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EQUITY RESEARCH

ADVICENNE

INITIATION OF COVERAGE

BUY, TP 7.6€
Up/Downside: 89%

Sales Take-Off that should be confirmed

The project development pipeline's progress should enable the group to expand its marketed product portfolio, fuel sales and accelerate revenue growth, expected from 2023.

Advicenne is a pharmaceutical company specialising in the development of drugs for children and adults with rare kidney and certain central nervous system diseases having still unmet medical needs. The company has generated 2021 revenue of €2.7m, +30% (total revenues at 3,3 M€), thanks to products under license (treatment of epilepsy) and a first internally developed product: Sibnayal® (treatment of dRTA, a kidney disease).

The company's development work is based on existing molecules (off-patent active ingredients that are free to be exploited) and innovations that allow the company to take out a patent. It involves either indicators or formulations or come from the result of combining several molecules. Thanks to the strategy deployed (use of existing molecules) and the targeted indicators (rare or orphan diseases), development times / regulatory stages and associated costs are reduced compared to pharmaceutical sector standards.

The group has already obtained marketing authorisations in Europe for some of its products in neurology: Ozaline® (moderate sedation, MA in 2018, license transferred to Primex in 2016), and a product in nephrology (mid-2021 in Europe dRTA indicator, Sibnayal®), and has a promising portfolio of products in Europe and on the American market (renal indicators ADV7103 project: dRTA in the US and cystinuria in Europe and in the US). Additionally, the group has signed the first distribution agreements to market its products (direct sales in France and the United Kingdom), which should boost the group's revenue (€1.6m in H1 2022) in the coming years, thus accelerating growth.

Revenue growth (sales and other products) should gradually offset R&D expenses, which should continue, leading to limited operational losses. Additionally, the group should benefit from significant revenue from the Primex contract (€33m by 2025). To enable the company to continue its growth, we estimate the need for external financing to amount to €30-35m over the next three years, covered in part by debt (additional EIB financing) and in part by capital increase.

The clinical, regulatory and operational newsflow should, in our opinion, lead to the share price taking off. Our target price of €7.6, obtained by adding the two parts together, offers a potential upside close to 90%. Therefore, we are initiating our coverage of the stock with a Buy rating.

TP ICAP Midcap Estimates	12/21	12/22e	12/23e	12/24e
Sales (m €)	2.7	3.4	4.2	5.7
Current Op Inc (m €)	-12.4	-12.0	-11.8	-10.4
Current op. Margin (%)	na	na	na	na
EPS (€)	-1.24	-1.06	-0.89	-0.69
DPS (€)	0.00	0.00	0.00	0.00
Yield (%)	0.0	0.0	0.0	0.0
FCF (m €)	-12.8	-15.3	-14.1	-13.6

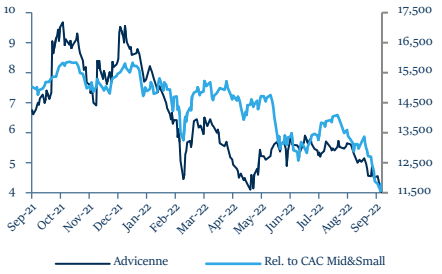
Valuation Ratio	12/22e	12/23e	12/24e
EV/Sales	16.4	14.5	11.4

Key data	
Price (€)	4.0
Industry	Heathcare
Ticker	ALDVI-FR
Shares Out (m)	12.189
Market Cap (m €)	49.0
Next event	RN 2021 : 28/04/2022

Ownership (%)	
BPI Investissement	22.6
IXO PE	7.7
Cemag	7.5
Irdi Soditec	4.4
Free float	55.8

EPS (€)	12/22e	12/23e	12/24e
Estimates	-1.06	-0.89	-0.69
Change vs previous estimates (%)	na	na	na

Performance (%)	1D	1M	YTD
Price Perf	-2.7	-27.0	-57.8
Rel CAC Mid&Small	-4.6	-18.7	-44.5



Analyst
Claire Deray - Sponsor Finance for TPICAP Midcap

Description

Advicenne is a pharmaceutical company specialised in drugs development suitable for children and adults for rare kidney diseases and certain diseases of the central nervous system with unmet medical needs.

SWOT Analysis

Strengths

- Portfolio of patents
- Products already on the market
- Healthy financial situation

Weaknesses

- Successive managment changes
- A level of activity that remains low
- On going research programms that need external financing

Opportunities

- Sales acceleration
- Distribution area extension
- New products launches

Threats

- Failure in R&D works
- Delays in products commercialisation
- Difficulties to find new financing

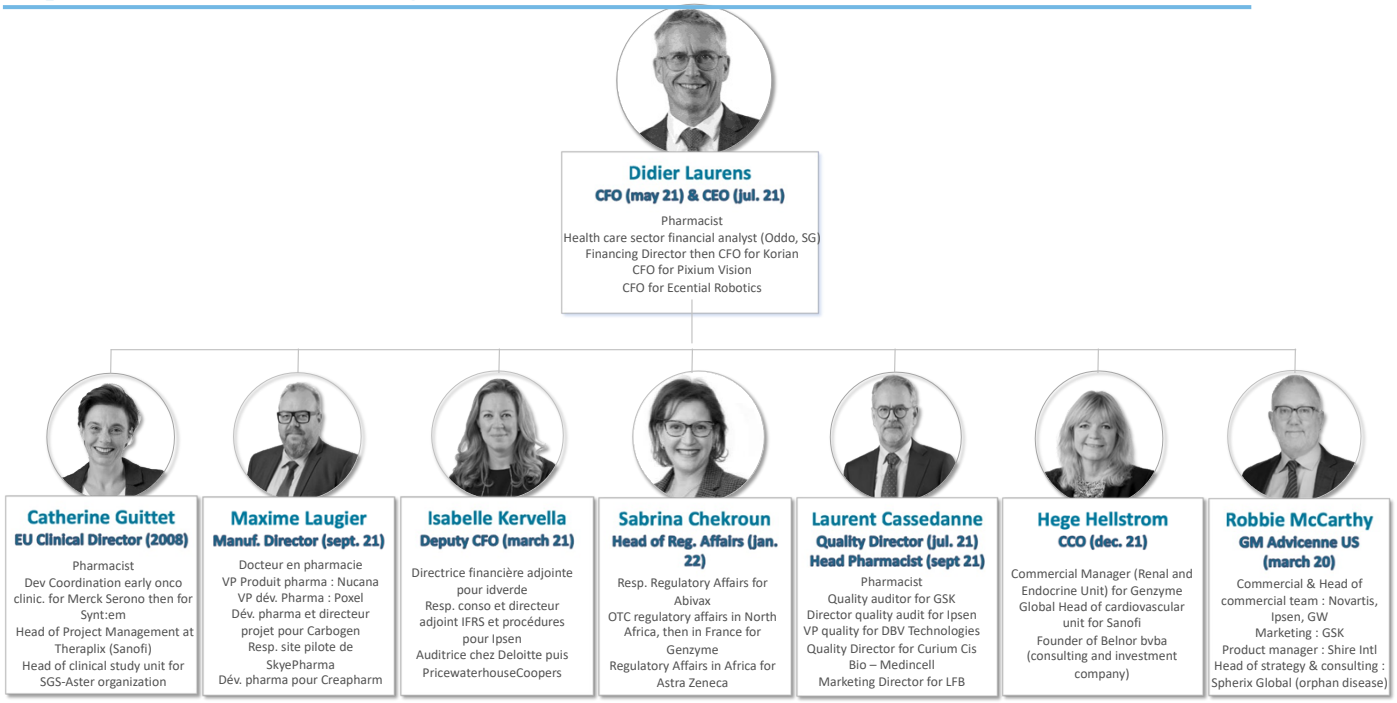
Overview

The company was founded in 2007, and listed at the end of 2017, by Luc-André Granier and Caroline Roussel-Maupetit, both experienced scientists with extensive knowledge of the drug industry. Their goal was to build and market a portfolio of products suitable for all ages of life, particularly pediatrics, to treat diseases with high medical needs, most often orphan diseases. Since its creation, Advicenne has focused on two areas in particular: the treatment of neglected or orphan diseases of the central nervous system (neurology division) and certain nephrological disorders (nephrology division).

The company's development is based on existing molecules (off-patent active ingredients that are free to be used); innovations that allow the company to take out a patent for the indicator or in the formulation or are the result of the combination of several molecules. The company's know-how lies in its proximity to clinicians, its regulatory expertise (upstream of studies, during studies, MA process), its project coordination expertise (clinical studies outsourced to CROs), and its clinical expertise (specificities of orphan diseases and pediatric treatments). The strategy is based on the development of proprietary products (Ozaline®, Sibnayal®, etc.), but also on the conclusion of licensing agreements to distribute in France products that meet the group's therapeutic objectives (Levidcen and Likozam).

