



advicenne

Pathbreaking treatments for rare diseases

Euronext: **ADVIC** | Nimes, France

February 2020, 11,

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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

Experienced management team



Luc-André Granier, MD, PhD
Co-founder and CEO

Previously worked at:



Caroline Roussel-Maupetit, Eng
Co-founder and
Chief Operating Officer

Previously worked at:



Ludovic Robin, Pharm.D, MBA
Chief Business and Strategy Officer

Previously worked at:

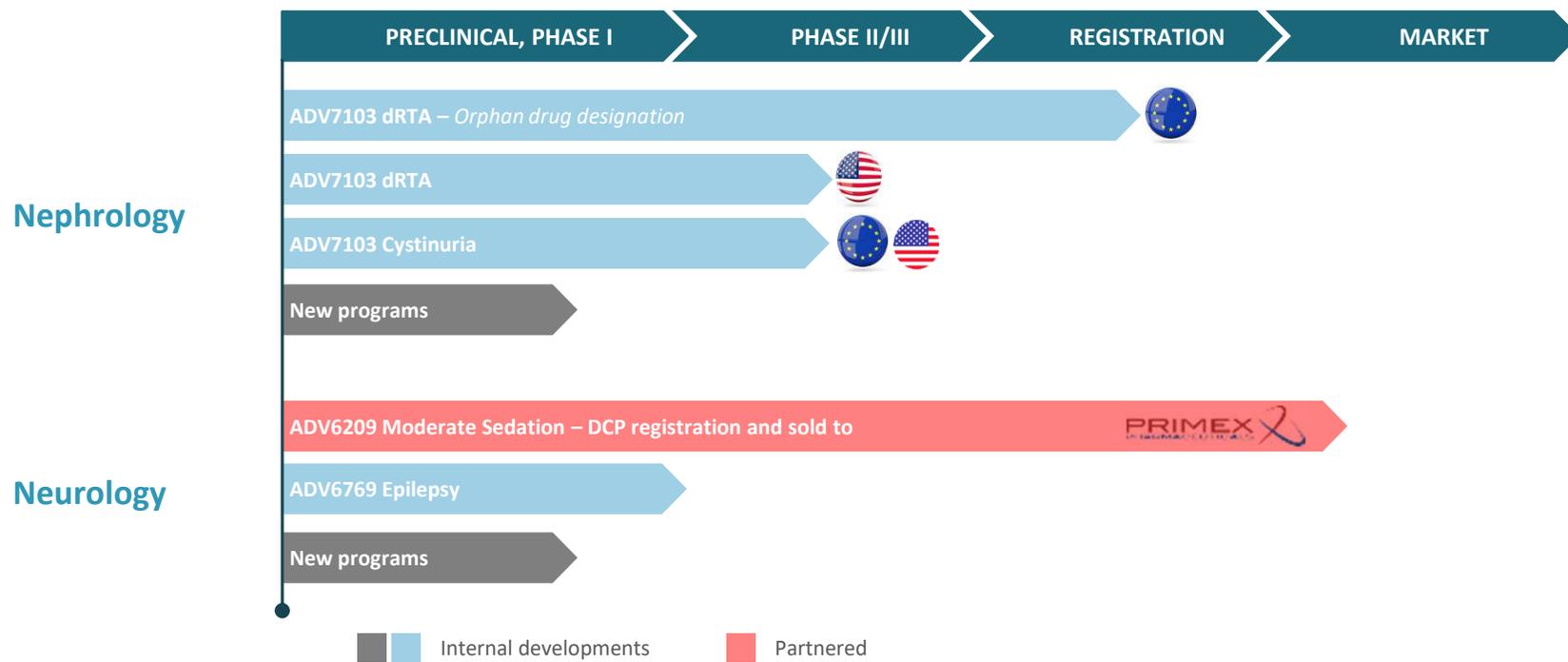


Paul Michalet, MBA, CEFA
Chief Financial Officer

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



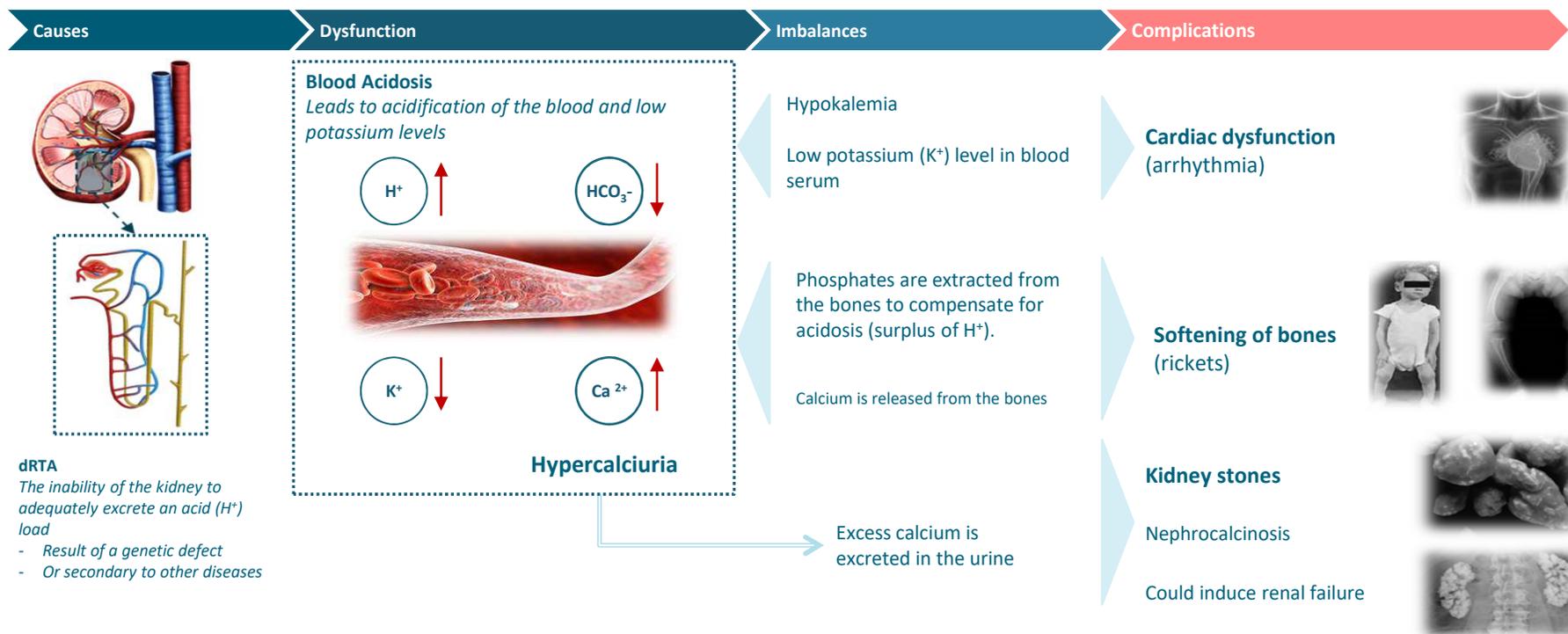
ADV7103 addresses two orphan tubulopathies
with severe debilitating consequences and significant unmet medical
needs: dRTA and Cystinuria



