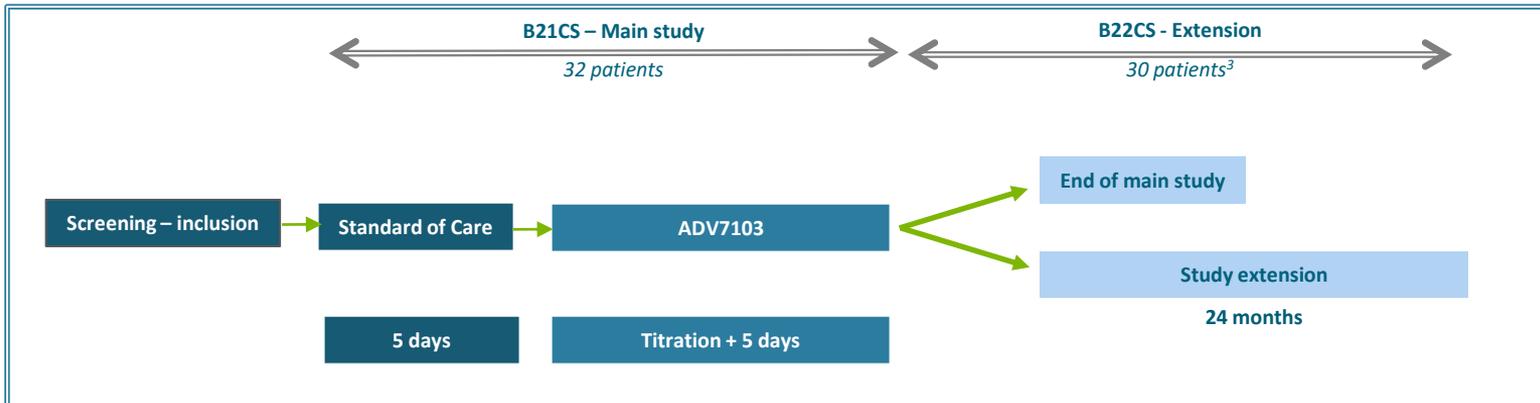
ADV7103 improves treatment efficacy and quality of life, especially in pediatric patients

Design of pivotal EU Phase III trial in dRTA

Key Characteristics of Trials

- **B21CS¹ – Pivotal study:** A multicenter, open-label, non-inferiority sequential study in 32 patients
- **B22CS² – Extension study (24 months)** of B21CS

Study design



Primary objective

Evaluate the relative efficacy of ADV7103 and SoC on correcting metabolic acidosis as measured on pre-morning dose blood bicarbonate levels

1: EudraCT number: 2013-002988-25
 2: EudraCT number: 2013-003828-36

Clinical studies published results

**SCIENTIFIC
REPORTS**

nature research

August 2020



Innovative prolonged-release oral alkalisant formulation allowing sustained urine pH increase with twice daily administration: randomised trial in healthy adults

C. Guittet¹, C. Roussel-Maupetit¹, M. A. Manso-Silván^{1,2}, F. Guillaumin¹, F. Vandenhende² & L. A. Granier^{1,2,3}

A multi-particulate fixed-dose combination product, consisting of a combination of two alkalisant salts formulated as prolonged-release granules, ADV7103, was developed to obtain a sustained and prolonged alkalisant effect. The specific release of both types of granules was shown in vitro through their dissolution profiles, which indicated that potassium citrate was released within the first 2–3 h and potassium bicarbonate up to 10–12 h after administration. The long-lasting coverage of ADV7103 was confirmed through a randomised, placebo-controlled, double-blind, two-period study, measuring its effect on urine pH in healthy adults ($n=16$) at doses of alkalisant agent ranging between 0.98 and 2.88 meq/kg/day. A significant increase of urine pH with a positive dose–response in healthy adult subjects was shown. Urine pH above 7 was maintained during 24 h with a dosing equivalent to 1.44 meq/kg twice a day, while urine pH was below 6 most of the time with placebo. The effect observed was non-saturating within the range of doses evaluated and the formulation presented a good safety profile. ADV7103 provided an effective prolonged release of alkalisant salts to cover a 12-h effect with adequate tolerability and could afford a twice a day (morning and evening) dosing in patients requiring long-term treatment.

