Path-breaking Treatments for Orphan Diseases

JP Morgan
London
September, 12th 2019

Luc-André GRANIER – CEO
Paul MICHALET - CFO

Euronext: **ADVIC**
Nimes, France

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Introducing Advicenne (Euronext: ADVIC)

- **Late clinical-stage specialty pharmaceutical company developing novel therapeutics for rare diseases**
- Lead asset, ADV7103 is pending EU marketing authorization for the treatment of a renal disease and was granted ORPHAN status.
- ADV7103 is also currently in pivotal Phase III trials in the US and Canada for its first indication and in pivotal Phase III trials in Europe for a second renal indication
- Market potential of several hundred million EUR
- Ozalin® granted EU marketing authorization in September 2018; developed entirely in-house; now sold to Primex Pharmaceuticals for commercialization
- Clinically de-risked: mature and balanced pipeline includes preclinical through late-stage assets
- Well financed, with about € 26 million of cash and equivalents at December 31, 2018* plus € 20 million loan facility from EIB in July 2019

** $30million with 1€ = $1.12. Unaudited data*

Our cash-efficient business model

From inception (2007) to 1st of January 2019

~€30m invested

MEDICAL NEEDS FOCUSED
Tailored approach

- **KOL driven with direct feedback from physicians**
- **Patient centric development**
- **Innovative drugs from known APIs**

TANGIBLE DEPLOYMENT
Orphan & pediatric indications

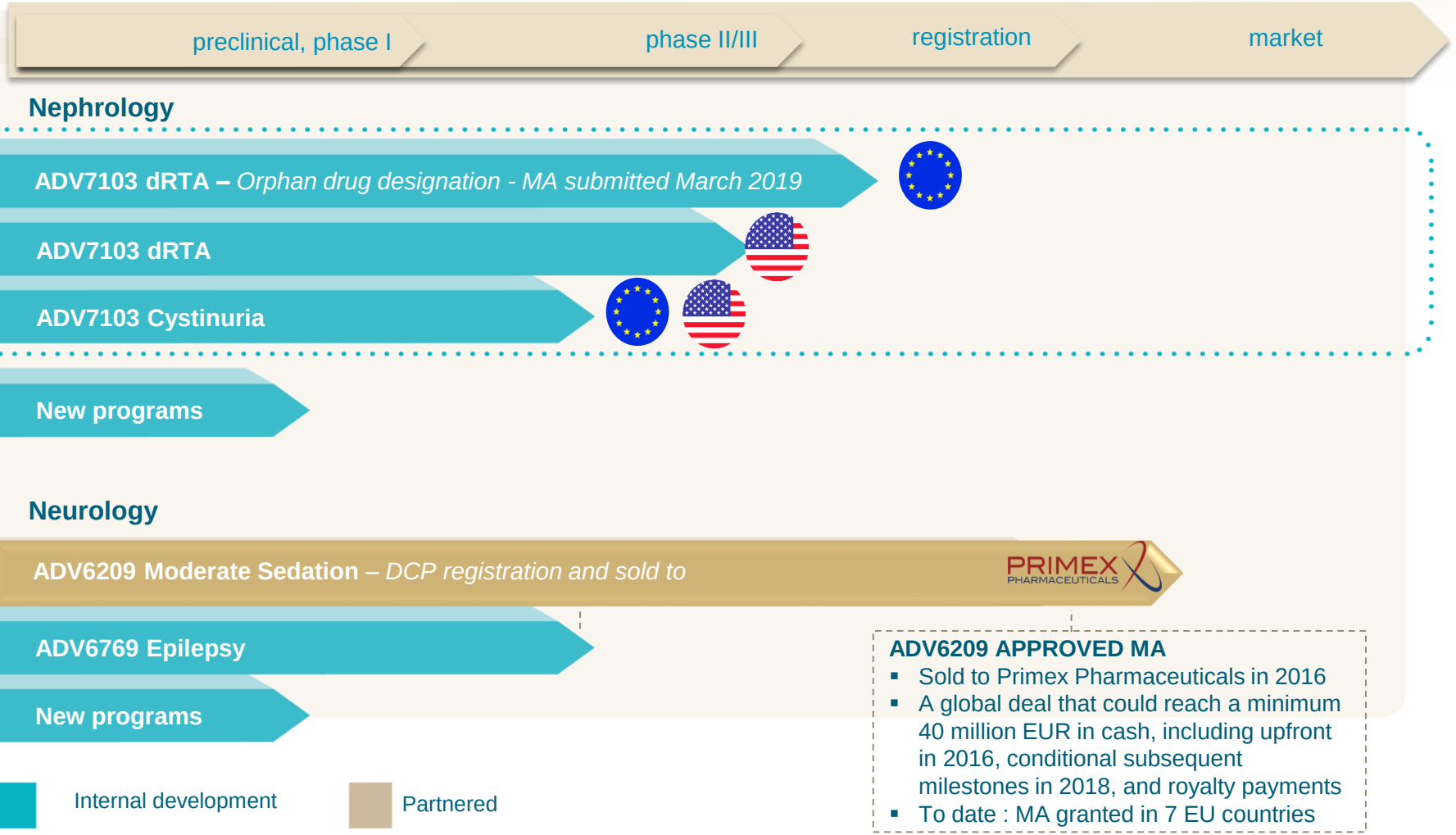
- **1 product already registered:** ADV6209 in Pediatric Moderate Sedation (EU)
- **2nd MAA pending:** ADV7103 in dRTA in (EU)
- **3 phase III studies ongoing:** ADV7103 in dRTA (EU & US) & in Cystinuria (EU)

