



# Pathbreaking treatments for rare diseases

Euronext: **ADVIC** | Nimes, France

March 2020



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# Late clinical-stage specialty pharmaceutical company developing novel therapeutics for rare diseases

- Lead asset, ADV7103, with a market potential of several hundred million EUR
  - pending EU marketing authorization for the treatment of a renal disease and was granted orphan drug status in Europe
  - currently in pivotal Phase III trials in the US and Canada for its first indication
  - currently in pivotal Phase III trials in Europe for a second renal indication
- Ozalin® granted EU DCP marketing authorization in September 2018
- Well financed, with approximately € 22 million of cash and equivalents at June 30, 2019\*, plus € 20 million loan facility granted by EIB in July 2019

# Seasoned management team



**André Ulmann, MD, PhD**

Interim CEO

- 30 years in pharma industry
- Previously Director at 



**Paul Michalet, MBA, CEFA**

Chief Financial Officer

- 30 years in executive management
- Previously worked at 



**Caroline Roussel-Maupetit, Eng**

Co-founder and Director of Operations

- Extensive background in pharmaceutical development
- Previously worked at 



**Sarah Delbaere**

Financial & Logistics Director

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



**Catherine Guittet, PharmD**

Head of Clinical Operations Department

- 30 years in clinical affairs
- Previously worked at 

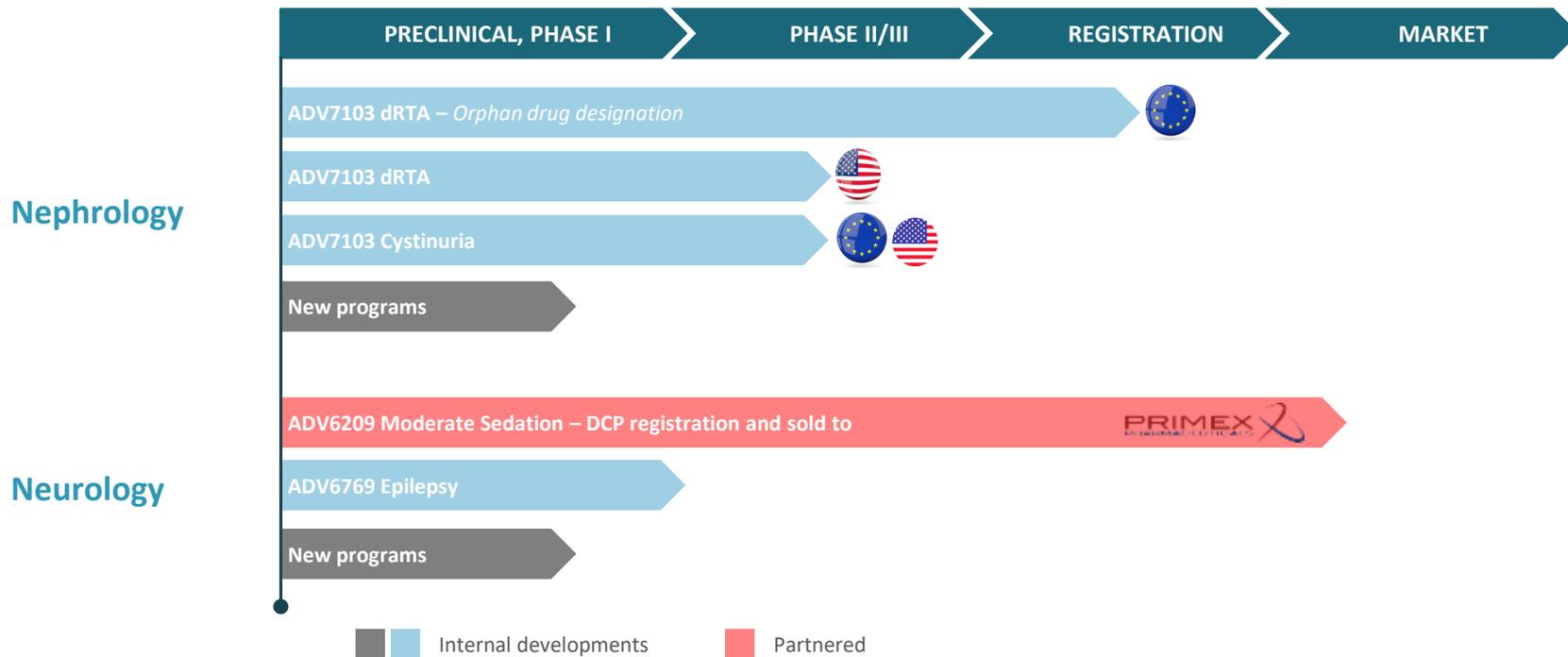


**Nathalie Lemarié, PharmD**

Director of Regulatory Affairs & Qualified Person

- 20 years in regulatory affairs
- Previously worked at 

# Mature and balanced pipeline



# ADV6209: 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€\*
  - Launching in EU in 2019-2020
    - Price per unit: about 20€/box
    - Favorable opinion (HAS) in reimbursement in children over 6 months to 17 years old
  - Approval in the US planned by 2021 (505(B)2)



\*Source: Primex Pharmaceuticals

# Targeting unmet needs in nephrology

- Numerous diseases with diverse causes
- Abnormal kidney functions 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 tubulopathies**