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

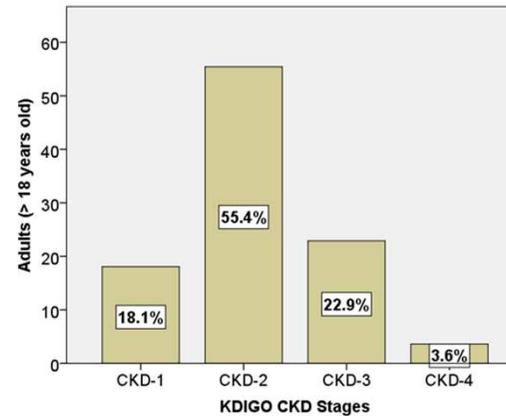
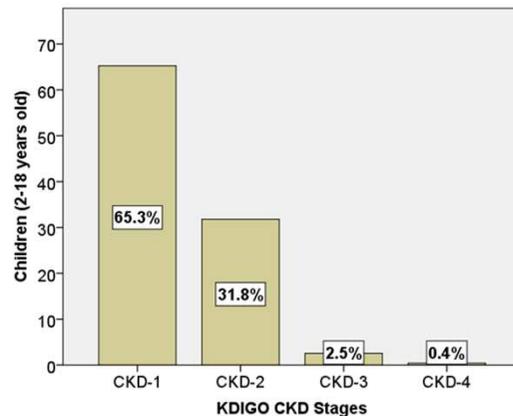
	<i>SLC4A1</i>	<i>ATP6V1B1</i>	<i>ATP6V0A4</i>	Variants of unknown clinical significance	Negative	Mutated
M/F, no. (%)	4/9 (44.4)	13/25 (52)	14/30 (46.6)	5/7 (71.4)	7/18 (38.9)	31/64 (48.4)
Age at onset of dRTA, mo	153.2	13.9	28.6	47.6	131.1	65.2
SNHL, no. (%)	1/8 (12.5)	23/25 (92)	17/30 (56.7)	3/7 (42.9)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

A long-term and significant medical need

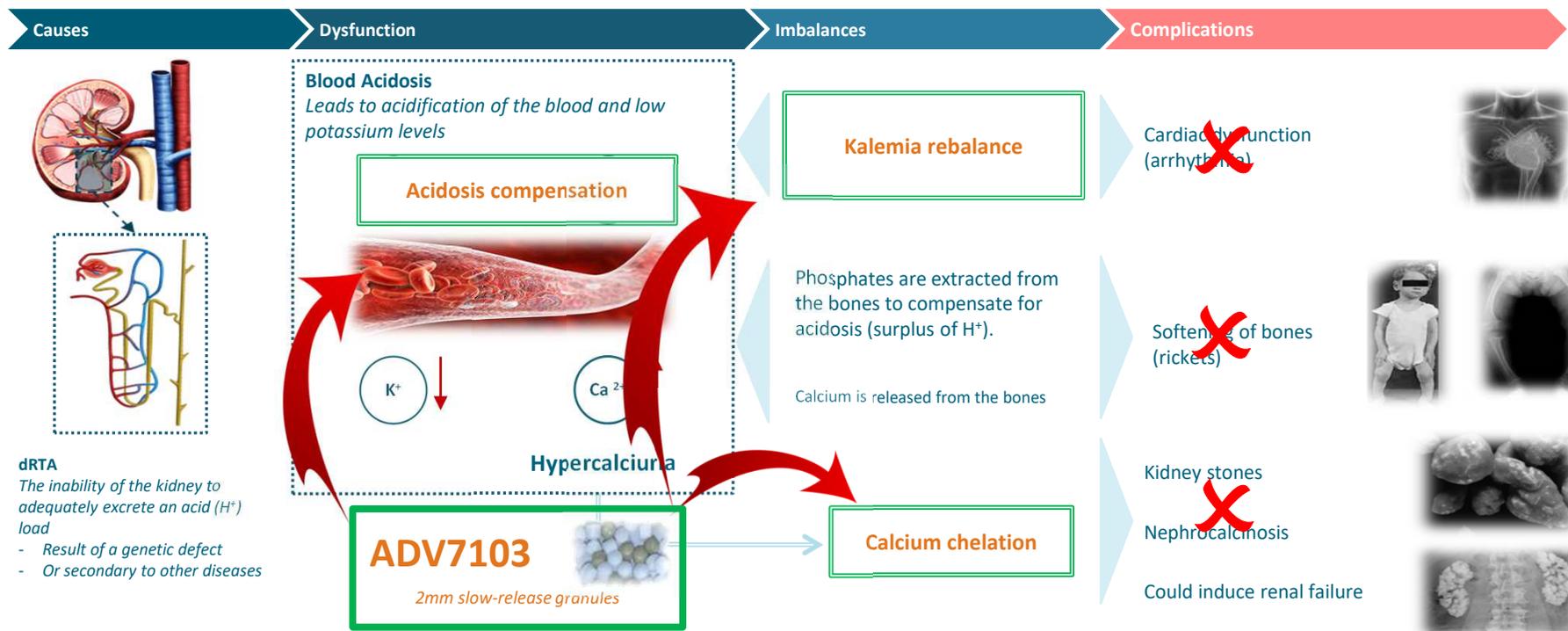
- CKD was evident in patients with long-term follow-up
 - Increased prevalence of CKD stage ≥ 2 in children (35%) and adults (82%)