After having accompanied the company's developments for more than 10 years, the co-founders departed from company in early 2020. After a few months, during which several managers succeeded one another (André Ulmann and Peter Meeus), Didier Laurens was appointed Chief Executive Officer in May 2021, and put in place an experienced management team that was able to continue the developments carried out by the historical teams, post the blockages linked to the health crisis, and launch the marketing and production phases of certain products.

Graph 1: Presentation of the Management Team



Source: Advicenne

Thanks to the strategy deployed (use of existing molecules) and the targeted indicators (rare or orphan diseases), development time / regulatory steps and associated costs have been reduced compared to pharmaceutical industry standards. In addition to the revenue generated by the company's activities and licensing agreements, since its creation, the company has raised €68m in capital (gross amount) and benefits from debt financing of €12m (EIB program for €7.5m and a state guaranteed loan for €4m). To date, the group has received marketing authorisation for three products in the neurological field: Ozaline® (MA in 2018, license transferred to Primex in 2016), Levidcen (MA in France in 2014) and Likozam (MA in France in 2016) and one product in nephrology (Sibnayal ®, AM mid-2021 in Europe), has a promising portfolio of products under development (epilepsy project ADV6769), renal problems (dRTA in the US and cystinuria project ADV7103), and has signed the first distribution agreements to market its products (direct sales in France and the UK), which should boost the group's revenue in the coming years (€2.7m in 2021 sales, +30%, for a total revenue at 3,3 M€).

The group should benefit from a newsflow regarding the success of its research programs, regulatory advances (MA, reimbursement, etc.) but also in operational terms: expected acceleration of sales. However, given the product pipeline, the profit horizon is still far away, and we believe that the company will need new external financing in the coming years (estimated at €30-35m for the next 3-4 years).

Targeted Therapeutic Areas

For nephrology

There are some 200 to 300 kidney diseases with unknown mechanisms, most of which have a hereditary component. Their prevalence is much lower than 1 per 2,000 and most of them have an orphan status.

They can be grouped into 5 categories, themselves subdivided into several syndromes:

- hereditary glomerulopathies: in particular cortico-resistant nephrotic syndrome, Alport syndrome
- renal dysplasia and cystic diseases: nephronophthisis and polycystosis
- metabolic diseases with renal involvement: cystinosis, cystinuria, Fabry disease
- tubular dysgenesis
- hereditary tubulopathies: nephrogenic diabetes insipidus, acidosis, monogenic hypertension

Generally, the consequences of tubular damage are variable depending on the location of the tubule and the existence or not of compensatory pathways. The most common clinical symptoms are:

- Leakage of minerals, salts, vitamins, etc. into the urine
- Imbalance of the internal environment (for example, water balance, acid-base balance disorders)
- Growth delay or defect (rickets, osteomalacia)

To date, the company has focused its research efforts on two rare, so-called orphan renal diseases: distal renal tubular acidosis (ATRd) (inability of the kidneys to effectively eliminate circulating acids in the blood, leading to numerous physiological complications) and cystinuria (a disease leading to large stones).

dRTA

dRTA (distal Renal Tubulopathy Acidosis) is caused by genetic abnormalities that lead to a defect in the excretion of H+ ions in the renal tubules. This excretion defect induces a metabolic acidosis, a low blood bicarbonate concentration, and biochemical and metabolic abnormalities in the blood and urine. The prevalence of this condition is not known, but based on in-house studies, the company estimates the prevalence (genetic and acquired forms) at 2.1 patients per 10,000 people in Europe. The target population (children from 6 months and adults) in this indicator is thus approximately 30,000 patients in Europe and 20,000 in the United States (genetic dRTA and best characterized acquired forms).

The clinical consequences of distal tubular acidosis are hypercalciuria with nephrocalcinosis (in 50% of children, excessive urinary calcium excretion that can lead to stones and even renal failure), chronic and repeated calcium lithiasis (urinary stones) (one per month on average), stunted growth (one child in two), osteomalacia (bone decalcification, 10 to 20% of adults), and cases of rickets (25% of children).

Apart from Sibnayal developed by the group, there is no other authorized treatment for this disease. Some forms of this disease (distal tubular acidosis or type I) can be treated, but if not treated (intake of about 25 cl of sodium bicarbonate 4 to 6 times a day), they can be deleterious, as is the case with type II proximal tubular acidosis, in which the administration of bicarbonate can cause hypokalemia (a drop in the concentration of potassium in the blood, which can have serious consequences on cardiac function).

This type of renal disease, for which there is no effective treatment, was the subject of the first clinical studies conducted on products developed in-house (product ADV7103), with marketing authorization (MA) in Europe obtained in 2021 (continental Europe and the United Kingdom) under the brand name Sibnayal®. Phase II/III is underway in the United States (Arena II study), with FDA approval expected in 2024, and the Group has put in place initial marketing agreements in Europe and the Middle East.

Cystinuria

Cystinuria is a disorder of cystine and dibasic amino acid transport. This transport defect results in excessive urinary excretion of cystine, which leads to the repeated formation of cystine stones (cystinic lithiasis). Cystine lithiasis accounts for about 1% of stones in adults and about 10% of stones in children. This hereditary anomaly affects approximately 1 in 7,000 people in Europe (Source: Orphanet) and between 1 in 10,000 (Source: Nord cystinuria) and 1 in 15,000 in the United States (Source: Orphanet Journal of Rare Diseases 2012). The target population for this second indicator is thus approximately 70,000 patients in Europe and 20,000 to 30,000 in the United States.

The stones are often large or even coralliform, multiple and bilateral in almost 80% of cases. The spontaneous evolution of the disease is marked by the occurrence of frequent calcified emissions or obstructive accidents requiring iterative and mutilating surgical interventions that can lead to chronic renal failure. After 15 to 20 years of follow-up, about 20% of patients have chronic pyelonephritis (permanent infection of the kidney), 10% have undergone unilateral nephrectomy (partial or total removal of the kidney) and slightly less than 5% are on dialysis. Life-long, preventive and daily medical treatment is absolutely essential to prevent the disease, its recurrence, avoid invasive procedures and preserve kidney function.

Current treatments are based on the correction of disorders resulting from tubular damage by various adapted supplements. These supplements are associated either with restrictive dietary measures or with therapeutics allowing to correct one of the symptoms induced by the tubular damage.

In terms of dietary measures, it is advisable to establish a diet low in methionine, the precursor of cysteine. Methionine is an essential amino acid, so it cannot be eliminated, but its intake can be limited to the physiological requirement, i.e. 1200 to 1400 mg/day. To do this, foods very rich in methionine must be eliminated and consumption of meat, fish, eggs and cheese must be limited to 120/150 grams per day. As it is, this diet is too restrictive to be followed regularly. It is also not recommended for children and adolescents in full growth.

There are other recommendations:

- Diuresis treatment (increasing the volume of urine to dissolve cystine). This treatment requires a regular distribution of fluid intake during the day and especially at night. In practice, the diuresis treatment is very demanding, many patients are unable to follow it.
- Alkalinization of the urine by sodium bicarbonate but is accompanied by digestive problems (diarrhea), by Vichy water rich in bicarbonate but exposes to fluorosis especially in case of renal insufficiency, potassium citrate (bitter solution and poor gastric tolerance).

In France, two drugs are indicated for the treatment of cystinuria in the second line, i.e. after the failure of alkalizing agents used in the first line treatment: Acadione® (tiopronine) and Trolovol® (D-Penicillamine). In the United States, tiopronine is marketed under the name Thiola® by the company Retrophin.

However, these two drugs, with similar chemical structures and fields of action, present numerous undesirable side effects, sometimes serious: gastrointestinal intolerance, stomatitis (inflammation of the oral mucosa), skin rashes, pemphigus (dermatological lesions), arthralgias (joint pain), polymyositis (pain in the muscles with reduced muscle strength), proteinuria (abnormal presence of proteins in the urine), nephrotic syndrome (dysfunction of renal filtration), thrombocytopenia (decrease of platelets in the blood), and even bone marrow aplasia (dysfunction of the bone marrow which makes it unable to produce blood cells: red blood cells, white blood cells and platelets), which requires regular medical and biological monitoring (proteinuria, blood count), and limits its prescription in particular for pediatric use. Acadione® contains in its excipients an endocrine disruptor (phthalates) in quantities above the admissible threshold. Consequently, its use is not recommended for children. The same disadvantages are found with Trolovol®. The pharmaceutical form of this speciality (300 mg tablet) may not be suitable for children under 6 years of age and underweight children because of its high dosage and the risk of misuse.

All the solutions currently available are restrictive, have side effects and are not suitable for the treatment of children. Advicenne has therefore launched the development of ADV7103 in this second renal indicator and has obtained orphan drug designation in Europe in December 2019. The Phase II/III study is underway in Europe: CORAL 1 project (marketing authorization expected in 2024), and the protocol for the Phase II/III study for the North American market is being finalized: CORAL 2 project.