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

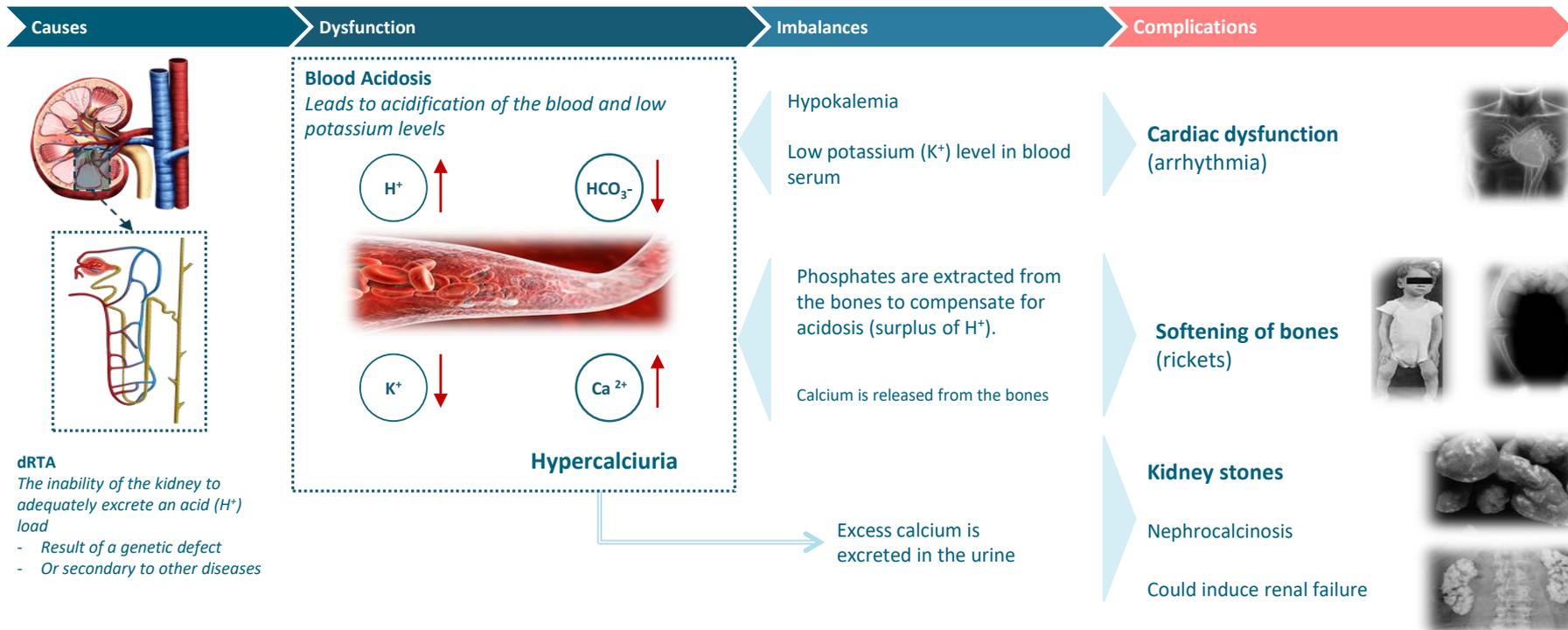


A photograph of a forest with sunlight filtering through the trees, creating a bright, hazy atmosphere. The sun is visible as a bright starburst in the upper center. The trees are tall and thin, with green foliage. The ground is covered in fallen leaves and undergrowth.

# 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

# 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**

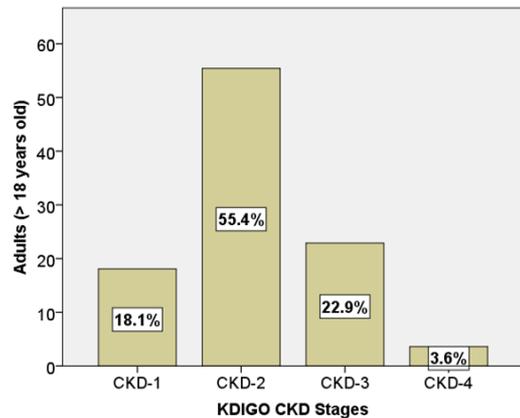
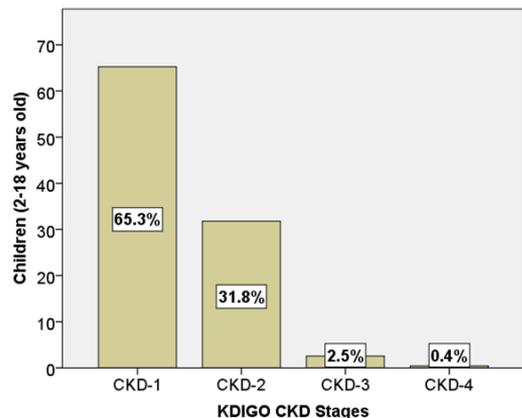
	<i>SLC4A1</i>	<i>ATP6V1B1</i>	<i>ATP6V0A4</i>	Variants of unknown clinical significance	Negative	Mutated
M/F, no. (%)	4/9 (44.4)	13/25 (52)	14/30 (46.6)	5/7 (71.4)	7/18 (38.9)	31/64 (48.4)
Age at onset of dRTA, mo	153.2	13.9	28.6	47.6	131.1	65.2
SNHL, no. (%)	1/8 (12.5)	23/25 (92)	17/30 (56.7)	3/7 (42.9)	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 m<sup>2</sup>), 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

# A long-term and significant medical need

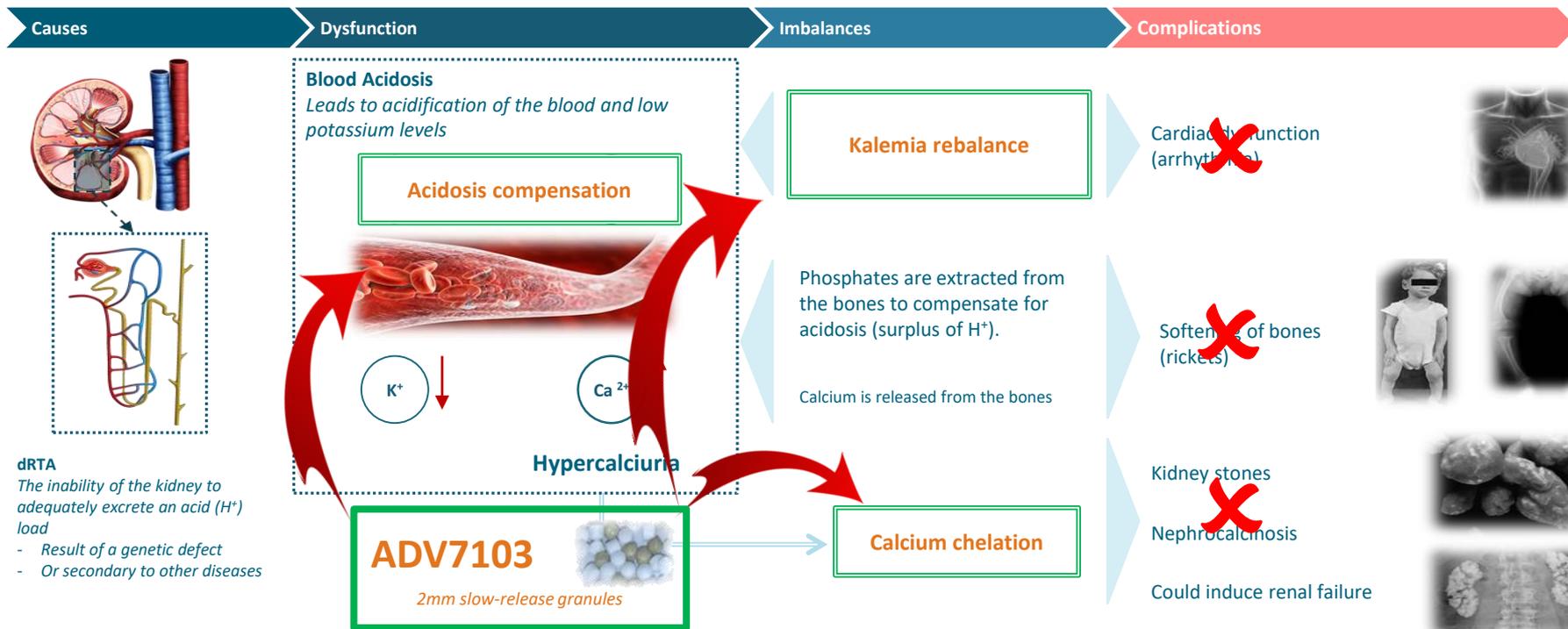
- CKD was evident in patients with long-term follow-up
  - Increased prevalence of CKD stage  $\geq 2$  in children (35%) and adults (82%)