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.

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 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 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

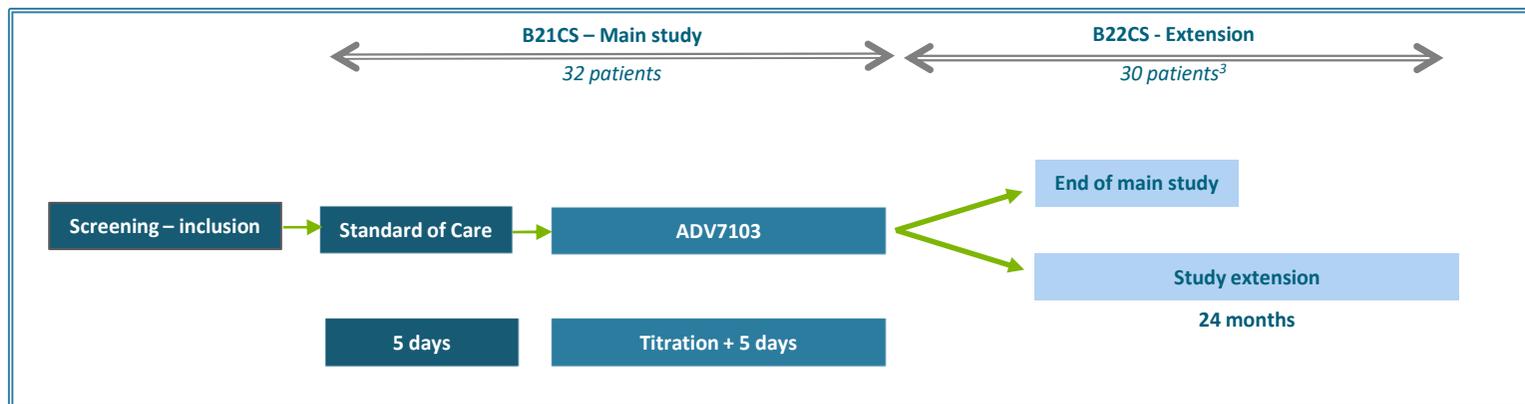


Design of pivotal EU Phase III trial in dRTA

Key Characteristics of Trials

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

Study design



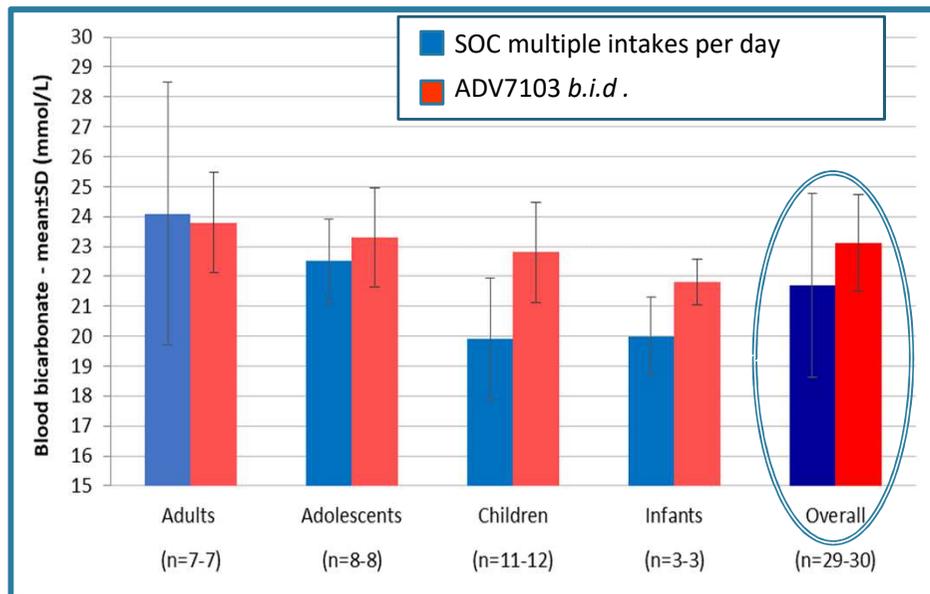
Primary objective

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



Phase III Data - Improved efficacy



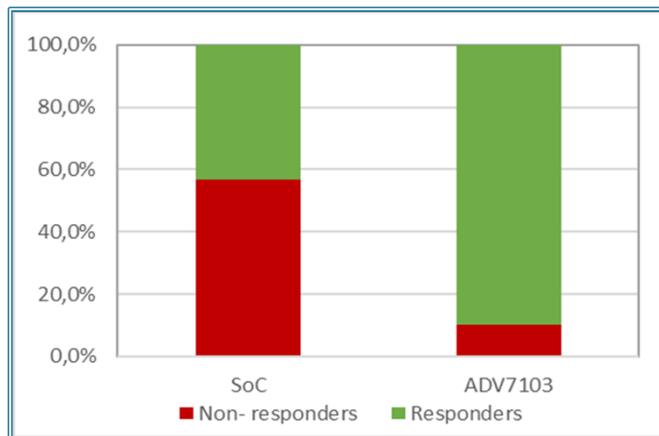
- Pivotal phase III results demonstrate significant efficacy