Pediatric Nephrology
<https://doi.org/10.1007/s00467-020-04693-2>

June 2020

ORIGINAL ARTICLE



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

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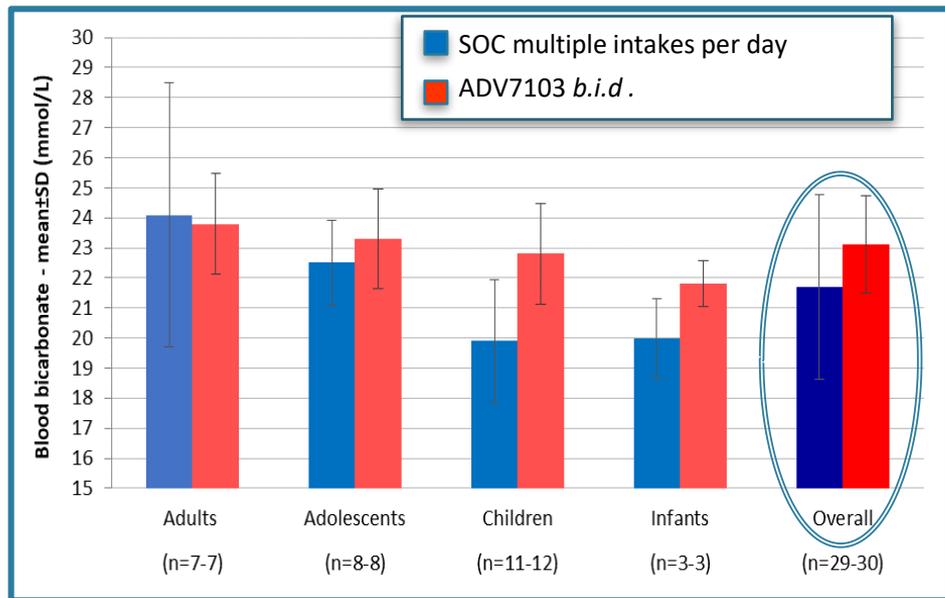
Abstract

Background Distal renal tubular acidosis (dRTA), due to impaired acid secretion in the urine, can lead to severe long-term consequences. Standard of care (SoC) oral alkalisants, requiring several daily intakes, are currently used to restore normal plasma bicarbonate levels. A new prolonged-release formulation, ADV7103, has been developed to achieve a sustained effect with an improved dosing scheme.

Methods In a multicenter, open-label, non-inferiority trial ($n=37$), patients with dRTA were switched from SoC to ADV7103. Mean plasma bicarbonate values and proportion of responders during steady state therapy with both treatments were compared, as were other blood and urine parameters, as well as acceptability, tolerability, and safety.

Results When switching from SoC to ADV7103, the number of daily intakes was reduced from a median of three to twice daily. Mean plasma bicarbonate was increased and non-inferiority of ADV7103 was demonstrated ($p < 0.0001$, per protocol), as was statistical superiority ($p = 0.0008$, intention to treat [ITT]), and the response rate increased from 43 to 90% with ADV7103 ($p < 0.001$, ITT). Urine calcium/citrate ratio was reduced below the threshold for risk of lithogenesis with ADV7103 in 56% of previously non-responders with SoC ($p = 0.021$, ITT). Palatability was improved (difference [95% CI] of 25 [10.7, 39.2] mm

Phase III Data - Improved efficacy

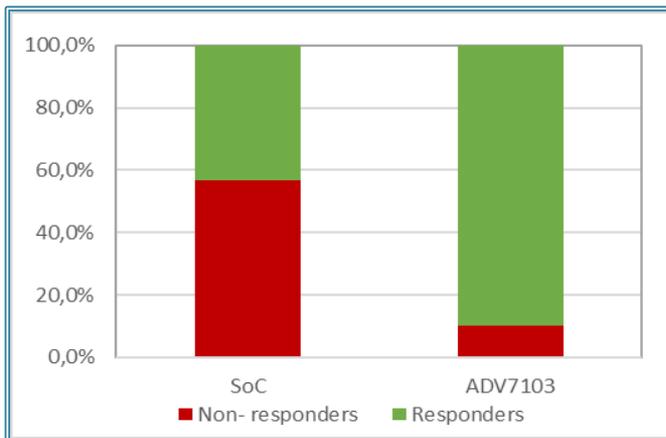


- Pivotal phase III results demonstrate significant efficacy
 - Non-inferiority is clearly demonstrated on primary endpoint (blood bicarbonate)
 - Significantly superior to SoC on primary endpoint
 - P-value = 0.0037 (Per Protocol)
 - P-value = 0.0008 (Intention to Treat)