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.

# dRTA treated with ADV7103



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

# ADV7103 delivers clear advantages

**ADV7103**



**“Standard” of Care (SoC)**



Improved efficacy (HCO <sub>3</sub> <sup>-</sup> )	✓	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 kalaemia	✓	3	✗	Potassium supplementation requirement
Improved gastrointestinal tolerance	✓	4	✗	Severe 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

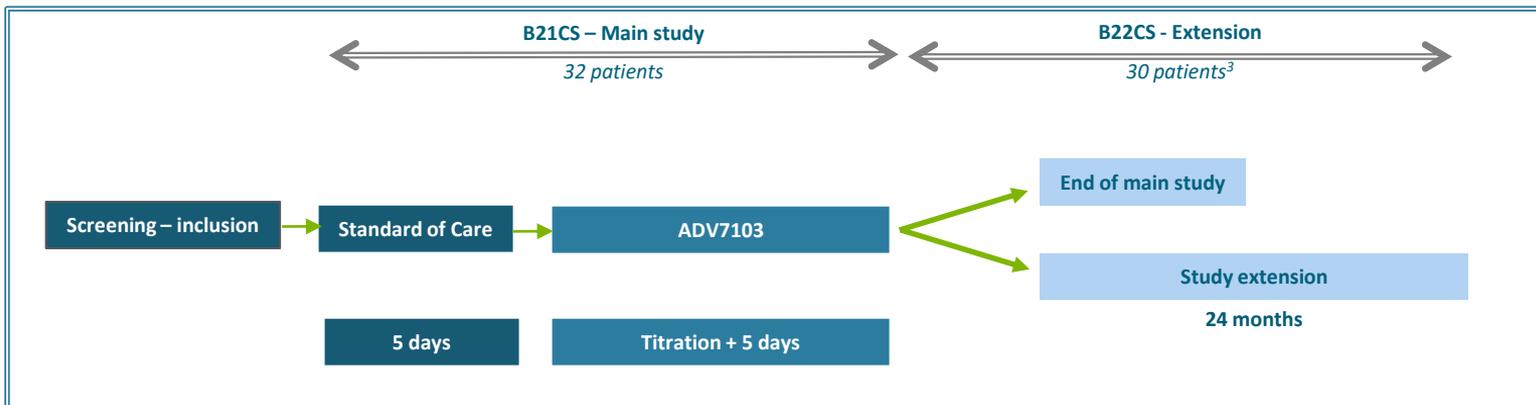
**ADV7103 improves treatment efficacy and quality of life, especially for pediatric patients**

# Design of pivotal EU Phase III trial in dRTA

## Key Characteristics of Trials

- **B21CS<sup>1</sup> – Pivotal study:** A multicenter, open-label, non-inferiority sequential study in 32 patients
- **B22CS<sup>2</sup> – Extension study (24 months)** of B21CS