Before developing its own research programs in the renal field, the group concluded distribution agreements in 2013 to exploit two drugs in the treatment of epilepsy with the development of treatments adapted to children: Ledvicen and Likozam and carried out research to develop products adapted to the sedation of children, in the neurological field.

Neurology

In neuropediatrics, Advicenne focuses its research and development on Moderate sedation and Epilepsy for the pediatrics indicators.

Moderate sedation

Moderate sedation is a hospital procedure that consists of sedating a child to allow the physician to proceed with a painful intervention, without the child experiencing fear or in a state of agitation that makes the intervention impossible.

Pain, a non-familiar environment, and separation from parents are all factors that reinforce children's apprehension and generate an anxious state that can delay recovery.

Sedation is also used in a variety of clinical situations to significantly reduce children's anxiety:

- Wound sutures
- Needle procedures
- Endoscopies
- Minor accidents and emergency procedures
- Diagnostic procedures such as MRIs and CT scans

The child is sedated for a few dozen minutes. He or she quickly regains consciousness after the procedure.

Benzodiazepines are one of the most used therapeutic classes, particularly midazolam, which has a short half-life (1.5 hours). Diazepam is less used because of its long half-life (39 hours) and its active metabolites responsible for delayed awakening. It takes between 5 and 7 times the duration of the half-life to eliminate the product from the blood and therefore all the side effects. Flunitrazepam also has a long half-life. Venous tolerance of these two products is poor. Midazolam has none of these disadvantages and has become the reference benzodiazepine in intensive care.

Oral administration of 0.3 mg/kg of midazolam has been shown to significantly reduce anxiety in over 70% of preschool children. For many resuscitation anaesthetists, midazolam is the most interesting sedative molecule, but historically it was only available intravenously in Europe. Midazolam is then administered either by infusion or by intermittent injections. However, in children, the loading dose (desired level of sedation) and the maintenance doses (prolongation of sedation) cannot be administered rapidly. The loading dose should be injected slowly and should be followed by a continuous infusion. This parenteral route of administration is most often anxiety-provoking for children, and in addition, loading dose is not recommended before 6 months of age. Oral administration of intravenous forms, currently the only ones marketed in Europe, has the disadvantage of offering a very strongly bitter solution. After oral administration, the product may be spit out in the case of children. Compliance is then incomplete, resulting in a delay in the onset of action of the drug and a loss of effectiveness.

On average, more than 25% of emergency room visits involve children under the age of 15. Among them, 10% would require vigorous sedation. Anesthetic pre-medication in the context of surgical operations concerns 1.6% of children under 15 years of age per year in Europe, of whom approximately 80% are pre-medicated.

Aware of the need to find an oral mode of administration for midazolam, in mid-2010, management launched the development of a product with a paediatric formulation (from 6 months to 17 years of age) intended for moderate sedation prior to a therapeutic or diagnostic procedure and for aesthetic premedication.

In collaboration with the Amiens University Hospital, Advicenne has developed a liquid formulation of midazolam (2mg/l) for oral administration, specifically designed to mask its bitterness: Ozalin® (ADV6209). After conducting and completing the clinical development of the drug candidate ADV6209 (Ozalin®), the company sold it to Primex Pharmaceuticals in 2016 (€7M received since the beginning of the partnership, of which €3M at the time of the MA in 2018, royalties on future sales). The first positive notifications were obtained in September 2018 and the MA was obtained in most European countries in 2020. Post effect Covid, in 2021, Primex directly, or via distribution partners, was thus able to launch the marketing of Ozalin® allowing the group to record its first royalties (€73K in 2020 and €19K in 2021 recorded as partnership revenues).

Epilepsy

Epilepsy is the most common neurological disease after migraines. It can cause seizures that can be very impressive. Epilepsy is a chronic neurological disease defined by the spontaneous repetition of seizures caused by the extreme hyperactivity of a group of neurons (nerve cells) in the brain.

It is estimated that there are approximately 450,000 people with epilepsy in France. Nearly 40 million people worldwide suffer from epilepsy, with a slight male predominance.

Epilepsy can start at any age, but it is more frequent in children and its forms are more varied. The main reason for this is incomplete brain maturation. More than half of all epilepsies begin in childhood: every year, about 4,000 new cases are diagnosed in children.

Childhood epilepsy is the number one neurological disease in children. Epilepsy covers a group of diseases that manifest themselves through repetitive epileptic seizures. These seizures are the clinical expression of a sudden, excessive and transient abnormal electrical discharge in the central nervous system. There are as many clinical expressions as there are brain functions, but the most frequent are loss of consciousness and convulsion.

With a prevalence of 0.5 to 1.0%, epilepsy is more frequent in children than in adults. Its incidence reaches 134/100,000 people in the first year of life, which means that more than 500,000 children in Europe suffer from epilepsy. In the majority of cases, children need long-term drug treatment.

There is not one, but multiple epilepsies or more precisely multiple epileptic syndromes with different prognoses and treatments.

Clinical semiology distinguishes between generalized and partial seizures:

- Generalized seizures mainly include the tonic-clonic generalized seizure (the most well-known and the most spectacular), massive myoclonus and absences (petit mal)
- Among the partial seizures, a distinction is made between simple partial seizures, without alteration of consciousness (including epilepsy with rolandic spikes) and complex partial seizures with alteration of consciousness, either immediately or secondarily.

Most childhood epilepsies have no adults equivalents.

In children, the most frequent form of epilepsy, Rolandic epilepsy (25% of cases), is most often manifested by seizures during which the child remains conscious but is no longer able to articulate. The jaw seems to be locked and the mouth is slightly deviated. There are often small movements in the mouth and sometimes in the arm. In general, seizures are infrequent. This epilepsy gets its name from the shape and location (in Rolando's sulcus, between the frontal and parietal lobes of the brain) of the electrical waves detected on the electroencephalogram. It disappears at puberty in almost 100% of cases.

Absences are the second most common form of epilepsy in children (10 to 15% of cases). Often difficult to diagnose, this form of epilepsy is characterized by brief breaks in contact lasting a few seconds, which occur daily. The child is not aware of these absences, but often suffers the consequences: learning difficulties, memory problems, etc.

In children, the social impact is particularly severe, leading to isolation and loss of self-esteem. Learning difficulties and memory problems are common in children with epilepsy. Seizures lead to attention deficits, especially in school-aged children with absence epilepsy.

Status Epilepticus is defined as a seizure lasting more than 30 minutes or iterative seizures (without recovery of normal consciousness between each seizure) lasting more than 30 minutes. It is the most frequent cause of neurological emergency for which the morbidity and mortality rate remains high (10 to 20%).

Among the most frequent epileptic syndromes, febrile convulsions, whose classification among epileptic syndromes is unjustified since most of these children have inherited a neuronal fragility such that a sudden rise in temperature, between 6 months and 5 years of age, leads to convulsions, usually of brief duration.

The benign nature of febrile seizures does not warrant long-term preventive treatment but may require emergency treatment to stop the seizure.

Historically, there have been few therapeutic alternatives: most antiepileptic drugs are difficult to use in children under 12 years of age because of the lack of age-appropriate formulation. Indeed, for the treatment of epilepsy in children, most of the products on the market exist only in tablets packaged for adults or sometimes in syrup (zarontin, leviteracetam liquid) containing a very high sugar content and having a rather poor palatability. Each of these forms of packaging has major drawbacks for children. Tablets dosed for adults must be crushed or cut into small pieces before being given to young children, making it difficult to adjust the dose; very sweet syrups may mask bitterness or off-putting tastes for children, but they are frequently contraindicated in epileptics when a ketogenic diet is introduced (sugar-free diet). In addition, the intake of quick sugar in children is strongly discouraged by the medical profession and health authorities.

Few products have been developed with a formulation perfectly adapted to the constraints of treating young children. Nevertheless, we can mention Depakine (valproate) in its so-called Micropakine form, coated microgranules, or topiramate (openable capsule containing coated granules), these two formulations remaining an exception to the rule.

Aware of the needs in this market segment, the directors concluded in 2013 exclusive distribution agreements for the French market for Likozam® (refractory epilepsy in the form of an oral solution, the only formulation suitable for children and patients with swallowing difficulties) with Rosemont Pharmaceutical (initial period of 5 years, tacitly renewed each year) and for Levidcen® (treatment of epilepsy in small coated granules particularly suitable for children) with Desitin (marketing authorization obtained in France in 2014). These two products have been the group's main source of revenue in recent years, together with the proprietary product Sibnayal® (MA in Europe since April 2021 and under ATU in France since March 2020).