Phase III Data - non responder/responder analysis in patients with dRTA

- 82.4% (14/17) of non-responders* became responders when switching from SoC to ADV7103
- Significant difference between treatments

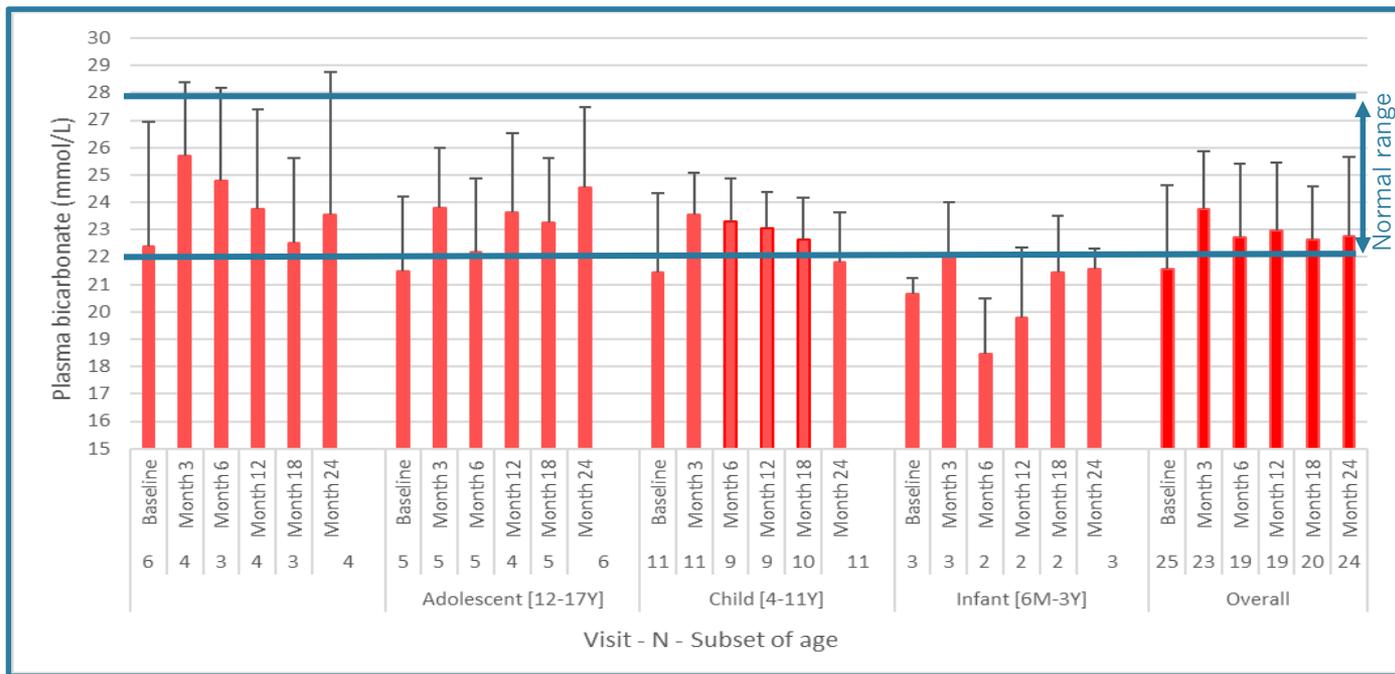


Number (%) of responders (R) and non-responders (NR) - ITT set (N=30)		
SoC	ADV7103	n/N (%)
R	R	13/30 (43%)
NR	NR	3/30 (10%)
NR	R	14/30 (47%)
R	NR	0 (0.0%)
p-value		<0.001

*Non-responders = Patients presenting abnormally low average blood bicarbonate levels (days 2, 3 and 4)