## Study design

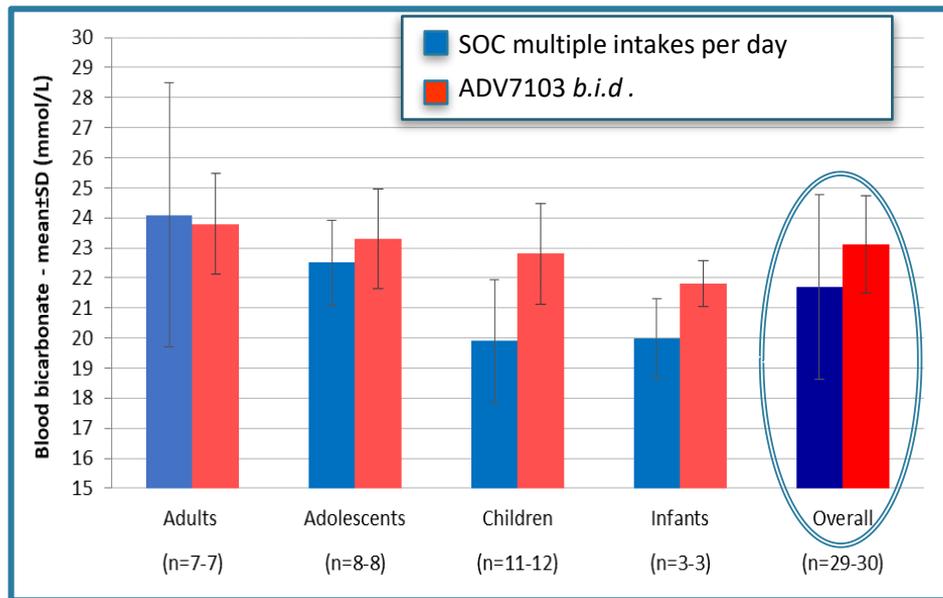


## Primary objective

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

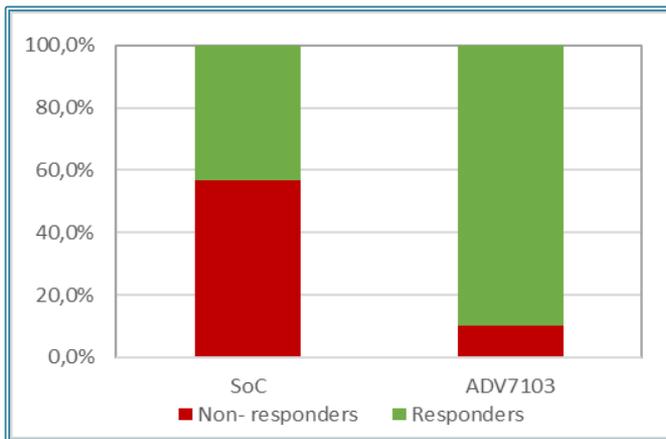
# Phase III Data - Improved efficacy



- Pivotal phase III results demonstrate significant efficacy
  - Non-inferiority is clearly demonstrated on primary endpoint
  - Significantly superior to SoC on primary endpoint, i.e. bicarbonatemia level
    - 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

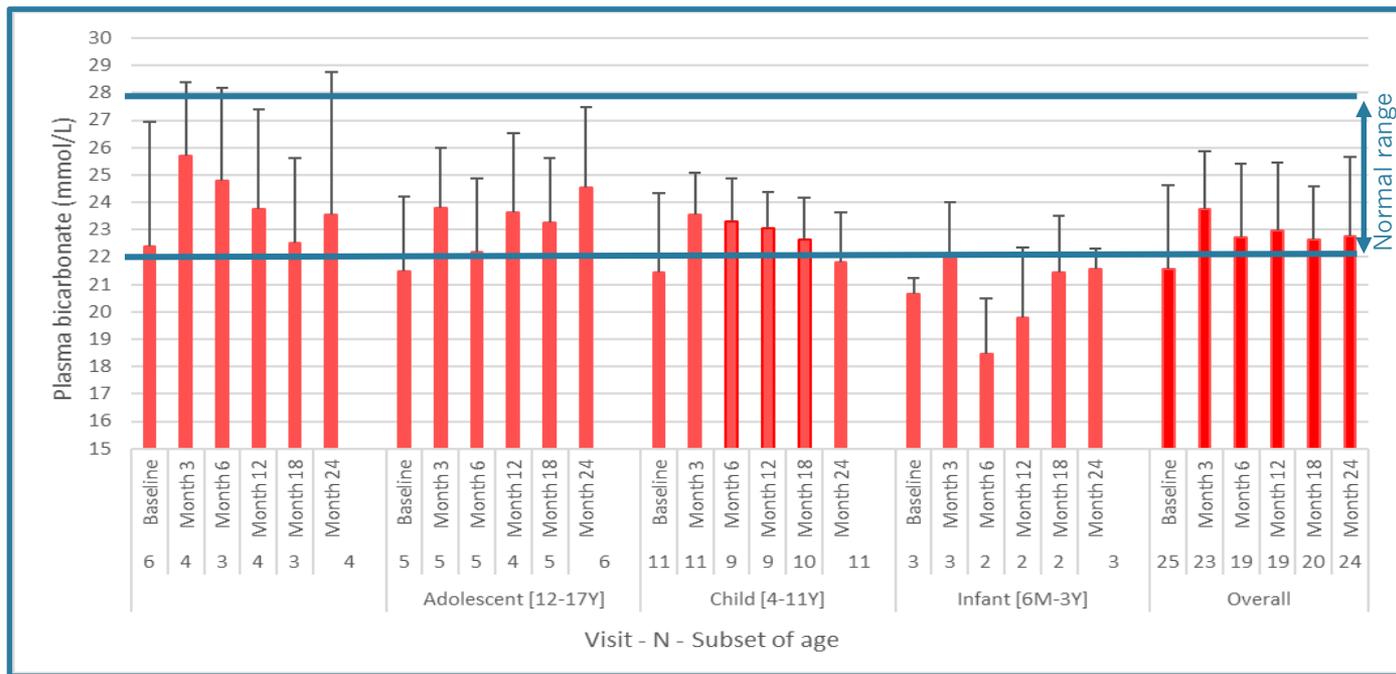


Number (%) of responders (R) and non-responders (NR) - ITT set (N=30)		
SoC	ADV7103	n/N (%)
R	R	13/30 (43%)
NR	NR	3/30 (10%)
NR	R	14/30 (47%)
R	NR	0 (0.0%)
<b>p-value*</b>		<b>&lt;0.001</b>

*Non-responders = Patients presenting abnormally low average bicarbonataemia values (days 2, 3 and 4), as defined by local laboratories*