BUSINESS ORIENTED
Partnerships

- **A deal of up to €40m with Primex Pharmaceuticals on ADV6209 in 2016** (upfronts + milestones + royalties)
- Commercialized products (France)
- Worldwide flagship product commercialization strategy with EU5 direct sales organization

A unique track record of efficient drug development

Mature and balanced pipeline



ADV6209 APPROVED MA

- Sold to Primex Pharmaceuticals in 2016
- A global deal that could reach a minimum 40 million EUR in cash, including upfront in 2016, conditional subsequent milestones in 2018, and royalty payments
- To date : MA granted in 7 EU countries

Source: Company information

** $44,8million with 1€ = $1.12.*

Experienced management team

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

Previously worked at:

Lilly

Caroline Roussel-Maupetit, Eng
Co-founder and Operations Director

Previously worked at:

synt:em

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

Previously worked at:

Shire

Paul Michalet, MBA, CEFA
Chief Financial Officer

Previously worked at:

metabolic explorer

Fermentalg

Source: Company information

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

KOL-driven product and development approach with a focus on nephrology and neurology Commitment to treatments adapted to both pediatric and adult patient populations

Nephrology scientific board

Prof. Pierre Cochat (Co-chairman)

Head of Pediatric Nephrology CHU Lyon

President of IPNA (International Pediatric Nephrology Association)

Hospices Civils de Lyon

Prof. Bertrand Knebelmann

Head of Nephrology at the Unit Necker Hospital Paris

Necker ENFANTS MALADES HÔPITAL UNIVERSITAIRE

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)

EMORY UNIVERSITY SCHOOL OF MEDICINE

Prof. Elena Levtchenko

Head of Pediatric Nephrology at the KU Leuven

President of ESPN

KU LEUVEN

Prof. Gema Ariceta

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

Vall d'Hebron Hospital

Prof. Detlef Bockenhauer

Head of Nephrology at the Great Ormond Street Hospital

Great Ormond Street Hospital for Children NHS Trust

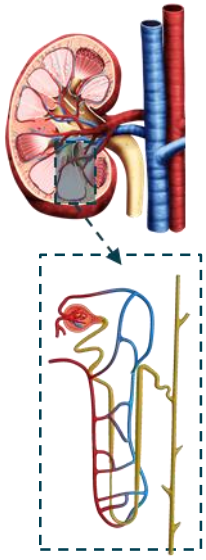
Source: Company information

ADV7103 Global Development - dRTA

EU & US

Consequences of distal renal tubular acidosis (dRTA)

Dysfunction → **Metabolic Acidosis** → **Imbalances** → **Complications**



dRTA

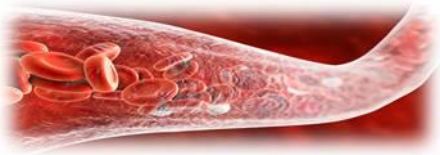
The inability of the kidney to adequately excrete an acid (H^+) load

- *Result of a genetic defect*
- *Or secondary to other diseases*

Metabolic Acidosis

Leads to acidification of the blood and low potassium levels

H^+ ↑ HCO_3^- ↓



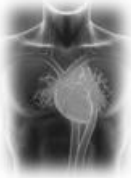
K^+ ↓ Ca^{2+} ↑

Hypercalciuria

Hypokalemia

Low potassium (K^+) level in blood serum

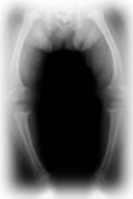
→ Cardiac dysfunction (arrhythmia)



Phosphates are extracted from the bones to compensate for acidosis (surplus of H^+).