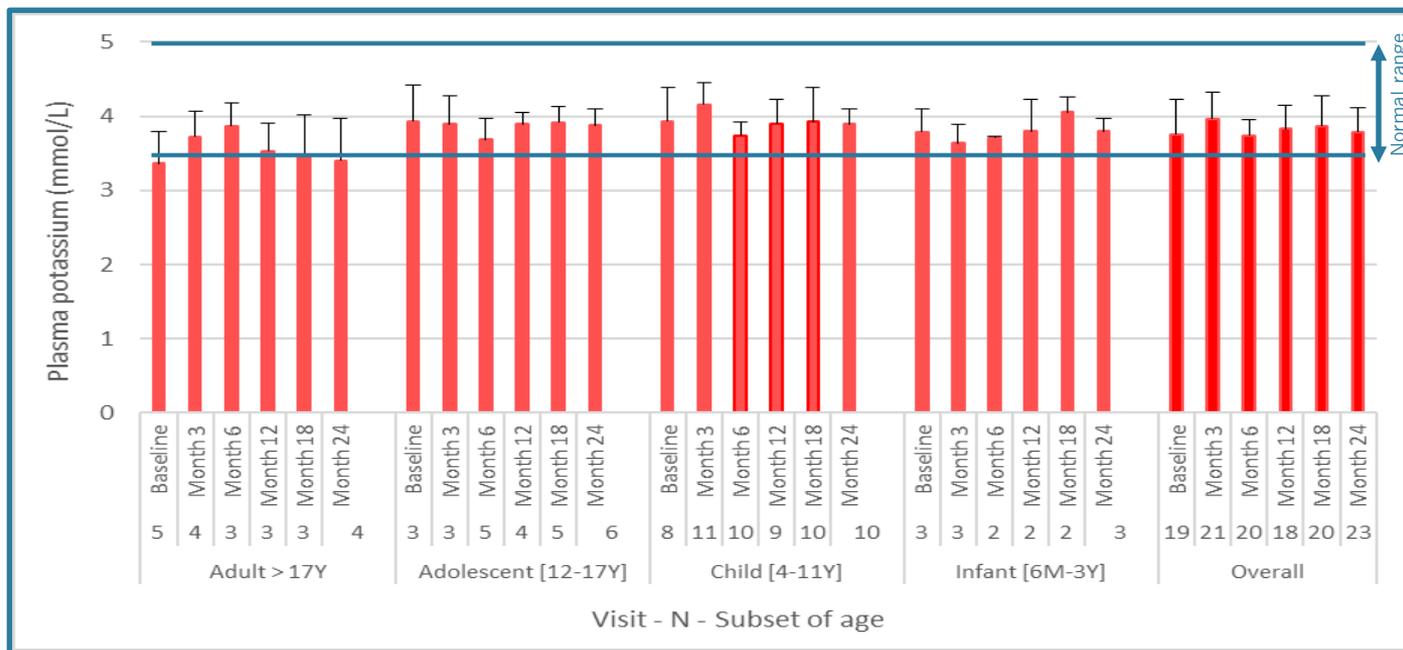
Phase III Data - Efficacy maintained after 24-month treatment

- Blood bicarbonate in normal range in 79% of patients



Phase III Data – plasma potassium normalized

- Normalized over 24 months



Phase III Data - Strong compliance observed

- Treatment compliance key to control metabolic acidosis and to avoid dRTA complications
 - Compliance was approximately 97% during short-term study (B21CS)*
 - During long-term study (B22CS)
 - Compliance of at least 75% was reported, with 93.3 % (month 3), 89.6% (month 6), 83.3% (month 12), 79.3% (month 18) and 79.3% (month 24)**
- Overall, treatment compliance was high under ADV7103

**In B21CS, compliance was defined by the patients who took at least 80% and no more than 125% of all planned treatments in that period*

***IN B22CS, compliance was defined as the proportion of treatment that has been taken versus what should have been taken, with the ranges <50%, [50-75%], [75-90%] and >= 90%*



Phase III Data – Improved acceptability vs. SoC

- Improved safety profile
 - Only 11% of adverse events were potentially related to treatment, all of mild intensity
- Improved quality of life over 24 months
 - Acceptability and gastro-intestinal (GI) tolerability were significantly improved and maintained in long term