- 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

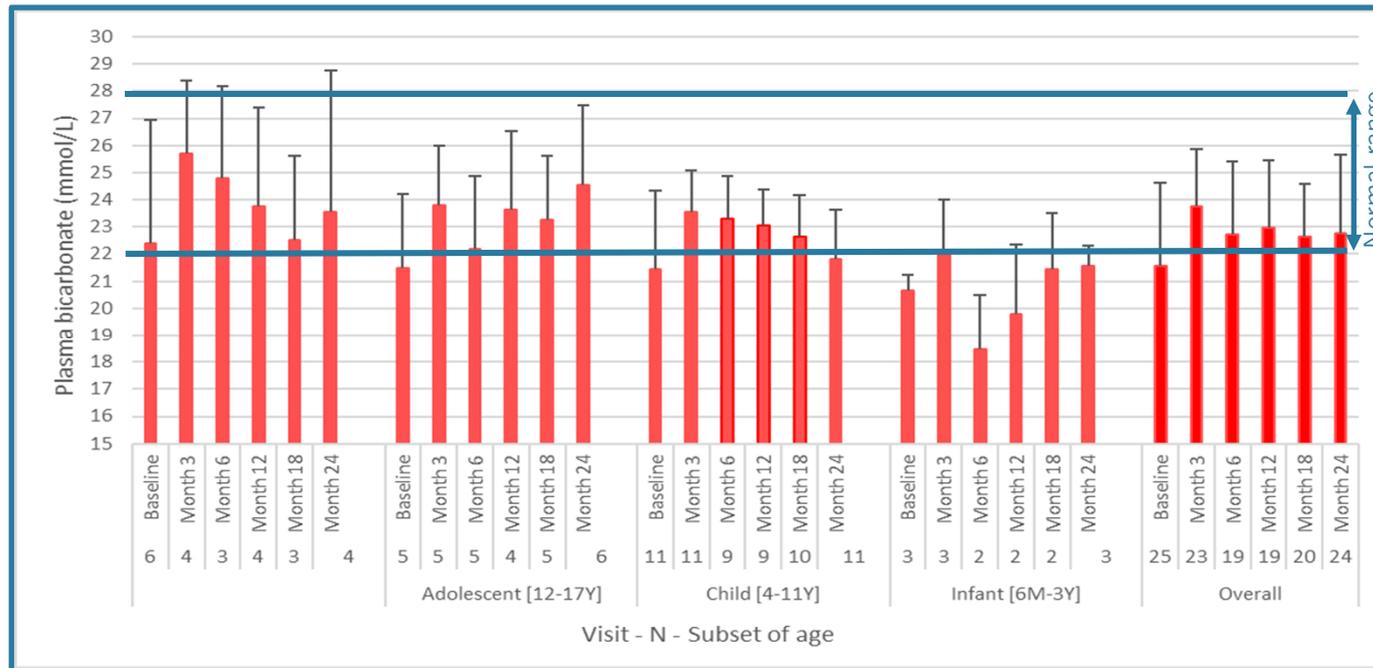


Number (%) of responders (R) and non-responders (NR) - ITT set (N=30)		
SoC	ADV7103	n/N (%)
R	R	13/30 (43%)
NR	NR	3/30 (10%)
NR	R	14/30 (47%)
R	NR	0 (0.0%)
p-value*		<0.001

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

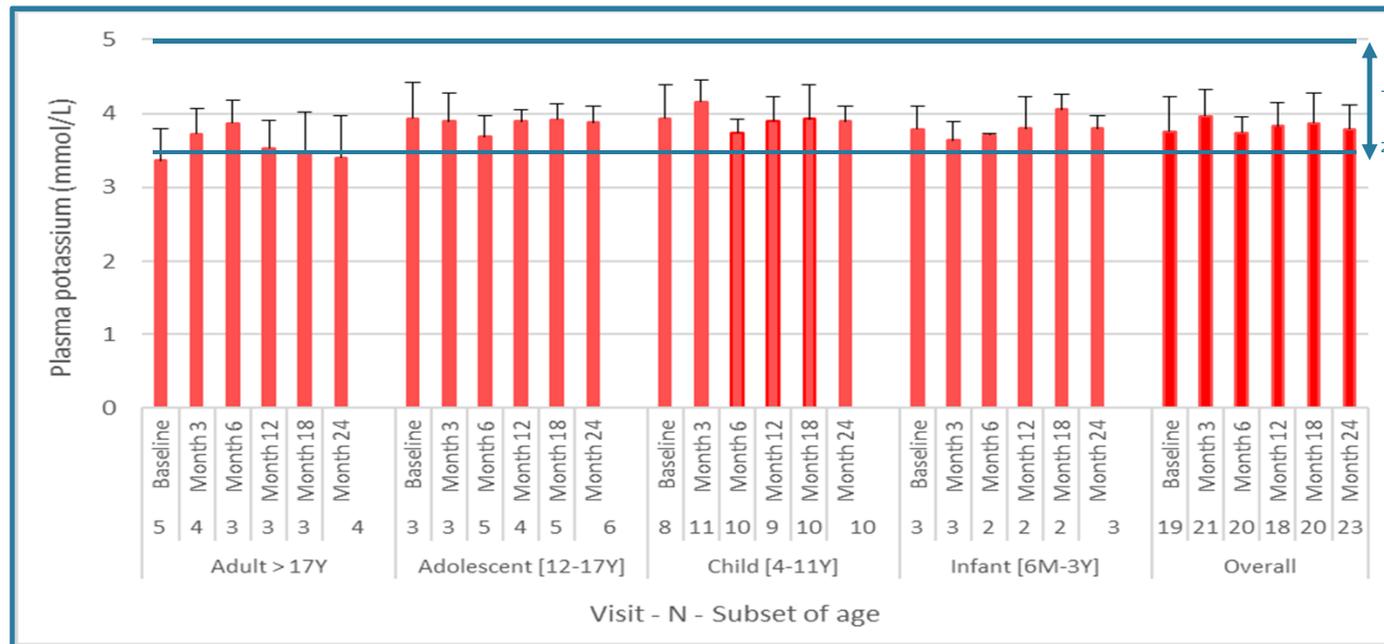
Phase III Data - Efficacy maintained after 24 months' treatment