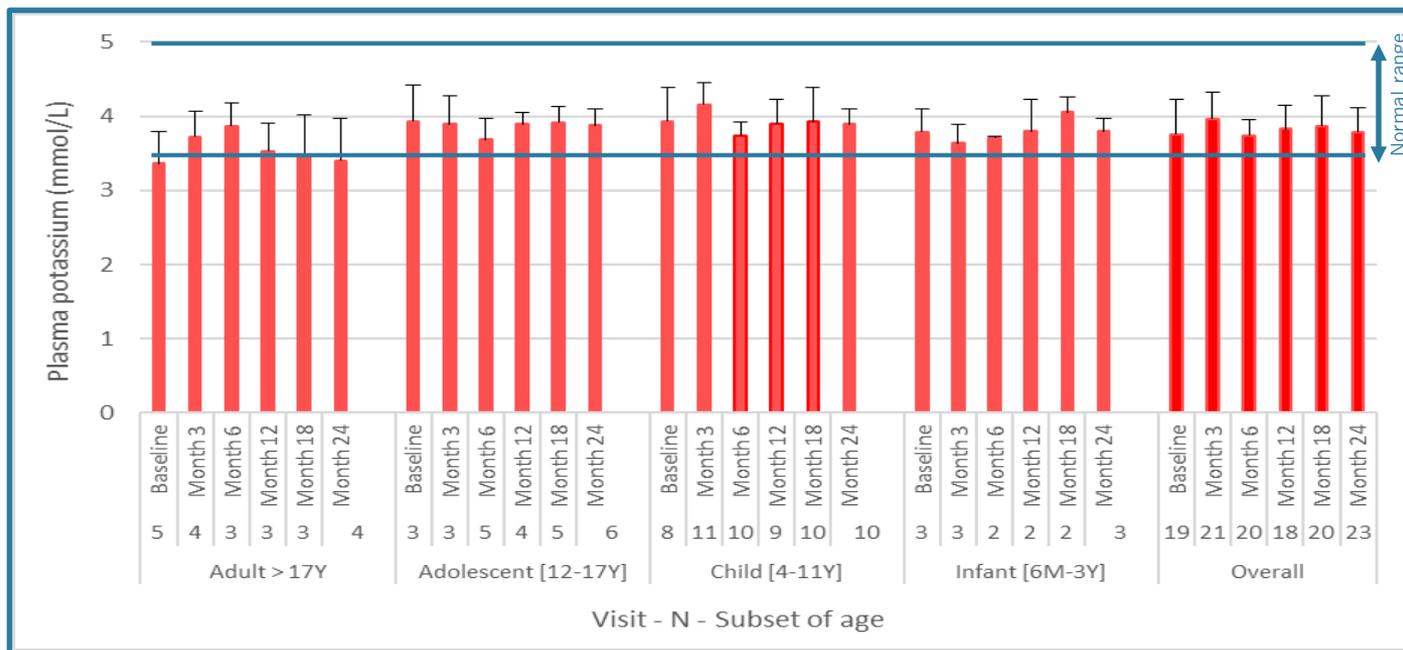
# Phase III Data - Efficacy maintained after 24 months' treatment

- Blood bicarbonatemia in normal range in 79% of patients



# Phase III Data - Kalaemia normalized

- Normalized over 24 months



# Phase III Data - Strong compliance observed

- Treatment compliance key to controlling metabolic acidosis and avoiding 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



# Phase III Data - Improved acceptability

- Excellent safety profile
  - Only 11% of adverse events were potentially related to treatment, all of mild intensity
- Strong improvement of 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

- Orphan drug designation (ODD) application submitted to the FDA in 2019
- One pivotal Phase III study in the US required by the US 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 open and actively recruiting
    - 40 patients to be included

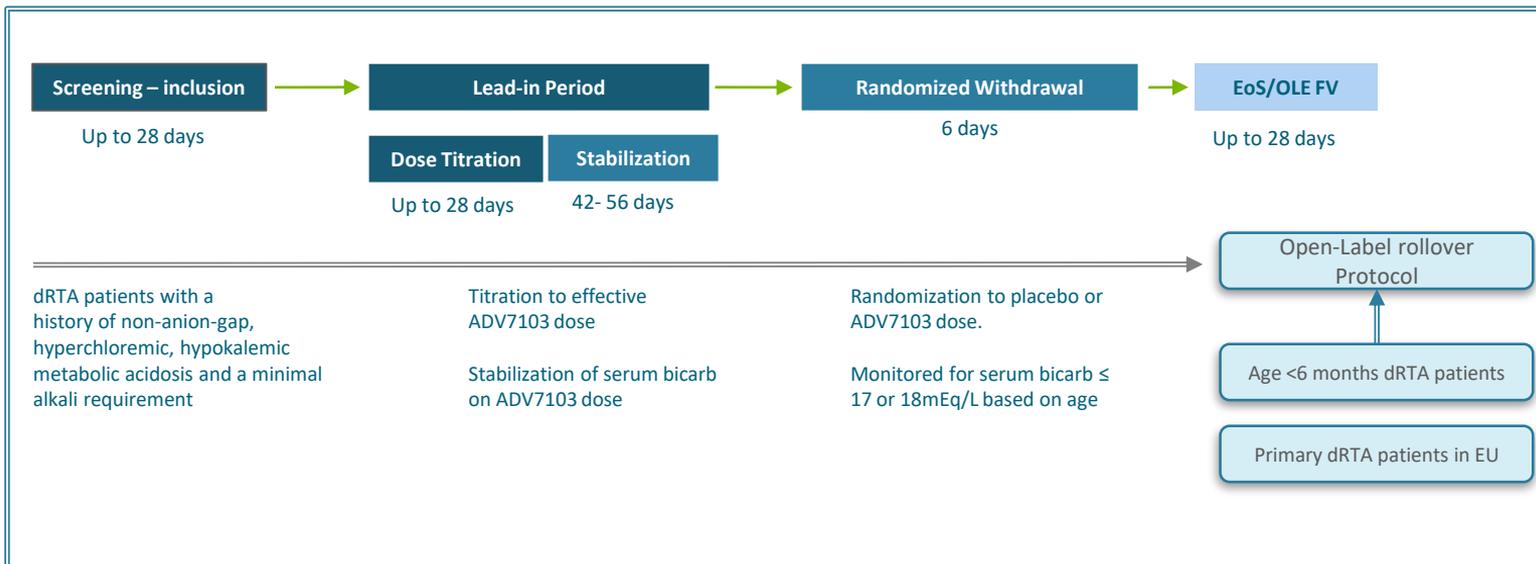


# Arena-2 study: design of the US trial

## Key Characteristics of Trials

- 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.