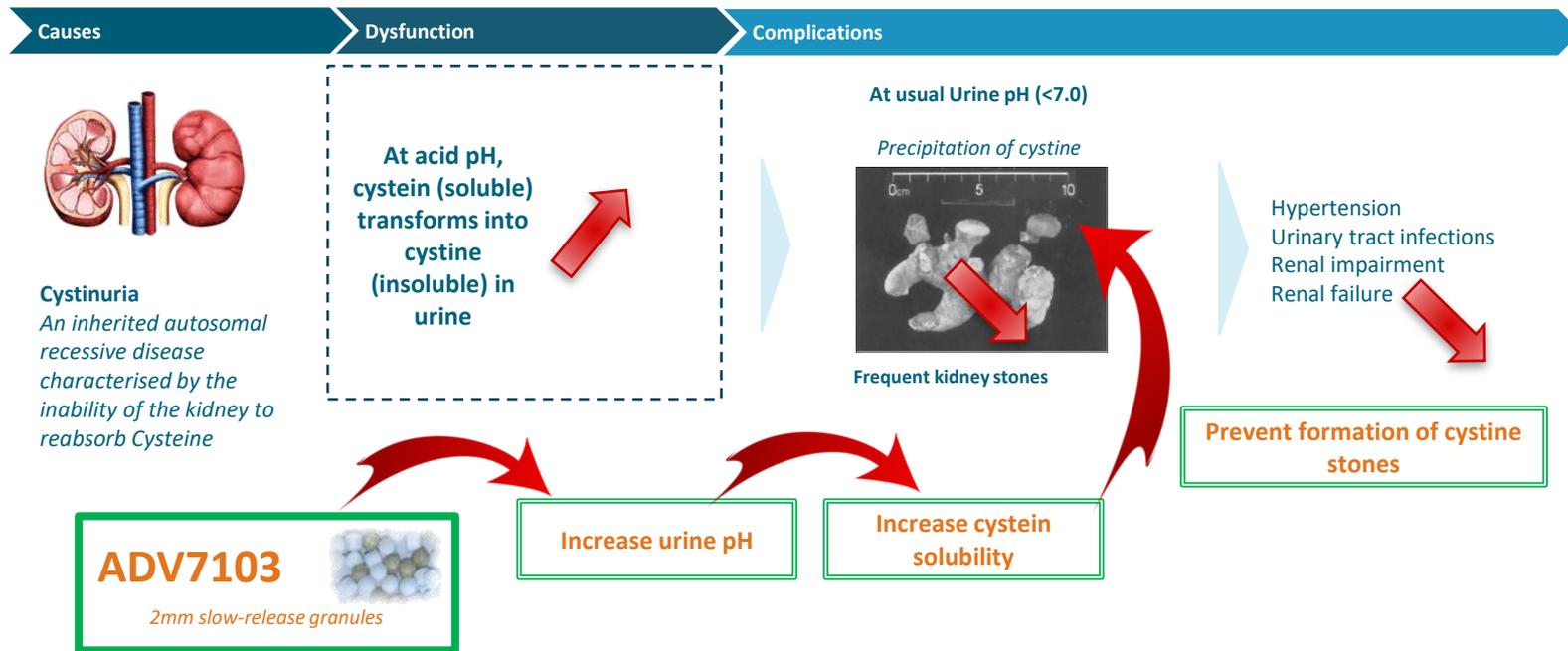
dRTA development plan in the US

- Only one pivotal Phase III study required by the FDA in addition to EU clinical package for registration
- Pivotal study in US & Canada
 - **ARENA-2 Study:** a multicenter, double-blind, placebo-controlled, randomized withdrawal study, evaluating the efficacy, safety, tolerability and acceptability of ADV7103 compared to SoC in dRTA patients in US and Canada.
 - Study on hold due to COVID-19 situation
 - FDA meetings scheduled for revisiting the protocol design to fit with COVID-19 situation

ADV7103 for Cystinuria

EU

What can we hope when treating Cystinuria with ADV7103 ?



Source: Advicenne, Orphanet: cystinuria, NORD cystinuria, Eggermann T. and al, Cystinuria: an inborn cause of urolithiasis, Orphanet Journal of Rare Diseases 2012; 7:19

ADV7103: Cystinuria clinical program



European Clinical Development Plan

- ODD designation approval (**Dec 2019**)
 - Protocol assistance procedure ongoing
- Positive clinical proof of concept for Cystinuria
 - Stabilizes urinary pH with only 2 doses per day
 - Significantly increases pH level with a positive dose-response
- CORAL study plan
 - Pivotal Phase III studies (B12CS & B13CS) to support EU registration
 - A 2-year extension study (B14CS) evaluating the safety, tolerability, compliance and acceptability of alkalizing treatments in patients with cystinuria
 - 72 patients to be included