Details of Pediatric field and orphan diseases

Approximately 50% of patients affected by orphan diseases are children and 80% of orphan diseases have a genetic component (Source: Neurological rare Disease Special Report 2015). Since orphan diseases can start at any age and patients with hereditary diseases can be treated for the rest of their lives, Advicenne is committed to developing therapeutic products that are formulated for all ages, from infancy to adulthood.

The pediatric field

In Europe, where the pediatric population (under 18 years of age) represents more than 100 million individuals, or 20% of the total population, more than 50% of the drugs prescribed to children and adolescents have not been evaluated and authorized for administration specifically to these age groups. These drugs are prescribed for an indicator, a dosage, a galenic form or at an age different from those specified in the MA, by extrapolating from the data available in adults, and without specific clinical trials having been conducted in children.

The difficulty with pediatric drugs is that they are intended for a non-homogeneous population (premature babies, newborns, very young children < 2 years, children < 11 years old and adolescents). Moreover, pediatric pharmaco-clinical development is different from development in adults, particularly in very young children. For ethical reasons, clinical trials are very restrictive in children.

Indeed, the number of children exposed, the duration of exposure to the product under investigation, invasive acts such as blood sampling and all procedures defined in the study protocol must be limited. Therefore, it is often unrealistic to expect that a clinical study in children can fully demonstrate the efficacy and safety of a product in all age groups covered by the pediatric population.

On the other hand, special attention is required when conducting pharmacokinetic studies in children. Indeed, a specific characteristic of very young children is the rapid maturation of drug metabolism functions by certain organs. Therefore, a dose adjustment may be necessary according to the age of the patient and based on the individual level of maturation of the organ functions.

In pharmaceutical terms, most drugs administered to children have not been developed for them but come from the off-label and "cobbled together" use of tablets, capsules or solutions intended for adults.

The development of a drug for pediatric use involves multiple choices and major constraints. To date, knowledge and experience in this field are still very limited, which partly explains why very few drugs are formulated for pediatrics.

Orphan diseases

A disease is considered rare or orphan when it affects less than 5 out of 10,000 people in Europe or 1 out of 200,000 people in the United States. However, there are currently between 6,000 and 8,000 cases of orphan diseases; in terms of the European population, this concerns between 30 and 40 million people, the majority of whom are children. Most orphan diseases have a genetic origin (80%), but some are the result of infections, allergies or environmental factors. They are most often chronic and disabling, requiring lifelong treatment.

In order to stimulate research and development of treatments for orphan diseases, the United States (Orphan Drug Act of 1983) and the European Union have introduced specific legislation, with the establishment of a centralized procedure for the designation of drugs, incentives such as the waiver of registration fees, exclusivity on the market following authorization by the Union (10 years in Europe and 7 years in the United States), scientific assistance for the MA files, requirements during clinical studies adapted to the restricted patient population, granting of subsidies, specific procedures for reimbursement requests, etc.

Given the facilities offered by orphan drug status, and the targeted indicators, the company aims to obtain this designation for the products developed. For example, ADV1703 obtained this status in Europe for the cystinuria indicator in 2019 and for the dRTA indicator in 2017 in Europe (waiver of the status in 2021 to avoid having to conduct new clinical trials and thus accelerate the marketing of Sibnayal®, applications underway in the United States.

Advicenne does not limit itself to the use of a single formulation technology but uses "state-of-the-art" galenic approaches that are best adapted to the physicochemical characteristics of the active ingredients (APIs), their ADME (Absorption - Distribution - Metabolism - Excretion) profile, the indicator and target population. Advicenne's mission is not to develop new formulation technologies or new excipients for which regulatory registration would be long and costly, but to develop treatments adapted to pathologies (orphan diseases) or to populations that are not well addressed (children, the elderly, etc.), involving specific problems.

Strategy and Positioning

Business model

The company's development work is based on existing molecules (off-patent active ingredients that are free to be used); innovations that allow the company to take out a patent are made either in the indicator or in the formulation or are the result of combining several molecules.

Advicenne uses and develops, if necessary, new statistical tools, meta-analysis and data modeling/simulation approaches to partially overcome the constraints of clinical studies in children: duration of exposure to the product, invasive acts such as blood sampling, limited procedures. All these new techniques help extrapolate efficacy and safety data in the target population from data obtained in adults or in groups of children of different ages.

Main components of the business model:

- Differentiated distribution vectors: willingness to set up a sales force in France and the United Kingdom, agreements with distribution partners, particularly in key countries in Europe (Germany, Italy and Spain), the United States and the rest of the world (agents or distributors). Rapid commercial deployment thanks to the targeting of niche markets with a limited number of reference hospitals (15 to 20 centers specialized in nephropediatrics in France for example) and powerful patient associations.
- Licensing/distribution agreements for drugs that meet needs identified by clinicians and whose development is finalized (Levidcen and Likozam, for example). These agreements complete the company's product portfolio and accelerate economies of scale. The products are registered through the Mutual Recognition Process or the decentralized registration procedure. Some of these products may also benefit from a Temporary Use Authorization (ATU) allowing early access to the French market.
- A fully outsourced manufacturing process with leading manufacturers, allowing great cost flexibility.

Since 2013, Advicenne has had pharmaceutical operator status, enabling it to file temporary use authorizations (ATU), which provide earlier access to the market, and to market the products in its portfolio in France. The MA (Marketing Authorization) is obtained under PUMA (Paediatric Use Marketing Authorization) or orphan status.

Given the choices made in terms of research, clinical studies and marketing, the Group has been able to carry out its development programs until it obtains marketing authorization and brings certain products to market with a small team: 20 to 25 people to date, 50% of whom work in the R&D department.

Main areas of expertise

Proximity to clinicians

Since its creation, Advicenne has developed close ties with clinicians who are in contact with patients on a daily basis. The company organizes numerous working meetings with them.

This atypical approach has made it possible to establish bonds of trust between Advicenne's development team and clinicians, and to share both their pediatric treatment issues and the constraints of industrial developments to provide pragmatic and rapid responses to their medical needs.

Advicenne has learned to work with many neuropediatricians and nephropediatricians. The company has thus become a privileged industrial partner for the development of any new product in their field.

Regulatory expertise

The regulatory strategy is integrated into all new projects from the outset to set up short, efficient development phases that are accessible to a lean structure such as Advicenne. This strategy also aims to obtain PUMA or orphan drug protection and seeks to enhance the value of the innovative therapeutic solutions proposed by Advicenne to prove their added medical value and negotiate attractive sales prices.

All the company's development plans have been evaluated and approved by the EMA or ANSM scientific advisory committee and/or the EMA pediatric committee.

Project coordination expertise

For all projects, preclinical and clinical studies as well as all formulation, production and control operations are subcontracted to quality partners all based in Europe and in the US, audited and qualified by Advicenne, and the local authorities.

Advicenne has acquired genuine expertise in the coordination of development projects for pediatric and/or orphan drugs. The company's highly flexible structure ensures that project managers, experts in their field, have a global vision of the constraints of the entire development chain for a new product: patient needs, pharmaceutical development, clinical development, regulatory constraints, pricing policy and financing.

This approach has created efficient and highly responsive interfaces and interactions between Advicenne's various departments, which is essential to the success of such projects.

Clinical expertise

Pediatric pharmaco-clinical development is different from development in adults, particularly in very young children. For ethical reasons (the number of children exposed, the duration of exposure to the product under investigation, invasive acts such as blood sampling and all procedures defined in the study protocol must be limited

To overcome these constraints, Advicenne uses and develops, if necessary, new statistical tools, meta-analysis and data modeling/simulation approaches. All these new techniques help extrapolate efficacy and safety data in the target population from data obtained in adults or in groups of children of different ages.

On the other hand, special attention is required when conducting pharmacokinetic studies in children. Indeed, a specific characteristic of very young children is the rapid maturation of drug metabolism functions by certain organs. Therefore, dose adjustment may be necessary depending on the age of the patient and based on the individual level of maturation of organ functions.

For ethical reasons, in all its clinical developments Advicenne seeks to minimize the number of children exposed, the duration of exposure to the drug under investigation and invasive procedures such as blood sampling. All studies comply with European Good Clinical Practices.