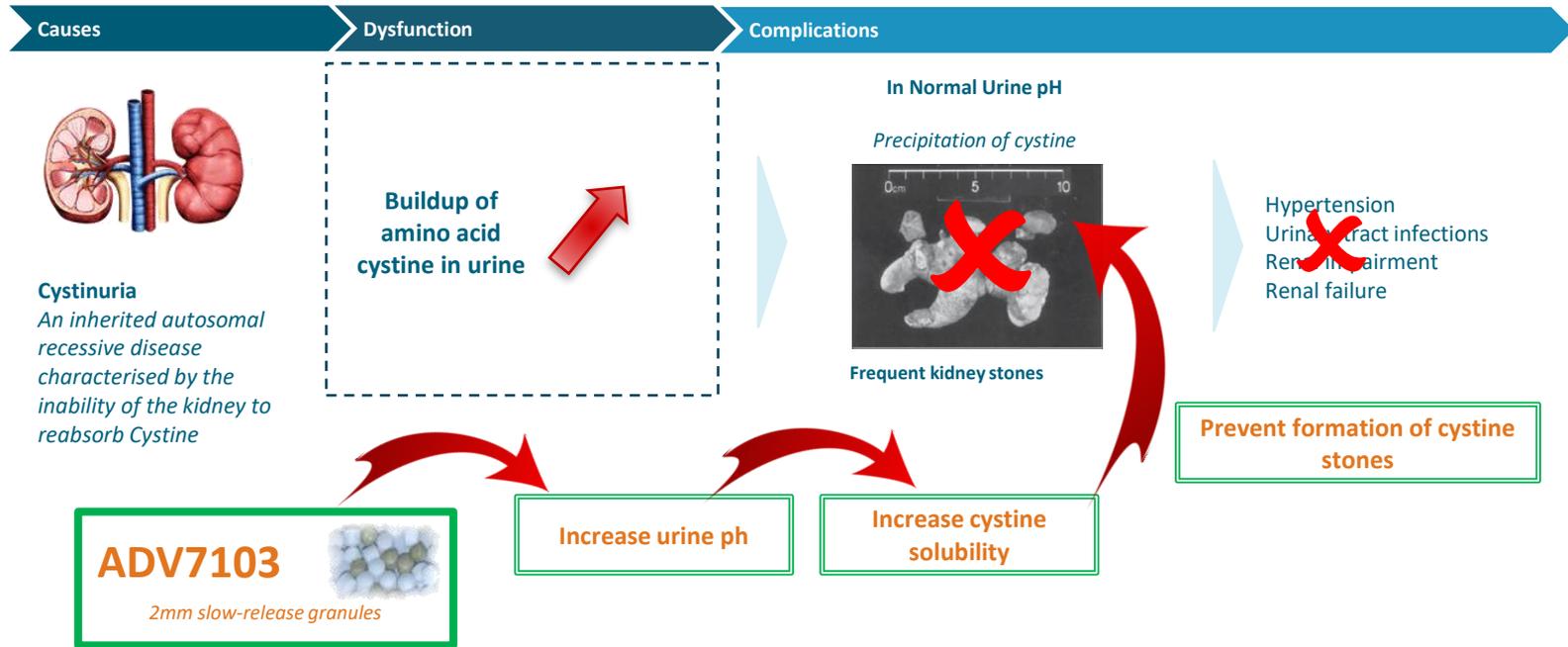
## Study design



# ADV7103 for Cystinuria

EU

# Consequences of Cystinuria



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) agreed 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 with results expected in 2021



*US Strategy under review*

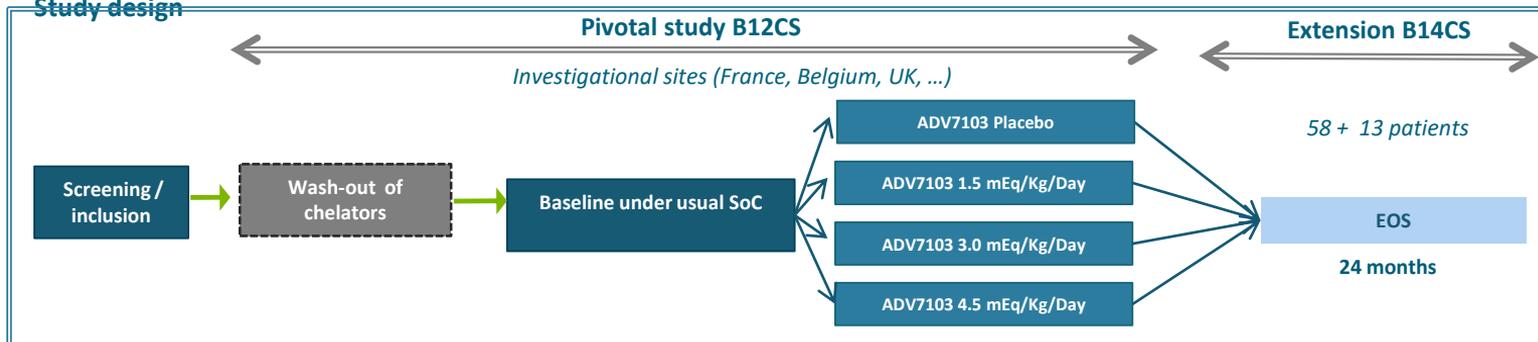
- ODD to be submitted soon
- Meeting with FDA planned in 2020

# CORAL study: Cystinuria EU clinical plan

## Key Characteristics of Trials

- Pivotal Phase III studies in patients with cystinuria
  - In Children 6 -17 years of age & adults (B12CS) : A multicentre, randomized, controlled versus placebo, double-blinded, 4 parallel arms, dose-ranging main study, to evaluate the efficacy, safety and tolerability, compliance and acceptability of repeated doses of ADV7103 after 7 days of treatment.
  - Children 0.5 - 5 years of age (B13CS) : An efficacy and safety exploratory study.
- Extension study (B14CS): a multicenter, open-label study evaluating the safety, tolerability, compliance and acceptability of alkalinizing treatments in patients with cystinuria.

## Study design



## Primary objective

To evaluate the effect of ADV7103 at three different doses compared to placebo on the percentage of urinary pH values  $\geq 7.0$  during 24h after a 7-day treatment

# ADV7103 Market needs

EU & US

# Nephrology Scientific Board



**Prof. Larry Greenbaum (Co-chairman)**

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

*President of APNA (American Pediatric Nephrology Association)*



**Prof. Pierre Cochat (Co-chairman)**

*Head of Pediatric Nephrology CHU Lyon  
President of IPNA (International Pediatric Nephrology Association)*



Hospices Civils de Lyon



**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

Source: Company information

# 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 unapproved alkalizing products administered every 4 to 6 hours



## SoC induces severe complications in the gastro-intestinal tract

- Not adapted for pediatric use
- Poor compliance



## Significant unmet medical needs

- Unregistered SoC requires 3 to 6 doses per 24 hours, 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 diseases: dRTA & cystinuria

## Two rare/orphan indications

### Addressable Global population

dRTA (genetic and acquired)