US Strategy under review

- Meeting with FDA planned in 2020
- ODD to be submitted in 2021

ADV7103 Market needs

EU & US

Nephrology Scientific Board



Prof. Larry Greenbaum

Head of Pediatric Nephrology at Emory University School of Medicine and Children's Healthcare of Atlanta

*President of APNA
(American Pediatric Nephrology Association)*



Prof. Elena Levtchenko

Head of Pediatric Nephrology at the KU Leuven

President of ESPN



Prof. Bertrand Knebelmann

Head of Nephrology at the Unit Necker Hospital Paris



Prof. Gema Ariceta

Head of Pediatric Nephrology at the Vall d'Hebron University Hospital of Barcelona (European Society of Pediatric Nephrology)



Prof. Detlef Bockenhauer

Head of Nephrology at the Great Ormond Street Hospital

Great Ormond Street Hospital for Children
NHS Trust



Significant unmet needs: dRTA & cystinuria



No approved first line treatment

- dRTA: SoC requires compounding of various unapproved products in an attempt to re-establish normal physiological functions
- Cystinuria: SoC combines diet, hyperdiuresis and compounding of various alkalinizing products administered every 4 to 6 hours



SoC induces frequent complications in the gastro-intestinal tract

- Not adapted for paediatric use
- Poor compliance



Significant unmet medical needs

- Unregistered SoC requires 3 to 6 doses per 24 hours, sometimes resulting in sleep disruption
- Lack of compliance adversely affects treatment efficacy
- Direct impact on quality of life, especially for pediatric patients

One product for two rare diseases: dRTA & cystinuria

Addressable Global population



dRTA (genetic and acquired)

Approx. 30,000¹

Approx. 20,000¹

Cystinuria

Approx. 70,000²

Approx. 20,000 – 30,000^{2,3}

1: Low range prevalence considered by the EMA for ODD (EU/3/17/1888)

2: Eggermann T. and al, Cystinuria: an inborn cause of urolithiasis, Orphanet Journal of Rare Diseases 2012; 7:19

3: NORD cystinuria

Source: Advicenne, ODD (EU/3/17/1888), European Medicines Agency, U.S. National Library of Medicines

The background of the slide is a photograph of a dense forest. Sunlight filters through the trees, creating a bright sun flare in the upper center. The ground is covered with green and brown foliage. A semi-transparent white rectangular box is overlaid on the right side of the image, containing the main title and a dark blue box with the text 'EU & US'.

Market access strategy

EU & US

ADV7103 for dRTA: Timelines to market

Industrial production

- Manufacturing agreement with Elaiapharm Lundbeck to secure the supply of ADV7103 for the commercial phase

Commercial deployment of ADV7103 under the brand name Sibnayal



Clinical development

- European ODD granted in 2017
- Positive results in a pivotal Phase III study (12 months)
- Positive results confirmed in an extension Phase III study (24 months)

Registration process

- Ongoing regulatory dossier with EMA
- Ongoing market access dossier
- Structuring the commercial organization

An adapted pricing policy for ADV7103

No approved treatment to Date

Current SoC is suboptimal and the need for an efficient treatment is obvious, with an early initiation to prevent long term complications

Orphan drug designation

Clinical benefit demonstrated for ADV7103 over SoC
Innovative product well adapted for pediatric community