- 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

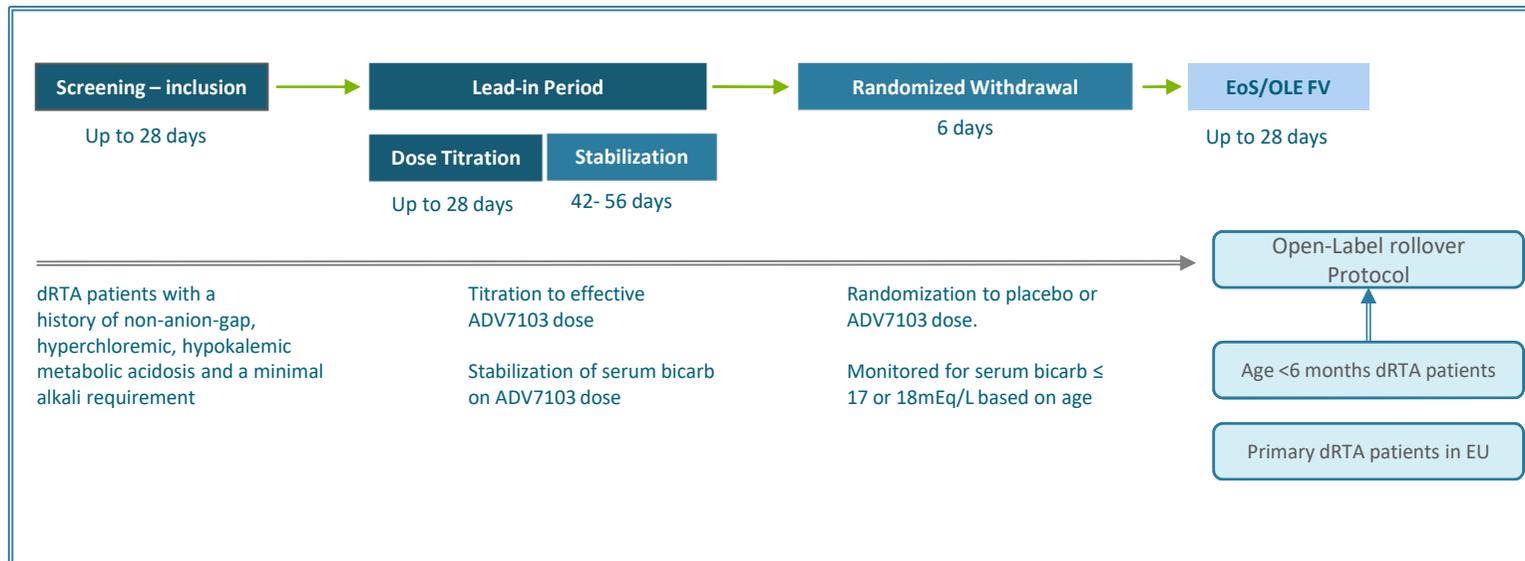


Arena-2 study: design of the US trial

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



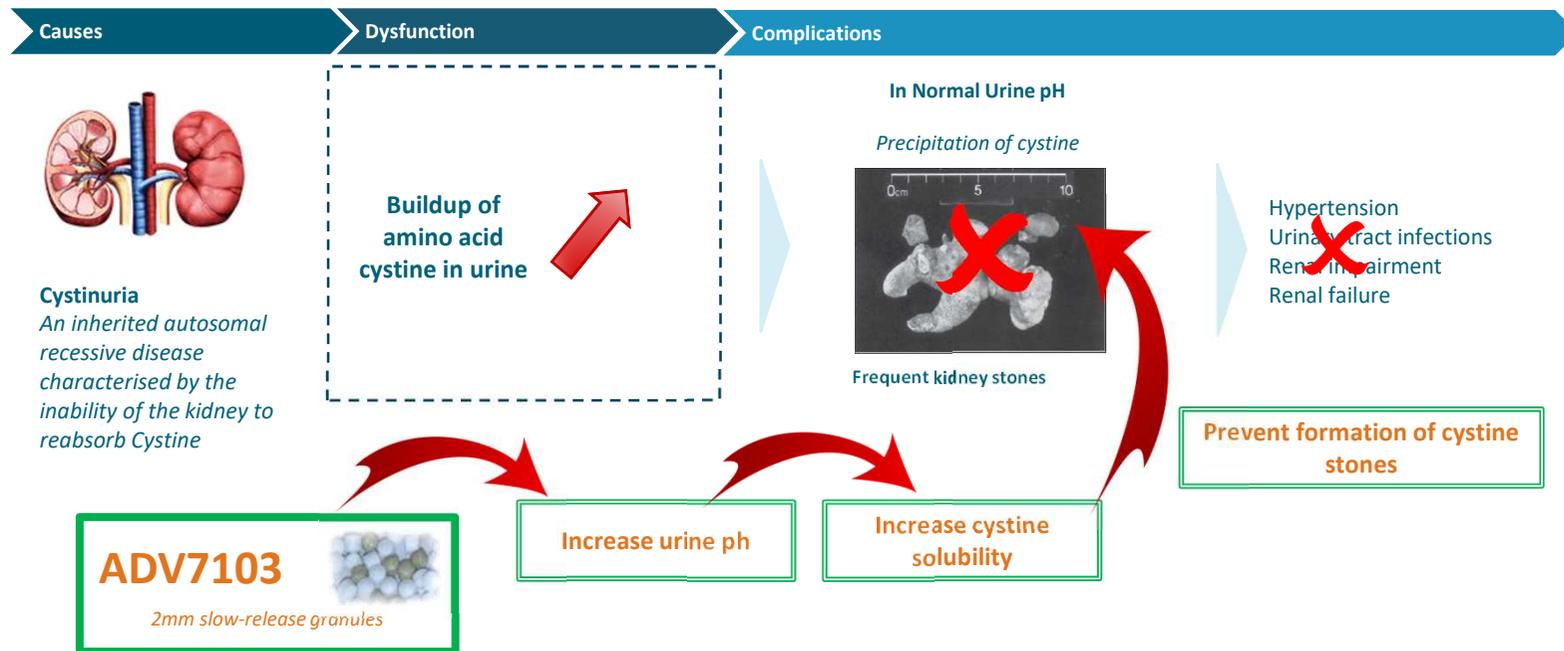


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ADV7103 for Cystinuria

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



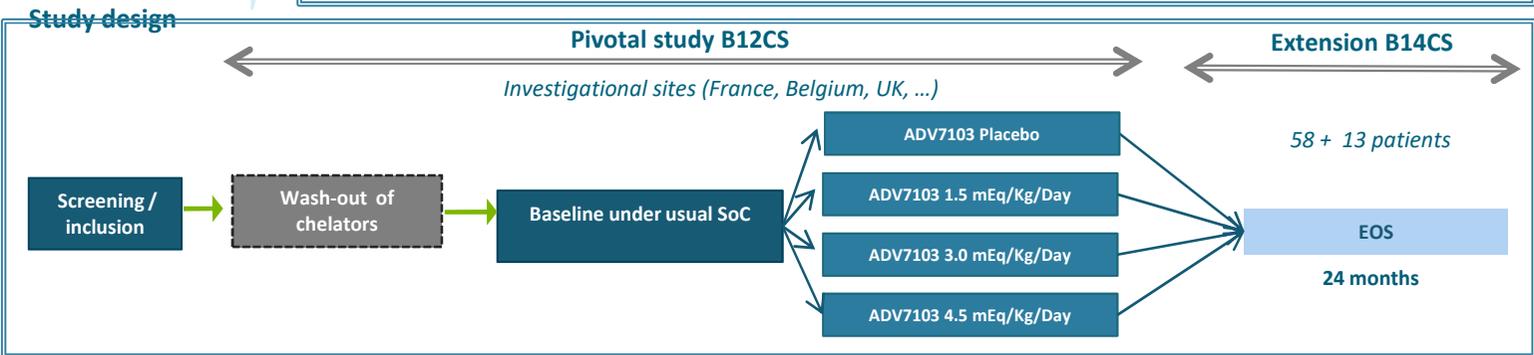
*US Strategy under
review*

- 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.



Primary objective

To evaluate the effect of ADV7103 at three different doses compared to placebo on the percentage of urinary pH values ≥ 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

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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. 30,000¹