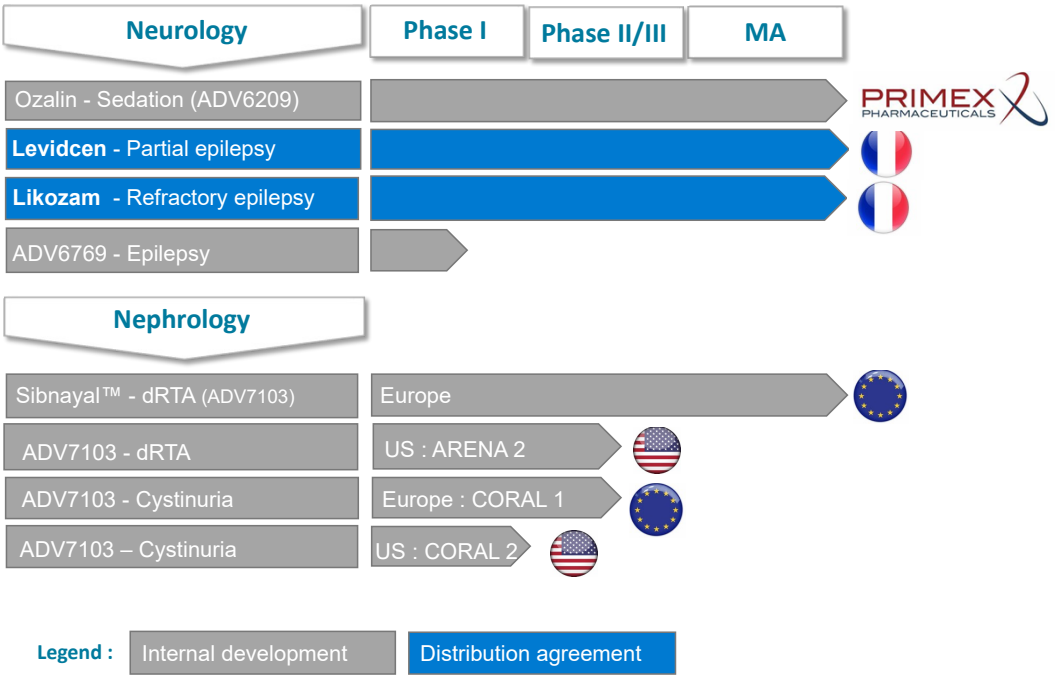
Thanks to the deployment of its expertise, since its creation, Advicenne has obtained:

- 3 ATUS ;
- orphan drug status in Europe for two of its products ;
- 2 agreements to distribute products in France (Levidcen with Desitin and Likozam with Rosemont Pharmaceutical);
- 2 marketing authorizations: Ozalin® (MA in 2018, license transferred to Primex in 2016) and Sibnayal® (MA mid-2021 in Europe and in the UK);
- reimbursement of 3 products ;
- 1 license agreement with Primex to market Ozalin® ;
- 4 distribution agreements to market Sibnayal® (direct sales in France and the UK).

The business model's flexibility allows the group to have a portfolio and a product pipeline that is already relatively well supplied, and which should continue to be enriched by new developments over the coming years.

Product range and current research programs

Graph 2: Summary of the product portfolio



Source: Advicenne

Neurology

Thanks to agreements signed in 2014, the group has an exclusive right to distribute Levidcen (Advicenne's registered trademark, Levetiracetam Desitin® for Desitin) and Likozam (Rosemont Pharmaceutical) on the French market. These two products currently account for most of the company's revenue: €2.7m in 2021 and €2.1m in 2022, or total revenues at 3,3 M€ after 2,7 M€ in 2022.

Levidcen®

The group obtained marketing authorization in France for Levidcen® (coated granules of 250 mg, 500 mg, 750 mg, 1,000 mg of the molecule Levetiracetam under license from Desitin) in October 2014 (decentralized procedure), and reimbursement in 2015 (65% rate). The small size (2 mm) of these granules makes them easy to swallow, especially for young children or the elderly. The HAS Commission considered that the medical service rendered (SMR) by Levidcen® is important in the indicators of the MA. Given that it is a new galenic form of an existing molecule, and not a new chemical entity that has demonstrated clinical superiority over the reference drug in clinical studies, Levidcen® has been granted an ASMR V (no improvement in medical service rendered) by the HAS.

Graph 3: Levidcen®

Source: Advicenne

Levidcen® is prescribed as monotherapy for the treatment of partial epilepsy seizures with or without secondary generalisation in adults and adolescents 16 years of age and older with newly diagnosed epilepsy. Levidcen® is to be used in combination with:

- in the treatment of partial seizures with or without secondary generalization in adults, adolescents, children and infants from 1 month of age with epilepsy
- in the treatment of myoclonic seizures in adults and adolescents aged 12 years and older with juvenile myoclonic epilepsy
- in the treatment of primary tonic-clonic generalized seizures in adults and adolescents aged 12 years and older with idiopathic generalized epilepsy

Likozam®

In 2014, the group obtained a Temporary Use Authorization for Likozam® in France (1mg/mL oral suspension of clobazam with graduated syringe) for the treatment of simple or complex partial epilepsies and resistant generalized epilepsies, when other appropriate combinations have proved ineffective or poorly tolerated, in children, as well as in adults with swallowing difficulties, in combination with another antiepileptic treatment.

Likozam® obtained its marketing authorization on February 10, 2016 (decentralized procedure) in various indicators. Likozam® is indicated in adults for the short-term (2-4 weeks) symptomatic treatment of severe anxiety, which is incapacitating or causes unacceptable distress. Likozam® should not be used for more than 4 weeks. Long-term chronic use as an anxiolytic is not recommended.

Graph 4: Likozam®

Source: Advicenne

In its opinion issued on 21 September 2016, the HAS Transparency Commission considered that the medical service rendered (SMR) by Likozam® was significant regarding the:

- short-term symptomatic treatment of severe, disabling or unacceptably distressing anxiety, including anxiety states associated with affective disorders
- treatment of partial or generalized epilepsy, in combination with another antiepileptic treatment in adults or children over 2 years of age, in case of failure of two consecutive monotherapies

On the other hand, the commission considered that the medical service rendered by Likozam® was insufficient in the short-term symptomatic treatment (2-4 weeks) of excitement and agitation in patients suffering from schizophrenia or other psychotic disorders for reimbursement by national solidarity.

The reimbursement rate proposed by the HAS is 65%. Advicenne has initiated discussions with the competent authorities in France with a view to obtaining the price of Likozam®. Since the Company obtained marketing authorization for Likozam® in France, the marketing of this drug has entered a transitional regime known as "post ATU". As such, until the decision regarding the reimbursement of Likozam® is made, the Company is authorized to market this drug at a price that it freely sets. However, if the final reimbursement price set by the regulatory authorities is lower than the price set by the Company, the Company will be required to reimburse the difference, which could be substantial, depending on the final price and the time required to obtain the decision. As a matter of prudence, the Group provides each year for a portion of the revenues generated by Likozam® and includes in the accounts only the net sales, after provision. For FY 2021, revenue from products marketed by the group reached more than €3.3m for a consolidated net turnover of nearly €2.7m, for a provision of around €600k (recorded in other current liabilities on the balance sheet, which amounted to approximately €2m at the end of June 2022).

Ozalin® - ADV 6209: Moderate sedation

Ozalin® is a liquid formulation of midazolam 2mg/ml (benzodiazepine) for oral administration specifically developed to mask its bitterness (suitable for children). This product is the result of a collaboration with the University Hospital of Amiens.

Graph 5: Ozalin®

Source: Advicenne

After conducting and completing the clinical development of the drug candidate ADV6209 (Ozalin®), the company sold it to Primex Pharmaceuticals in 2016 (€7M received to date and royalties on future sales). The first positive notifications (decentralized procedure launched in 2016) were obtained as early as September 2018 (France, UK, Italy, Netherlands, Norway, Denmark, Sweden and Finland). In February 2020, Primex Pharmaceuticals announced that it had obtained marketing authorization in eight new European countries: Germany, Austria, Spain, Portugal, Ireland, Belgium, Greece and Poland.

The product has been commercially launched by Primex or its partners in certain countries. Indeed, to facilitate access to the product in certain territories, Primex has signed agreements with local distributors such as POA Pharma (Denmark, Finland, Norway, Sweden), Nordic Pharma (France) or Sintetica for the UK.

However, the commercial launch of Ozalin® was significantly penalized by the COVID-19 epidemic, with many countries suspending surgical procedures deemed non-priority. In this unfavorable context, the group did record the first royalties in fiscal year 2020, and then 2021, on Ozalin®, but for only €73k and €19k respectively (recorded in partnership revenues). In the original 2016 agreement, the partnership anticipated total revenues of €40m by 2025 (including milestones and royalties). With only €7m received to date (mainly in milestones: upfront and obtaining the MA), Advicenne is expected to receive close to €33m by 2025 thanks to the Primex contract.

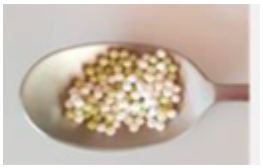
Other research projects in neurology

In addition to the products presented, the group has selected and is already studying complementary products, such as the ADV6769 project, a pediatric formulation of an anti-epileptic drug, developed for the treatment of certain severe partial epilepsies and epilepsies with rolandic paroxysms that do not respond to conventional anti-epileptic treatments. Other projects could be under study, and thus feed the product pipeline for the coming years.