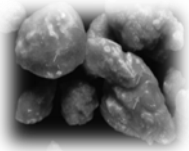
Calcium is released from the bones

→ Softening of bones (rickets)



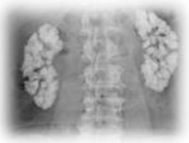
Excess calcium is excreted in the urine

→ Kidney stones



→ Nephrocalcinosis

→ Could induce renal failure



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

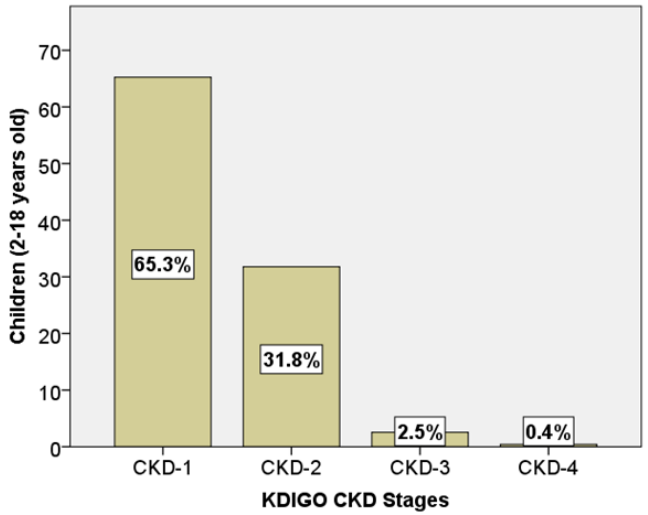
dRTA: a severe debilitating orphan renal disease

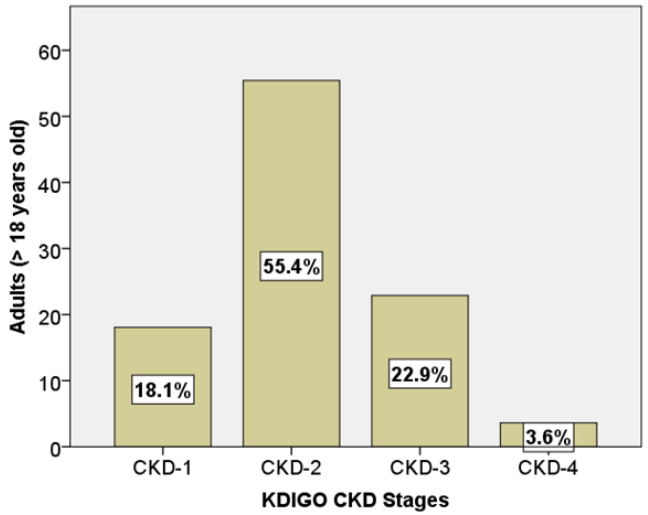
Table 5 | Clinical features of patients included in the study

	SLC4A1	*ATP6V1B1*	*ATP6V0A4*	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^2), dRTA, distal renal tubular acidosis; FTT, failure to thrive; M/F, male/female; SNHL, sensorineural hearing loss.

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

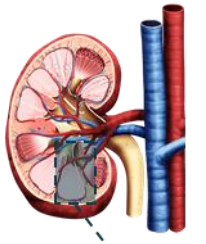




Lopez-Garcia et al, Treatment and long-term outcome in primary distal renal tubular acidosis 2019 NDT in press

dRTA treated with ADV7103

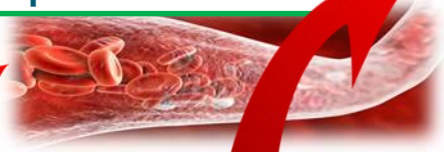
Dysfunction | Metabolic Acidosis | Imbalances | Complications