Approx. 70,000²



Approx. 20,000¹

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

Market access strategy

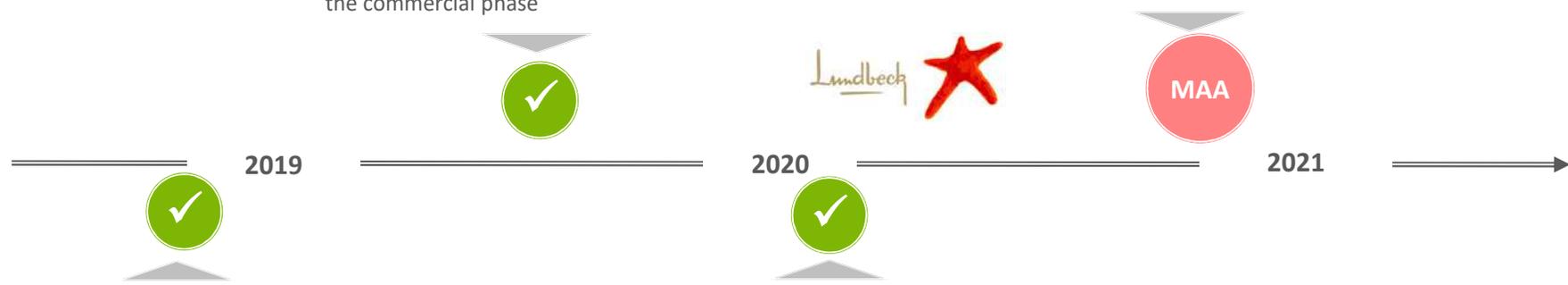
EU & US

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



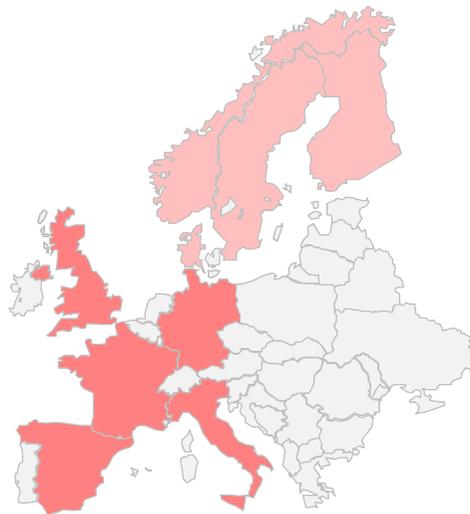
Clinical development

- 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



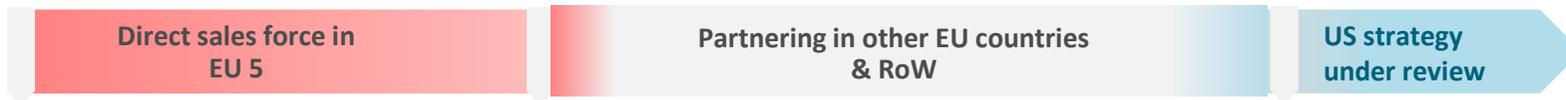
- Limited prescribing centers
 - Develop KOL relationships
 - Communicate among the specialist community



- Advanced ongoing discussion with potential partners



- Commercial strategy to be decided in 2020



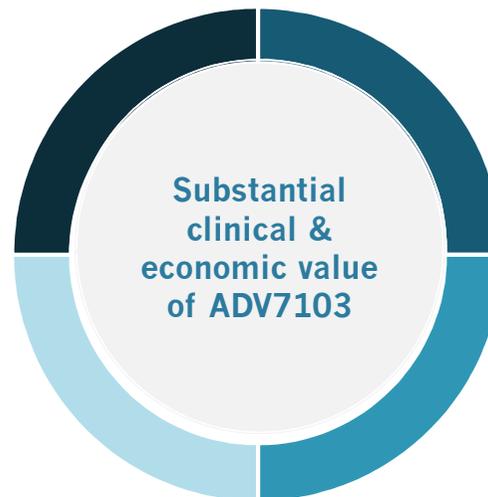
An adapted pricing policy for ADV7103

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

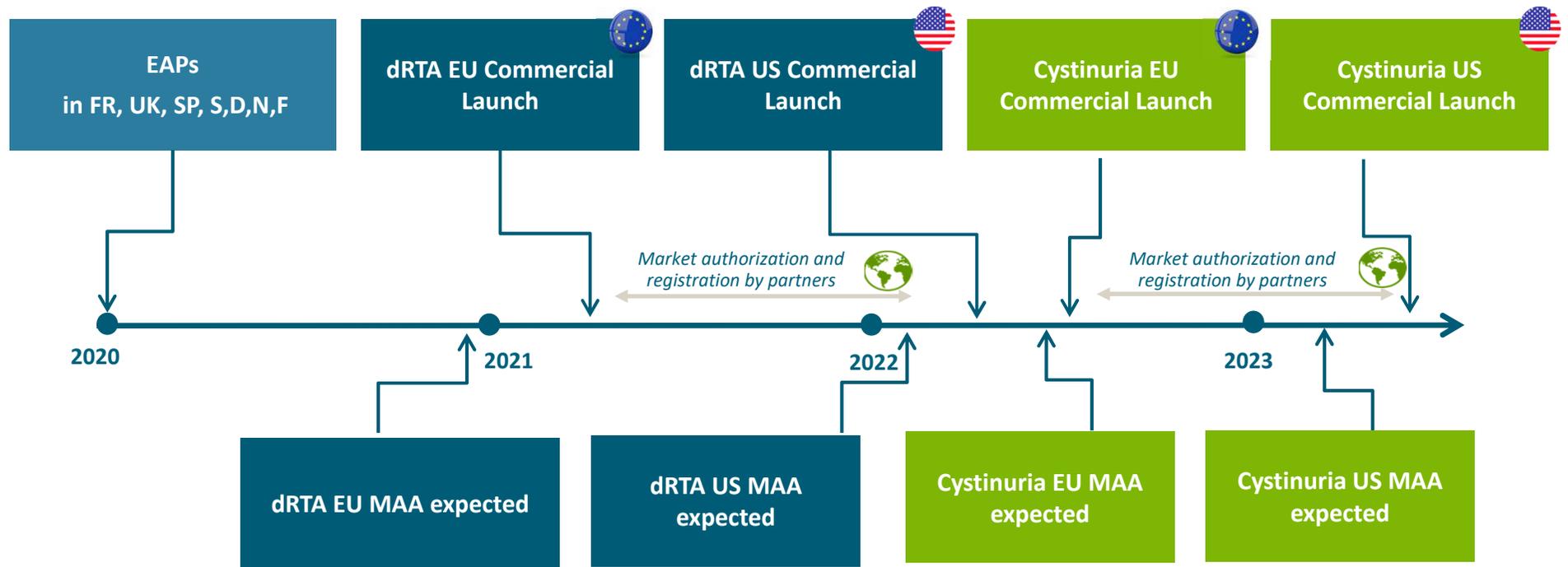
High expectations from physicians and patients for an efficient and easy-to-use treatment

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

Source: a pharmacoeconomic study on dRTA conducted by Advicenne

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Progressive commercial launch in both indications