Nephrology

ADV7103 is a product in the form of mini-tablets (2mm particularly adapted to children) with prolonged release combining two alkaline salts for which the kinetics of release were optimised to maximize their absorption and their duration of action: potassium citrate (prolonged release of 3 hours) and potassium bicarbonate (prolonged release of 12 hours) for the treatment of renal tubulopathies.

Graph 6: ADV7103



144 granules

432 granules

Source: Advicenne

The innovative formulation has a triple advantage:

- it is tasteless and easy to swallow by young children
- there is a reduction of gastric side effects
- the posology is 2x/day for 24-hour effectiveness

This last point is important because current products do not effectively cover the entire sleep period, requiring patients to take the treatment in the middle of the night (waking up twice a night), which in practice is difficult to follow, especially for children, leading to risks of delayed growth. A gradual release of the active ingredient during the night allows the treatment to be effective until the patient wakes up, without any additional burden for the patient.

Advicenne targets two orphan applications: cystinuria and distal renal tubular acidosis (dRTA), for which studies are already well advanced.

AD7103-dRTA

In the field of ATLD, following the ARENA 1 study, ADV7103 was approved by the EMA (European Medicines Agency, MA for Europe and the United Kingdom) in mid-2021 under the brand name SIBNAYAL® (no protection linked to orphan drug status, but patents until 2031 and supplementary protection certificates currently under review to increase intellectual property protection to 2036). This study demonstrated its efficacy on the main biological disorders caused by the disease and confirmed its acceptability for the pediatric target. According to the protocol, the efficacy of ADV7103 was shown to be equivalent to currently used treatments and its superiority over the latter was established by additional statistical analyses. No other drug has been approved by regulatory authorities for the treatment of ATRd, regardless of its form (genetic or acquired). Sibnayal® (ADV7103) is thus the only drug approved for the treatment of ATRd in Europe but is also the only one in advanced clinical development for ATRd in the United States. The target population (children aged 6 months and older and adults) in this indicator is approximately 30,000 patients in Europe and 20,000 in the United States (genetic ATRD and the best characterized acquired forms).

Advicenne has since entered into partnerships with three companies for the marketing of SibnayalTM in Europe: FrostPharma AB for the Nordic countries (Jan. 2022), TwinPharma for the Benelux countries and ExCEEd Orphan for Central and Eastern European countries (Dec. 2021); and (Dec. 2021); and with a company Taïba Healthcare (June 2022) for distribution in certain Middle Eastern countries (Saudi Arabia, Oman, United Arab Emirates, Qatar, Kuwait, and Bahrain) through an early availability program.

Sales of Sibnayal® in Europe should fuel the group's growth from 2022 onwards (post ATU status, 65% reimbursement rate and sales price under negotiation). The first industrial production batches of Sibnayal® have been made with Elaiapharm (a French company specialised in the manufacture of pharmaceutical preparations).

In December 2021, the company received the final opinion of the Transparency Commission of the French National Authority for Health: eligibility for reimbursement, obtaining a SMR (Medical Service Rendered) of Moderate level and obtaining an ASMR (Improvement in Medical Service Rendered) of level IV for Sibnaya® (65% reimbursement rate), in the treatment of Distal Renal Tubular Acidosis (DRAA) in adults, adolescents and children over 1 year old. Negotiations to set the price of the drug in France are still ongoing, as are the reimbursement rates and accepted prices in most European countries (negotiations led by distributors). For the United Kingdom, the company obtained reimbursement from the Scottish authorities for Sibnayal® last September. Negotiations are still ongoing for the United Kingdom, but do not hinder the marketing of the product (hospital by hospital agreement).

The positive results of the European study have enabled the company to launch a pivotal II/III clinical trial of ADV7103 for ATRd in the United States (ARENA 2 study) at the end of 2018, for which the Company has obtained IND (Investigational New Drug) status from the FDA and approval from Health Canada to expand patient recruitment in Canada. Two people have been recruited in the United States to supervise and direct the conduct of this study and future developments in that country. The FDA has accepted the modified protocol for the pivotal Phase III trial.

ARENA-2 is a Phase III, prospective, multicenter, randomized, double-blind, pivotal clinical trial to include 32 patients in the United States and Canada. The primary objective is to evaluate the safety and efficacy of ADV7103 versus placebo in preventing the development of metabolic acidosis in children (aged 6 months to 18 years) and adults (aged 18 to 65 years) with primary ATRd. As for the European study, an extension study is planned to measure the effects of the treatment over time (24 months).

Enrollment of the first patient in this Phase III study occurred in the third quarter of 2019. The COVID-19 pandemic led to the temporary suspension of the study. Given the difficulty of following up patients in hospital, which is still the case at present, particularly for children, the Group has made changes to the protocol in order to be able to follow up patients at home and has finalized the technical elements necessary for these adjustments, such as the selection of personnel authorized to collect samples, the validation of the equipment used to ensure the integrity of the samples, and the central laboratory that will be in charge of analyzing the samples and the data obtained. All these elements have been given the green light by the FDA, and the group is examining the timetable for resuming recruitment, which we believe will probably be at the end of 2022 or beginning of 2023.

Obtaining reimbursement in the first countries where the group has distribution agreements and concluding new agreements should enable the group to complete its coverage of European countries, and even beyond (first agreement in the United States), and thus probably accelerate revenues from Sibnayal®. In addition, as the ARENA 2 study in the United States is well advanced, we believe that the group could obtain marketing authorization for the North American market by 2024.

Cystinuria – ADV7103

Based on the dRTA Phase I clinical study that demonstrated the safety of ADV7103, Advicenne is preparing Phase II/III studies in cystinuria: CORAL 1 study in Europe and CORAL 2 in the US. The group obtained a protocol authorization from the ANSM as early as April 2018, obtaining orphan drug designation from the EMA for ADV7103 in the treatment of cystinuria in December 2019 (application in progress for orphan drug designation in the United States, filing in 2021, request for additional information from the FDA).

The clinical program entitled CORAL includes, as for dRTA, several studies: the main study (the latter study concerns only young children aged between 6 months and 5 years inclusive) and an extension study to assess the long-term safety of ADV7103 (52 and 78 weeks). The CORAL 1 study for Europe was initiated and the first patients were enrolled, but due to the health crisis, it was stopped. The protocol of the CORAL1 study is currently being reviewed to see to what extent it can be modified to optimize the conduct of this study and the recruitment of patients, which could be carried out in partnership with a hospital, for example. The CORAL2 Phase II/III study, which aims to address the United States, has not yet been launched.

In the field of cystinuria, the orphan drug designation in Europe should accelerate the research and regulatory phases (less costly development, orphan drug file in progress in the United States), and the MA could be obtained, according to us, by 2024 in Europe and 2025-26 in the United States (launch of phase II/III estimated for late 2024-early 2025). Although the Coral 1 and 2 studies are less advanced than the dRTA projects, they nevertheless benefit from the results of the latter, particularly in terms of (limited) side effects, which could, if successful, offer real alternatives to patients suffering from cystinuria, given the cumbersome nature of current therapeutic solutions and the sometimes very serious side effects of treatments, particularly for children.

Although Covid has slowed down developments (clinical, commercial, etc.), the group has nevertheless managed to sustain double-digit growth in its activity. Given a stabilizing health situation and the advancement of the product pipeline, we believe that the group could experience a strong acceleration in revenues as early as 2022, which should be confirmed in the following years.

Activity Levels That Should Confirm a Takeoff

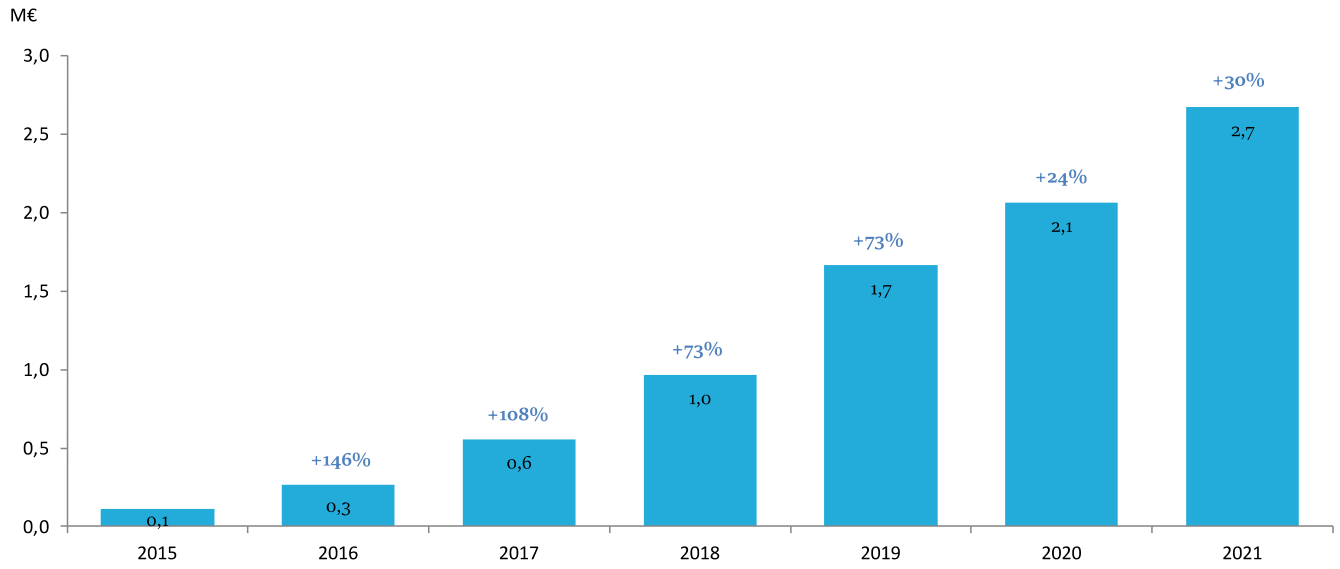
Already significant revenue that is rising sharply