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

Metabolic Acidosis
Leads to acidification of the blood and low potassium levels

Acidosis compensation

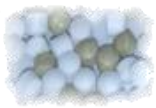


K^+ ↓

Ca^{2+} ↑

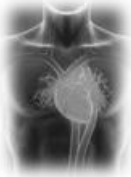
Hypercalciuria

ADV7103
2mm slow-release granules



Kalemia rebalance

Cardiac dysfunction (arrhythmia)



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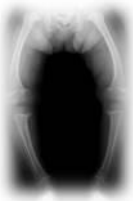
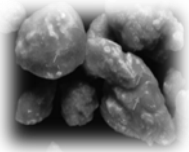


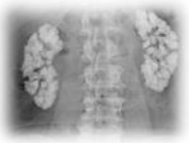
Calcium chelation

Kidney stones

Nephrocalcinosis

Could induce renal failure





Source: Company information, 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

- ✓ Improved efficacy (HCO3-)
- ✓ High Responder rate
- ✓ Only two intakes a day (12h)
- ✓ Full night coverage
- ✓ Normalized kalaemia
- ✓ Improved gastrointestinal tolerance
- ✓ Adapted to pediatric patients
- ✓ Tasteless
- ✓ Improved acceptability
- ✓ Improved compliance

Standard of Care

- ✗ Sub-optimal efficacy
- ✗ High Non Responder rate
- ✗ Requires 3-6 treatments a day (<4h)
- ✗ Difficult night coverage
- ✗ potassium supplementation requirement
- ✗ Severe gastrointestinal intolerance
- ✗ Not adapted to pediatric patients
- ✗ Bad taste
- ✗ Poor acceptability
- ✗ Poor compliance

ADV7103 addresses clear unmet need in orphan nephrology and improves efficacy and quality of life especially for pediatric patients

ADV7103 demonstrates superiority over SoC

- **Study results demonstrate significant efficacy**
  - **Non-inferiority is clearly demonstrated on primary endpoint**
  - **ADV7103 is significantly superior to SoC on primary endpoint**
    P-value = 0.0047 (Per Protocol) – 0.0032 (Intention to Treat)
  - **Increasing responder rate with ADV7103**
- **Efficacy was maintained after 24 months of treatment**
  - Blood bicarbonatemia in normal range in 79% of the patients
- **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**
- **Strong compliance observed**
  - 93.3% and 89.6% of patients treated with ADV7103 were compliant after 3 and 6 months, respectively

dRTA clinical development plan in the US

- **Initiation of US clinical operations in 2018**
  - Dr Linda Law, appointed US VP Clinical Development and Medical Affairs
  - Two project leaders appointed
  - CRO to monitor the study in the US
- **IND clearance in September 2018**
- **Health Canada clearance in October 2018**
- **Study open and actively recruiting**

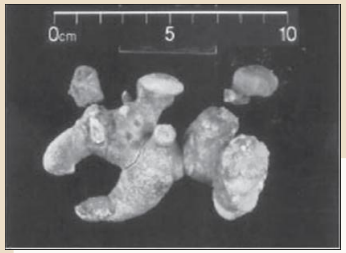
- **One pivotal Phase III study in the US required by the US FDA in addition to EU clinical package for registration**
- **B23CS : Pivotal study in US & Canada**
  - 3 to 5 central sites, 12 to 18 recruiting centers to be opened
  - 40 patients to be included

Source: Company information

ADV7103 for Cystinuria

ADV7103: A second indication - cystinuria

Frequent Kidney Stones



An inherited autosomal recessive disease characterized by the inability of the kidney to reabsorb cystine

Major Complications

Hypertension
Urinary tract infections
Renal impairment
Renal failure

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
- Strong supportive information linking increase of pH with solubility of cystine

A pivotal Phase III study agreed to with EMA to support registration in EU

- Study ongoing in FR, BE
- To be opened in the UK
- 72 patients to be included

US Strategy under review

- ODD to be submitted soon
- Meeting with FDA before year end

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

ADV7103 Market potential

One product for two diseases: dRTA and cystinuria

Market: High demand with few competitors

- **No approved first line treatment**
  - dRTA: SoC requires compounding of various unapproved products in an attempt to re-establish normal physiological functions
  - Cystinuria: SoC is diet, hyperdiuresis and compounding of various alkalising unapproved products administered every 4 to 6 hours
- SoC induces **severe complications** in the gastro-intestinal tract
- Not adapted for **pediatric use**
- **Poor compliance**