Cystinuria



**Approx. 30,000<sup>1</sup>**

**Approx. 70,000<sup>2</sup>**



**Approx. 20,000<sup>1</sup>**

**Approx. 20,000 – 30,000<sup>2,3</sup>**

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 flare in the upper center. The ground is covered with green and brown foliage. A semi-transparent white 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: 12 months from 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 Sibnaya



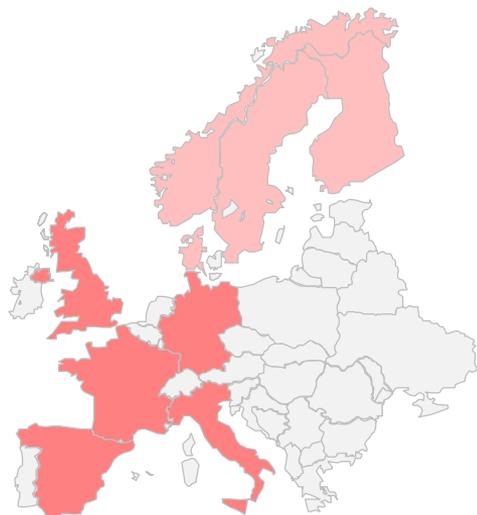
## Clinical development

- 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

# Progressive commercial deployment in key markets



- Limited prescribing centers
  - Develop KOL relationships
  - Communicate among the specialist community



- Advanced ongoing discussion with potential partners



- Commercial strategy to be decided in 2020



**Direct sales force in  
EU 5**

**Partnering in other EU countries  
& RoW**

**US strategy  
under review**

# 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

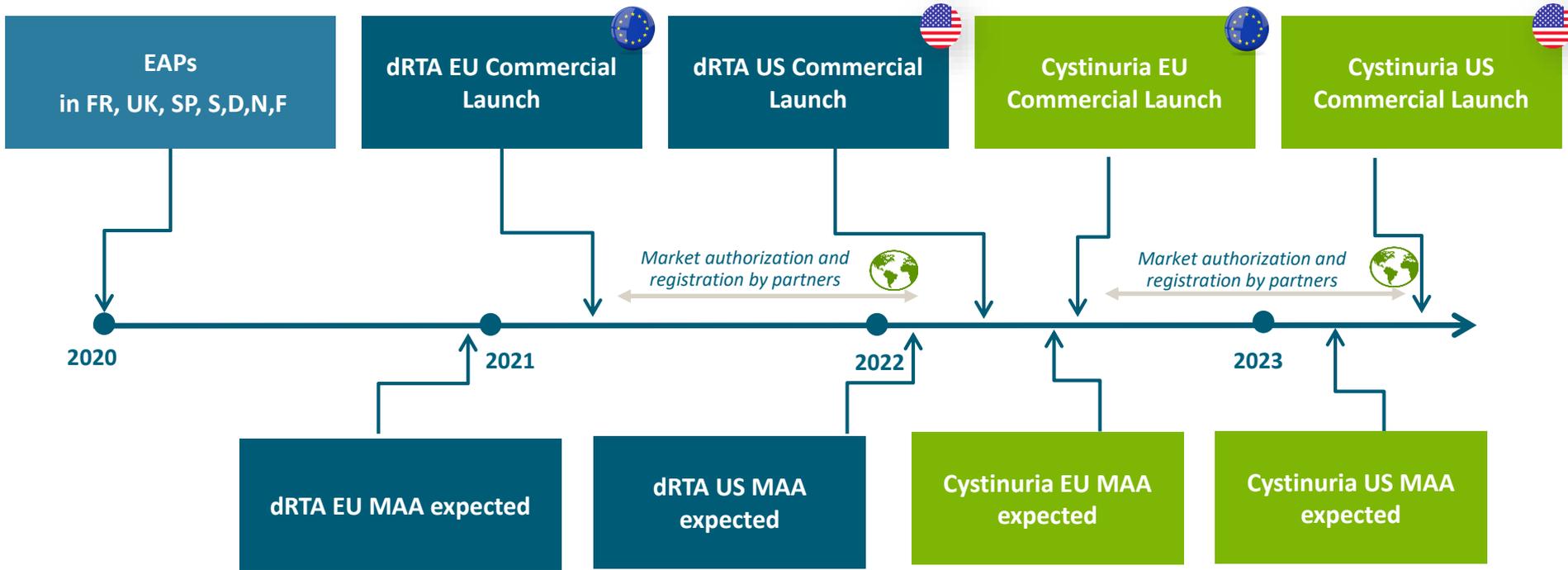
The current costs associated with patient management are substantial, reaching up to **£22,000 / year in the UK**

## Strong market demand

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

**Building a robust pharmacoeconomic core dossier to support orphan drug pricing of ADV7103**

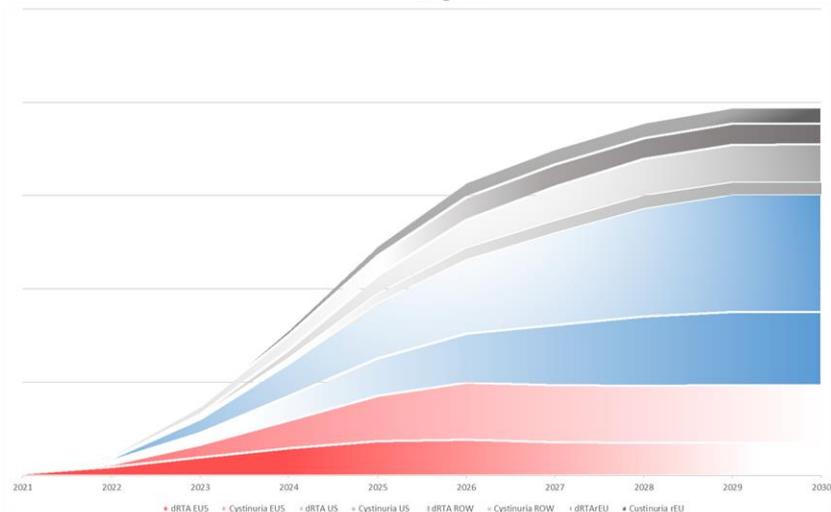
# Progressive commercial launch in both indications



# A niche but high value market

- Market geographical segmentation
  - EU5 : 25%
  - US : 50%
  - RoW : 25%
  
- Pricing strategy to maximize revenue
  - Expectations ranging from 15 to 80k€ per year per patient depending on geography

A market potential of several hundred million  
EUR



Source: Recommended price based on pricing studies performed by Advicenne

The background of the slide is a photograph of a forest. Sunlight is streaming through the trees, creating a bright flare in the upper center. The ground is covered with green and brown foliage. A semi-transparent white box is overlaid on the right side of the image, containing the text 'IP & Financials'. A dark teal rectangular block is positioned at the bottom right of the slide, partially overlapping the white box.