A high burden of diseases

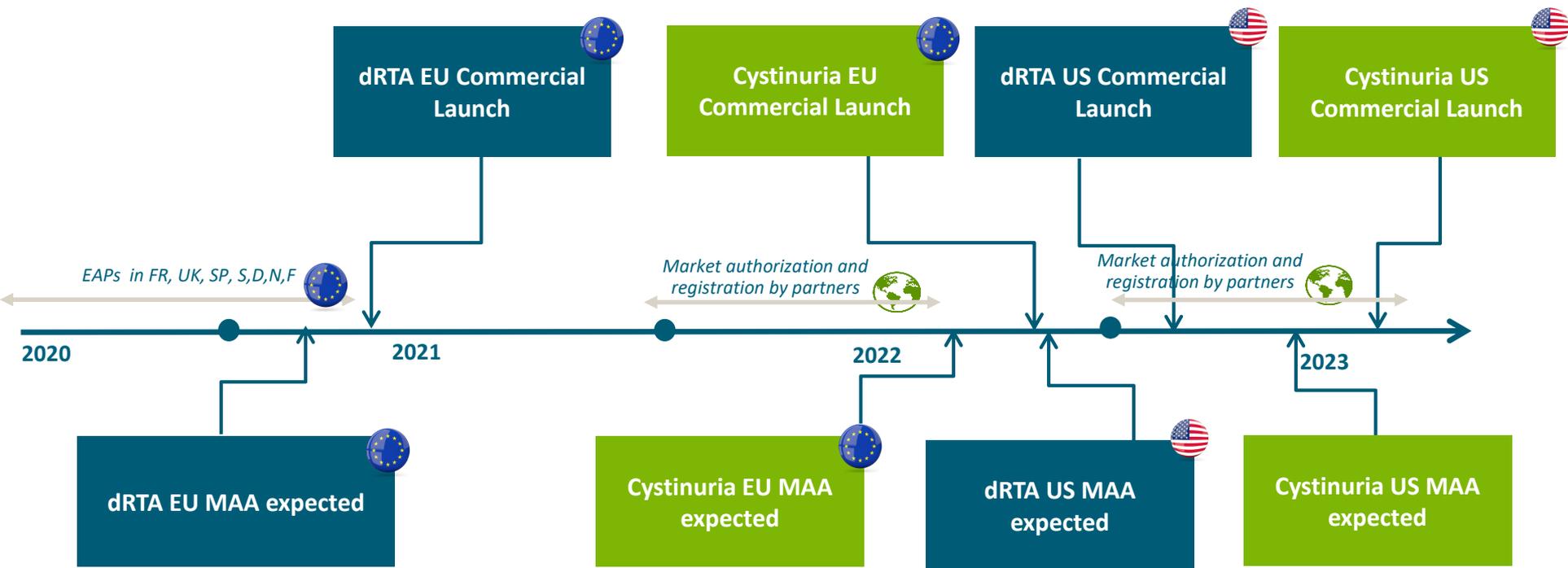
The current costs associated with patient management are substantial, reaching up to **£22,000 / year in the UK**

Strong market demand

High expectations from physicians and patients for an efficient and easy-to-use treatment

Building a robust pharmaco-economic core dossier to support orphan drug pricing of ADV7103

Progressive commercial launch in both indications



The background of the slide is a photograph of a sunlit forest. Sunbeams (crepuscular rays) are visible, streaming through the trees from the upper center. The ground is covered in green and brown foliage. A semi-transparent white rectangular box is overlaid on the right side of the image, containing the text 'IP & Financials'. Below this box, there is a solid dark teal rectangular shape. A thin vertical line is positioned on the far right edge of the slide, extending from the top to the bottom of the white box area.

IP & Financials

Broad IP estate offers protection through 2031

IP number of the EU patent	Description	Geographies	Expiry date
2640365	<ul style="list-style-type: none"> • Solid pharmaceutical composition of the granules of potassium citrate • treatment/prevention of urinary lithiasis and related diseases 	<ul style="list-style-type: none"> • 15 EU countries including EU5 	2031
2640364	<ul style="list-style-type: none"> • Composition of the bicarbonate salt granules • Treatment/prevention of urinary lithiasis and related diseases 	<ul style="list-style-type: none"> • 15 EU countries including EU5 	2031
2640363	<ul style="list-style-type: none"> • Combination of bicarbonate salt and citrate salt granules • Treatment/prevention of Cystinuria 	<ul style="list-style-type: none"> • 15 EU countries including EU5 	2031

- Additional IP protection notably through know-how and brand names for all marketed or soon-to-be marketed product
- ODD's extend IP protection and provide market exclusivity
- All products under development and undisclosed are proprietary and will bring in-house IP

Financial highlights

- Approximately €17.8 million* (\$20 million) in cash and cash equivalents at June 30, 2020
 - €16.6 million (\$19 million) in December 2019
- Streamlined operations with a headcount of 32 (20 in R&D)
- Cash sufficient to fund operations through numerous value-creating inflection points in the next 12 months
- €12.5 million debt facility authorization remaining from EIB (July 2019)