ADV7103 close to market for dRTA (one-year lag for Cystinuria)

MA approval S2 2020
Ongoing market access dossier 2019
Build commercial organization in EU 5 2019 - 2020
→ **Product launch** *Early 2021*

2019 – 2020 **Pivotal Phase III trial** → **FDA filing and review: 2021** → **Product launch** *2022*

1: Marketing Authorization Application (MAA)
Source: Company information

One product for two diseases: dRTA and cystinuria

Two rare/orphan indications

Addressable Global population		
dRTA (genetic and acquired)	Approx. 30,000[1]	Approx. 20,000[1]
Cystinuria	Approx. 70,000[2]	Approx. 20,000 – 30,000[2,3]

Significant unmet medical needs

- Unregistered Standard of Care (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

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

dRTA : a rare and severe sub-optimally treated disease with short and long terms consequences affecting a limited population

	EU5	
dRTA Treated population	**> 23 000[1]**	**> 14 300[2,3]**
Primary dRTA	> 5 080[1]	> 1 216[2]
Secondary dRTA	> 18 011[1]	Approx. 13 115[3]

ISPOR May 2019
1: distal Renal Tubular Acidosis, a rare renal condition that is often undiagnosed: UK study using CPRD database (syneos)
2: Estimate of prevalence of primary distal Renal Tubular Acidosis among the US population with employer-sponsored health insurance (stratevi)

ACR 2019
3: Estimate of Prevalence of Secondary Distal Renal Tubular Acidosis Among Patients with Sjogren's Syndrome and Systemic Lupus Erythematosus in a US Population with Employer-Sponsored Health Insurance" (Stratevi)

Cystinuria: well defined debilitating and painful disease leading to major renal impairments with guidelines but with limited results on a very demanding population

	EU5	
Cystinuria diagnosed/treated population	**[24 000 – 32 000]**	**[10 000 – 45 000]**
Advicenne CPRD	Approx. **24 000**[1]	
Advicenne US data base		-
Company 10K		10 000 – 12 000
RKSC		33 000
NORD report		[32 000- 45 000]
DelveInsight	Approx 32 000	Approx. 23 000
Severe Cystinuria population deemed retained	**Approx. 15 000**	**[7 200 – 10 000]**

ISPOR MAY 2019
1: Cystinuria, a rare renal condition that is often undiagnosed: prevalence UK study using CPRD database (syneos)

Commercial strategy

European approval and first product launches

- **Build a robust pharmacoeconomic core dossier to support orphan drug pricing of ADV7103 (EU and US) for both indications**
  - Target population
  - Value proposition
  - Pricing strategy

- **Build commercial organization in EU5 (France, Germany, Italy, Spain, UK)**
  - Limited prescribing centers
    - Develop KOL relationships
    - Communicate among the specialist community
  - Limited marketing and sales resources required: 4-6 sales reps per country
  - Good overlap between dRTA and Cystinuria prescribers
  - Establish platform for additional products

- **Establish partnerships to generate sales outside the EU5**
  - US: Clinical development and registration by Advicenne, US strategy under review
  - Other EU countries: European Market Authorization by Advicenne, commercialized by partners
  - RoW: Market authorization and registration by partner

Broad IP estate offers protection through 2031

IP number	Description	Geographies	Expiry date[1]
2640365[2]	▪ Solid pharmaceutical composition of the granules (tablets) of potassium citrate (including its particular release profile) ▪ Medication in treatment/prevention of urinary lithiasis and related diseases	▪ 15 European countries including EU5 ▪ Japan ▪ United States	Nov 18, 2031
2640364[2]	▪ Composition of the bicarbonate salt granules (including its 12-hour continuous release profile) ▪ Medication in treatment/prevention of urinary lithiasis and related diseases	▪ 15 European countries including EU5 ▪ Japan ▪ United States	Nov 18, 2031
2640363[2]	▪ Combination of bicarbonate salt and citrate salt granules (two compounds of ADV7103) and their respective release profile ▪ Medication in treatment/prevention of Cystinuria	▪ 15 European countries including EU5 ▪ Japan ▪ United States ▪ Canada ▪ Other countries	Nov 18, 2031