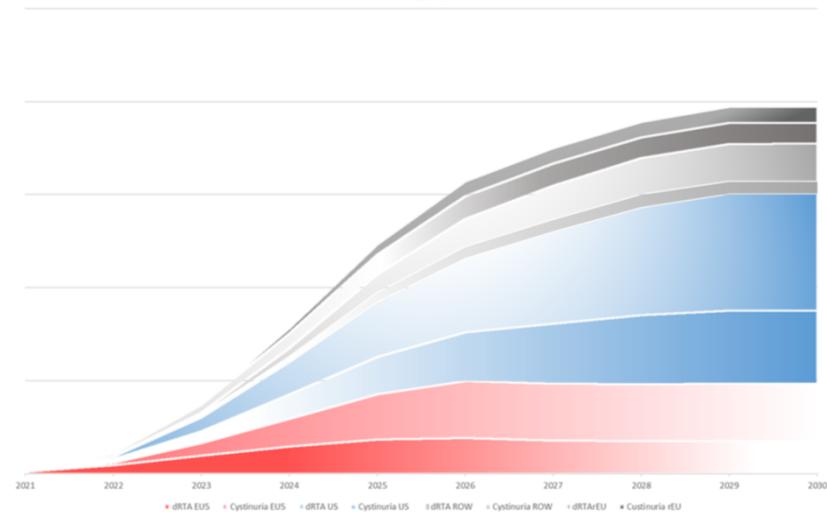


A niche but high value market

- 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

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 € 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

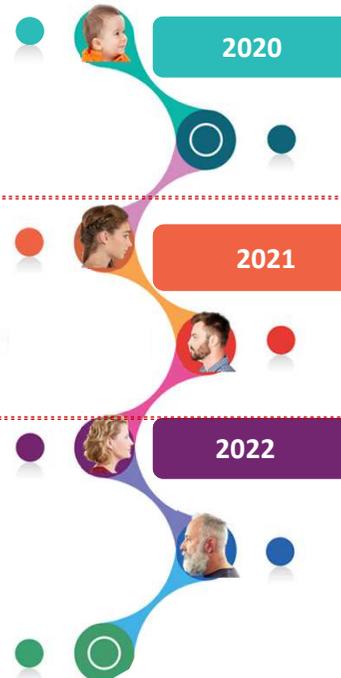
ADV7103 dRTA

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)



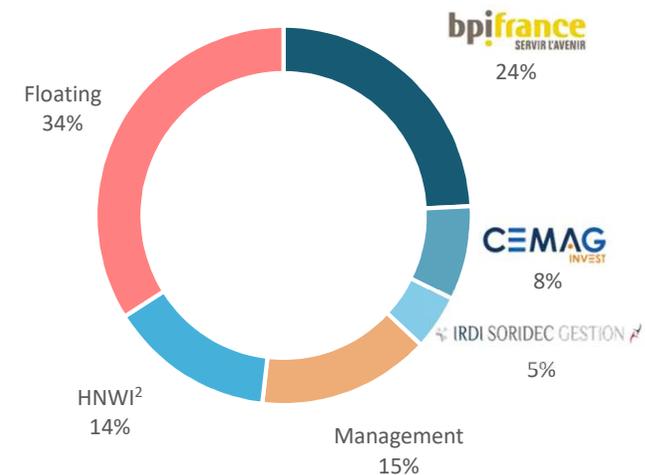
1: On a fully diluted basis as of January 1st, 2020

2: High-net-worth individuals

Source: Company information

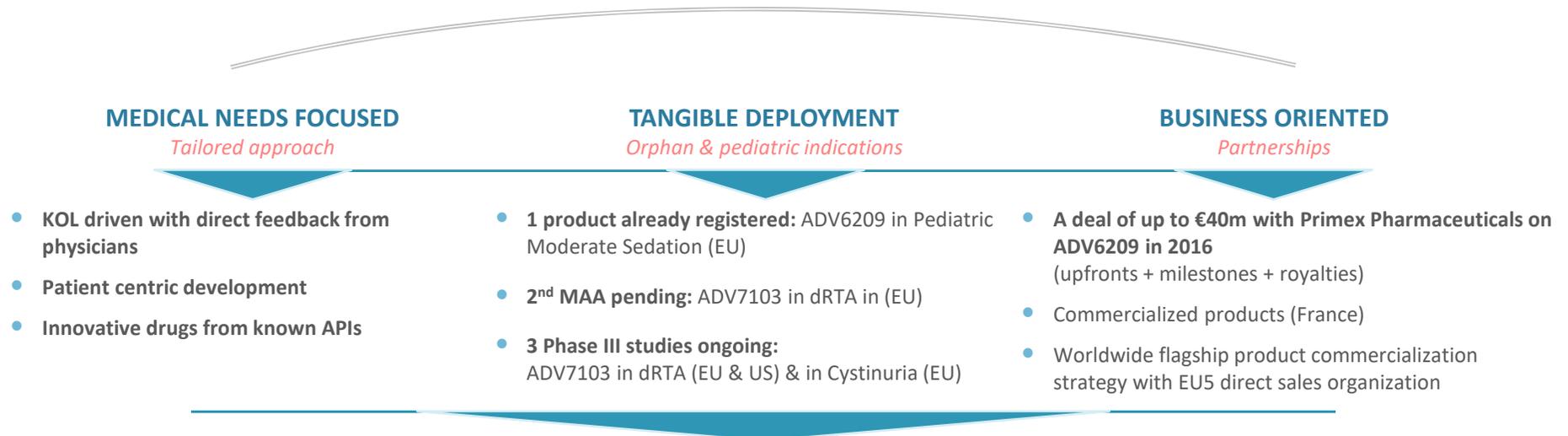
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SHAREHOLDERS AND INVESTORS¹



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

Thank you for your
attention

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