Euronext: **ADVIC**

COMPANY OVERVIEW

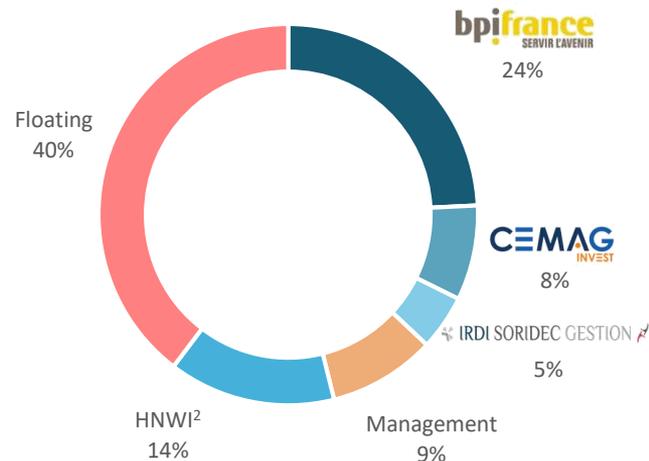
- Specialty pharmaceutical company
- Headquarters in Nîmes, France
- Founded in 2007
- Number of issued shares: 8,418,644
- Financing:
 - Approx. €30m in private rounds
 - €27.8m at listing on Euronext Paris in 2017
 - €20m loan facility from EIB, 12,5M€ remaining to draw
- Cross listing on Euronext Brussels on June 12, 2019

ANALYSTS COVERAGE

- France – Guillaume Cuvillier (FR)
- France – Jean-Pierre Loza (FR)
- UK - Samir Devani (ENG)



SHAREHOLDERS AND INVESTORS¹



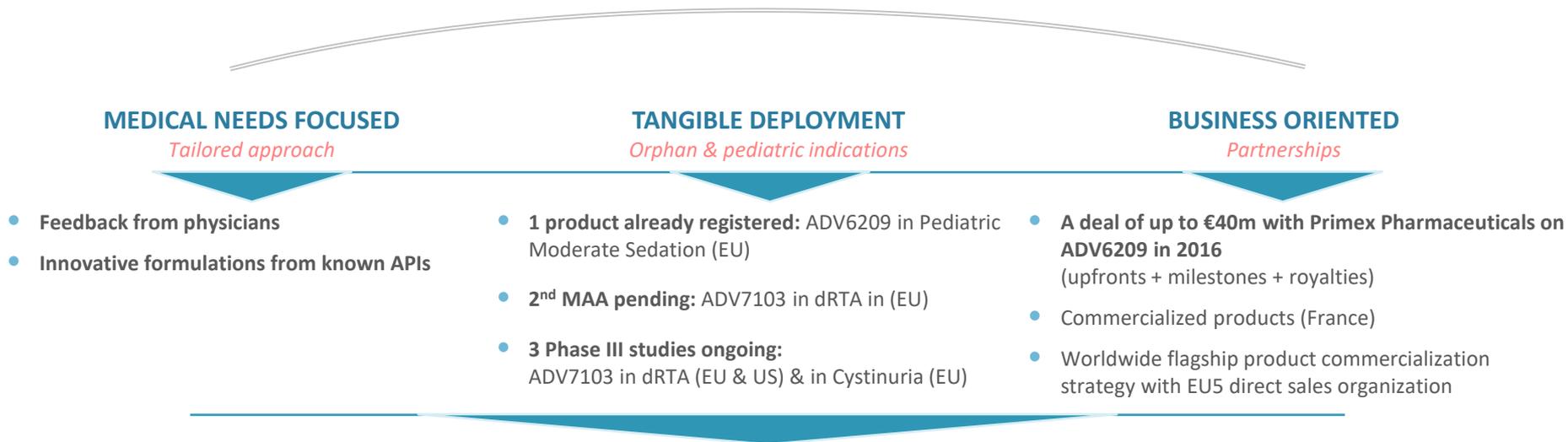
1: On a fully diluted basis as of March 31st, 2020

2: High-net-worth individuals

Source: Company information

Our efficient business model

Development approach with a strong commitment to treatments adapted to both pediatric and adult patient populations



A unique track record of efficient drug development

A photograph of a dense forest with tall, thin trees. Sunlight filters through the canopy, creating a bright starburst effect in the upper center. The ground is covered in green and brown foliage.

Thank you for your
attention

www.advicenne.com