Constantly growing revenue

Thanks to the granting of marketing authorizations for Levidcen in 2014, Likozam in 2016, and Sibnayal in 2021 (delayed by the health crisis), the group has been recording sales for several years, and this has been growing steadily, even if the health crisis has slowed the pace somewhat in 2020 and 2021.

The group has thus generated sales of nearly €2.7m in 2021 (net of provisions, price difference between the post ATU sales price and the sales price that could be authorized by the health authorities, amounting to a €3.3m gross), including €1.7m linked to the licensing agreements for Levidcen and Likozam, and €1m linked to Sibnayal, for which marketing authorization was obtained mid-year (post ATU status, 65% reimbursement obtained, sales price under negotiation). Cumulatively since 2015, the group has thus generated €8.3m in revenue.

Graph 7: Consolidated revenue trends



Source: Advicenne

Other significant revenue

In addition to gross revenue, the group benefits from other income sources, including:

- Tax credits (nearly €6.2m in cumulative since 2015), mainly in the form of research tax credits for about €1m/year given the investments made in R&D programs.
- Royalties (more than €7m in total since 2015) corresponding to the sale of Ozalin (moderate sedation) to Primex, which has made payments at certain milestones (in 2016, 2017 and 2018) and royalty payments (share of sales), which are still low, as distribution of the product has been penalized by the health crisis.

Table 1: Other revenue trends

K€	2015	2016	2017	2018	2019	2020	2021
Tax credit*	491	638	877	842	851	1 430	1 061
Fees	0	909	1 091	5 000	0	73	19
Subsidies	211	78	4	111	61	0	0
Others	4	0	43	8	9	0	17
Total Other revenues	**706**	**1 625**	**2 015**	**5 961**	**921**	**1 503**	**1097**

*CIR, CICE, CI

Source: Advicenne

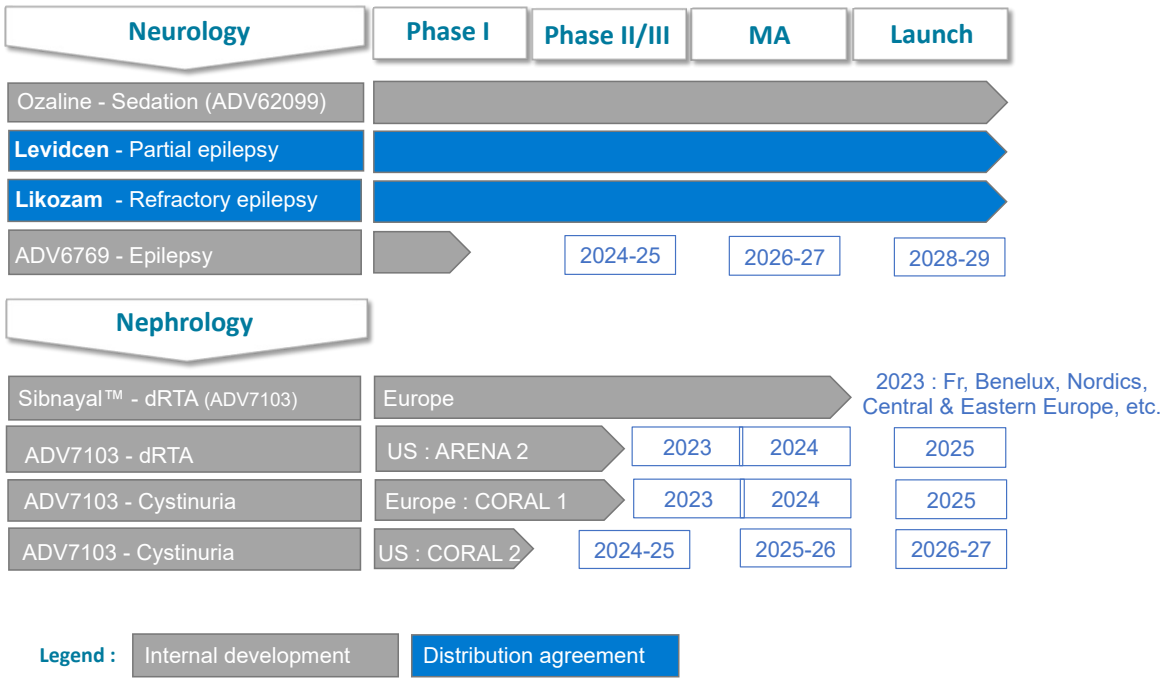
Overall, cumulative other income earnings since 2015 have amounted to nearly €14m.

Confirmation of a Historic Sales Take-Off with New Launches Planned

In terms of earnings, the group will continue to benefit from:

- the rise in sales of Levidcen and Likozam
- a growing contribution from Sibnayal® :
  - direct sales (75 hospitals/centers already addressed): obtaining reimbursement for Sibnayal® in France and Scotland (marketing price under negotiation), and deployment underway in the UK
  - the roll-out of distribution agreements signed at the end of 2021 and beginning of 2022 with FrostPharma AB for the Nordic countries (Jan. 2022), TwinPharma for the Benelux countries and ExCEEd Orphan for the Central and Eastern European countries. (Dec. 2021) Taïba Healthcare (June 2022) for selected Middle Eastern countries (Saudi Arabia, Oman, United Arab Emirates, Qatar, Kuwait, and Bahrain) through an early availability program
  - the signature of new distribution agreements in Europe (Southern Europe, Germany, etc.)
- time-sequenced new market introductions:
  - ADV7103 dRTA in the United States, estimated end of 2024, and commercialisation from 2025
  - ADV7103 cystinuria in Europe MA estimated for end of 2024, and commercialization from 2025
  - ADV7103 cystinuria in the United States MA estimated for 2025-2026, and commercialization from 2026-2027
  - ADV6769 epilepsy : MA, re-launch of studies estimated in 2024-2025

Graph 8: Product pipeline forecasts



Sources: Advicenne, TPICAP Midcap

Revenue forecasts

Revenue growth expected to accelerate

After a year 2020 marked by the effects of the health crisis, the growth in sales of licensed products in France (levidcen and likozam) resumed in 2021 and should be confirmed, and sustain a double-digit growth rate.

For proprietary products, since distribution agreements in Europe were obtained at the very end of 2021 for Sibnayal® (ADV7103 in Europe), and reimbursement rates are still being negotiated, activity should only just take off in 2022, and the momentum should be confirmed the following years with the gradual opening of all European countries. Given the developments underway in the United States, we do not expect a significant contribution from North America before 2025 (see valuation section for details of forecasts by geographic area).

In the cystinuria indicator, the European launch (post-CORAL 1 study) is scheduled for 2024, which should generate post-UTA revenues, and then more significant revenues from 2025 onwards (time to deploy a distribution network and obtain price/reimbursement levels). For the North American zone, the CORAL 2 study being slightly less advanced, we anticipate revenues by 2026 (see the valuation section for details of forecasts by geographic zone).

For the other indicators/research areas, at this stage we do not anticipate any revenues within 4-5 years.