# 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"> <li>• Solid pharmaceutical composition of the granules of potassium citrate</li> <li>• treatment/prevention of urinary lithiasis and related diseases</li> </ul>	<ul style="list-style-type: none"> <li>• 15 EU countries including EU5</li> </ul> 	2031
2640364	<ul style="list-style-type: none"> <li>• Composition of the bicarbonate salt granules</li> <li>• Treatment/prevention of urinary lithiasis and related diseases</li> </ul>	<ul style="list-style-type: none"> <li>• 15 EU countries including EU5</li> </ul> 	2031
2640363	<ul style="list-style-type: none"> <li>• Combination of bicarbonate salt and citrate salt granules</li> <li>• Treatment/prevention of Cystinuria</li> </ul>	<ul style="list-style-type: none"> <li>• 15 EU countries including EU5</li> </ul> 	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 € 22 million\* (\$24 million) in cash and cash equivalents as of June 30, 2019
  - €27,8 million (\$31 million) raised in successful IPO in December 2017
- 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
- € 20 million debt facility authorization from EIB (July 2019)

# Upcoming value-creation milestones

## ADV7103 dRTA

## ADV7103 Cystinuria

Orphan drug designation (ODD) in the US  
 End of US pivotal Phase III trial  
 European MAA granted ±18 months after filing

New Drug Application (NDA) filing US  
 Commercial launches EU

MAA granted US  
 Commercial launch US



2020

2021

2022

ODD granted in US  
 Completion of European pivotal Phase II/III trial

Data from European pivotal Phase II/III trial  
 MAA filing EU

Commercial launch

# Euronext: **ADVIC**

## COMPANY OVERVIEW

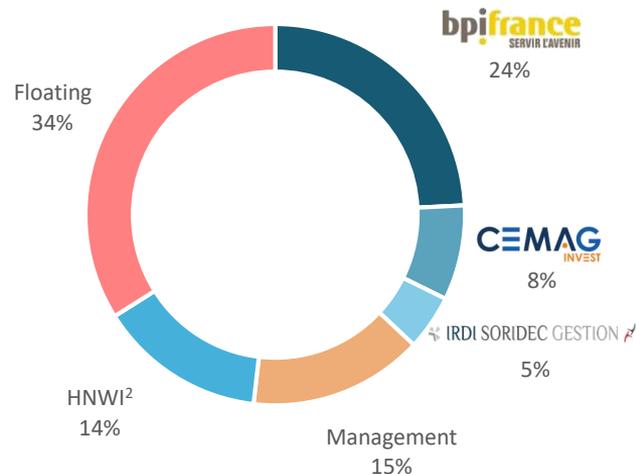
- Specialty pharmaceutical company
- Headquarters in Nîmes, France
- Founded in 2007
- Number of shares: 9,285,894
- Financing:
  - Approx. €30m in private rounds
  - €27.8m at listing on Euronext Paris in 2017
  - €20m loan facility from EIB, not yet drawn
- Cross listing on Euronext Brussels on June 12, 2019

## ANALYSTS COVERAGE

- France - Jamila El Bougrini (FR)
- UK - Samir Devani (ENG)



## SHAREHOLDERS AND INVESTORS<sup>1</sup>



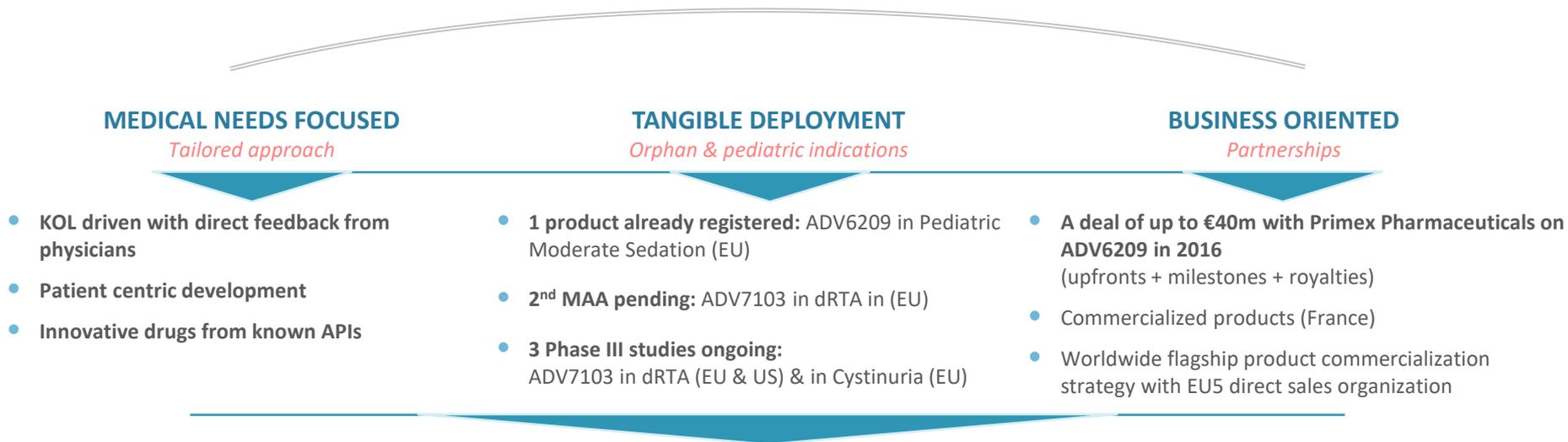
1: On a fully diluted basis as of January 1<sup>st</sup>, 2020

2: High-net-worth individuals

Source: Company information

# Our efficient business model

A KOL-driven product and 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. A semi-transparent white box is overlaid on the right side of the image, containing the text "Thank you for your attention".

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