1: Priority date is Nov 18, 2010
2: IP number of the European patents

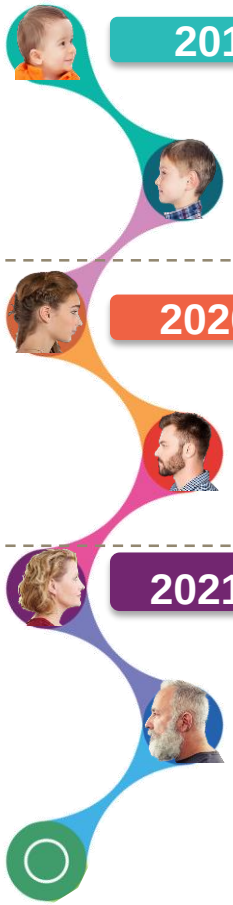
Financial Highlights

- **Approximately € 26 million* ($30 million) in cash and cash equivalents as of December 31, 2018**
  - €27 million ($31 million) raised in successful IPO in December 2017
- Streamlined operations with a headcount of 32 (21 in R&D)
- Cash sufficient to fund operations through numerous value-creating inflection points in the next 18 months
- € 20 million debt facility authorization from EIB (July 2019)

Upcoming value-creation milestones

ADV7103
dRTA

ADV7103
Cystinuria



2019

Start US pivotal Phase III trial

MAA filed EU (Q1 19)

Open European sites for European Phase II/III study

2020

Orphan drug designation (ODD) in the US

End US pivotal Phase III trial

European MAA granted 16-18 Month after filing

ODD granted in US and EU

Completion of European pivotal Phase II/III trial

2021

New Drug Application (NDA) filing US

Commercial launches EU

Data from European pivotal Phase II/III trial

MAA filling EU

Start US pivotal Phase III trial

Euronext : ADVIC

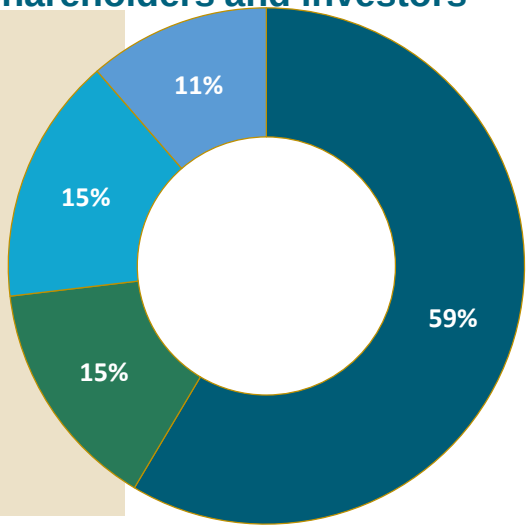
Company overview

- Specialty pharmaceutical company
- Headquarters in Nîmes, France
- Founded in 2007
- Raised approx. € 30 M in private rounds
- Listing on Euronext Paris December 6, 2017 (€ 27,8 M raised)

Analysts coverage

- Jamila Elbougrini (FR)
- Anita Ye & Dylan van Haaften (ENG)
- Samir Devani (ENG)

Shareholders and investors[1]



- Private equity funds
- HNIW[2]
- Management & employees
- Free float

1: On a fully diluted basis as of January 2018
2: High-net-worth individuals

Source: Company information

Summary highlights

1 De-risked Product Portfolio

- Strong clinical data demonstrates **superiority of ADV7103 in dRTA over SoC,**
- **European Marketing authorization submitted to the EMA in March 2019**
- **IND** open for pivotal Phase III trials in the US
- **MA granted in EU** for Ozalin® in moderate sedation

2 "Niche-buster" Potential

- **ADV7103 is a child-friendly treatment for two orphan nephrology indications**
- "Niche-buster" potential in well defined populations with no approved treatments in dRTA
- ADV7103 to drive company's value-generating news flow over the next 18-24 months

3 Proven and Unique Strategy

- **Unique R&D approach driven by input from Key Opinion Leaders**
- Track record of successful product development, notably with Ozalin®
- Focus on treatments and their commercialization suitable for both children and adults

4 Experienced Management Team

- **Experienced management team with years of successful performance in drug development, regulatory strategy and commercialization**

Thank you

www.advicenne.com

CONTACTS

Luc-André GRANIER – CEO
Email: lag@advicenne.com – Cell: +33 6 19 20 29 50
Paul MICHALET – CFO
Email: pmichalet@advicenne.com – Cell: +33 6 11 33 83 83