Table 2: Summary of revenue trends

M€	2020	2021	2022E	2023E	2024E	2025E
Licence (Levidcen, Likozam)	1,2	1,7	2,0	2,4	2,8	3,0
Chg	-	40%	20%	20%	15%	10%
ADV7103 dRTA	0,8	1,00	1,37	1,8	2,9	4,3
Chg	-	25%	37%	x1,3	x1,7	x1,5
o/w Direct distribution	*0,8*	*1,0*	*1,35*	*1,71*	*2,70*	*3,50*
*o/w Indirect distribution**	-	-	*0,01*	*0,06*	*0,22*	*0,78*
ADV7103 Cystinuria	-	-	-	-	0,0	0,7
Chg	-	-	-	-	-	-
o/w Direct distribution	-	-	-	-	*0,00*	*0,66*
*o/w Indirect distribution**	-	-	-	-	*0,00*	*0,02*
Others	-	-	0,0	0,0	0,0	0,0
Total consolidated sales	**2,1**	**2,7**	**3,4**	**4,2**	**5,7**	**8,0**
Chg	**24,0%**	**29,5%**	**26,2%**	**23,7%**	**36,3%**	**40,7%**
Total sales of products	2,7	3,3	3,9	5,2	8,2	14,5
Chg		22,2%	18,3%	32,2%	59,3%	76,7%

*Transfer pricing margin under IFRS

Sources: Advicenne, TPICAP Midcap

Overall, our revenue forecast is for a double-digit increase to €3.4m for 2022. In our opinion, trend should be confirmed in the following years with the contribution of Sibnayal®'s distribution in Europe (increasing power of direct distribution, distribution agreements and via extension of the network), with the North American zone and the cystinuria indicator as a relay. We are expecting revenue of nearly €8.0m in 2025.

It should be noted that due to the choice of indirect distribution and the accounting implications, only the margin on transfer prices is included in consolidated sales and not total sales, and royalties are included in other revenues. The potential revenue generated by the portfolio products is much higher: more than €14m expected by 2025. In addition, due to the delays linked to studies and regulations, the Cystinuria indicator only becomes significantly contributive by 2026-2027 in our scenario (details of activity forecasts by indicator and by geographic area are presented in the valuation approach).

Other revenue that should continue to make a significant contribution to results

While we expect R&D investments to be maintained, as clinical studies are to be conducted in part on the US market, we anticipate a reduction in the CIR to €0.7m/year for the coming years (€1m in previous years).

The product Ozalin® (moderate sedation) has been launched commercially by Primex directly or through partners in some countries such as POA Pharma for the Nordic countries (Denmark, Finland, Norway, Sweden), Nordic Pharma (France) or Sintetica for the UK. Thanks to these agreements and the reduction of the effects of the health crisis (return to a more normal rhythm of surgical procedures), sales of Ozalin® should probably accelerate in the coming years, and thus the royalties received by the Group (share of sales). The asset transfer agreement foresees a minimum revenue of €33m over a period of 7 years (i.e. by 2025, as the marketing authorization was obtained in 2018 in most countries). As a precaution, and as it is difficult to anticipate the ramp-up of Ozalin® sales (in the hands of Primex and its partners), we have anticipated a slight increase in Primex royalties: €100K expected in 2022, €250K in 2023, €500K in 2024 and in 2025 the balance to reach the €33m minimum revenue, amounting to €32.15m.

Regarding royalties to be received on distribution contracts, the amounts are expected to grow in parallel with the opening of countries for the dRTA indicator, in particular the American market from 2024 (MA) and 2025 (market launch). For cystinuria, given the time needed to finalize the clinical studies, we do not expect a significant contribution in terms of royalties before 2026.

Table 3: Forecasted changes in Other revenue

K€	2017	2018	2019	2020	2021	2022E	2023E	2024E	2025E
Tax credit*	877	842	851	1 430	1 061	700	600	500	500
Fees	1 091	5 000	0	73	19	109	284	632	32 553
O/w Ozalin/Primex	*0*	*0*	*0*	*0*	*0*	*100*	*250*	*500*	*32 150*
O/w dRTA	*0*	*0*	*0*	*0*	*0*	*9*	*34*	*132*	*390*
O/w Cystinurie	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*13*
Subsidies	4	111	61	0	0	0	0	0	0
Others	43	8	9	0	17	0	0	0	0
Total Other revenues	**2 015**	**5 961**	**921**	**1 503**	**1097**	**809**	**884**	**1 132**	**33 053**

*CIR, CICE, CI

Source: Advicenne

Losses Under Control

Results impacted by research investments

Historic results

Thanks to favorable product mix effects (increased sales of Sibnayal®), the MB/Sales ratio increased significantly in 2021 to 63.6%, allowing to generate a 44% growth of the gross margin for a sales increase of only 29%.

While the group benefited from the increase in gross margin and revenue related to other income, over the last three years, the acceleration of research programs (ADV7103 studies on different indicators and territories) led to an increase in R&D costs (x2, expensed) and the structuring of the company to support the regulatory, production and marketing phases led to an increase in administrative and commercial costs (x2), and thus to a deepening of operating losses over the last three years: -€14.2m in 2019, -€14.1m in 2020 and -€12.4m in 2021, compared to -€5.9m in 2017 and -€5.2m in 2018.

Table 4: Historic operational trends

M€	2015	2016	2017	2018	2019	2020	2021
Sales	**0,1**	**0,3**	**0,6**	**1,0**	**1,7**	**2,1**	**2,7**
Change	**-**	**146%**	**108%**	**73%**	**73%**	**24%**	**29%**
Charges	0,0	-0,1	-0,3	-0,5	-0,7	-0,9	-1,0
Gross Profit	**0,1**	**0,2**	**0,2**	**0,5**	**1,0**	**1,2**	**1,7**
% of sales	**59,6%**	**63,1%**	**43,6%**	**50,8%**	**58,4%**	**57,0%**	**63,6%**
G&A et commercial expenses	-1,1	-1,6	-3,3	-4,5	-7,4	-8,4	-6,0
O/w Commercial expenses	*-0,7*	*-1,0*	*-1,8*	*-2,3*	*-3,4*	*-4,6*	*-4,5*
O/w G&A	*-0,4*	*-0,7*	*-1,5*	*-2,2*	*-4,0*	*-3,8*	*-1,6*
R&D expenses CIR excl.	-3,1	-3,2	-4,9	-7,1	-8,5	-8,0	-8,8
Others revenues	0,7	1,6	2,0	6,0	0,9	1,5	1,1
O/w Fees	*0,0*	*0,9*	*1,1*	*5,0*	*0,0*	*0,1*	*0,0*
O/w CIR	*0,5*	*0,6*	*0,9*	*0,8*	*0,9*	*1,4*	*1,1*
EBITDA	**-3,4**	**-3,1**	**-5,9**	**-5,2**	**-14,0**	**-13,7**	**-12,0**
Depreciation and amortisation	-0,1	-0,1	-0,1	-0,1	-0,2	-0,4	-0,4
EBIT	**-3,4**	**-3,2**	**-6,0**	**-5,3**	**-14,2**	**-14,1**	**-12,4**
Financial result	-0,2	-0,4	-0,1	0,3	0,1	-0,7	0,0
NP	-3,6	-3,6	-6,1	-5,0	-14,2	-14,8	-12,3

Source: Advicenne

In view of the losses, the group regularly has recourse to external financing, whether through capital increases or debt financing.

Regular financing needs

Due to its positioning: use of CROs for the research stages, outsourced production, and distribution largely via partnerships, and commercial phases still in their early stages, capex and WCR have historically been quite low. Overall, over the last 5 years, the group has generated a negative FCF of €10m.

Table 5: Historic cash flow statement

M€	2015	2016	2017	2018	2019	2020	2021
Cash flow	-3,2	-3,0	-5,0	-4,5	-13,3	-13,6	-11,8
Capex	-0,2	0,0	-0,3	-0,1	-0,9	-0,6	-0,3
Change in WCR	0,5	3,0	-0,8	-5,7	3,8	1,9	-0,7
FCF	**-2,9**	**0,0**	**-6,1**	**-10,3**	**-10,4**	**-12,3**	**-12,8**
Disposals	0,0	0,0	0,0	0,1	0,0	0,0	0,0
Financial invesments	0,0	0,0	0,0	0,0	-0,1	-0,1	-0,1
Dividends	0,0	0,0	0,0	0,0	0,0	0,0	0,0
Others	0,0	0,0	0,0	0,0	0,0	0,0	0,0
Cash excess (deficit)	**-2,9**	**0,0**	**-6,1**	**-10,2**	**-10,5**	**-12,3**	**-12,9**

Source: Advicenne

Thanks to the fundraising carried out pre-IPO and at the time of the IPO in 2017, the financing obtained from the EIB and a private placement carried out in the summer of 2021, the group's financial health has remained strong, despite the increase in operating losses.

An ability to attract investors

Since the creation of the company, management has proven its ability to attract investors. Main historical fundraising events:

- 2007: €125k at the company's creation
- 2008-20212: First round of fundraising: €0.9m in total from private investors
- 2011: Second round of financing of €5.1m in two tranches (2011 and 2013) from InnoBio (BPI) and IXO Private Equity funds and private individuals
- 2013: Third round of financing of €3.8m from the historical funds
- 2015: Issue of convertible bonds for €2.5m
- 2017: Fourth financing round of €15.8m (at €14.88/share) completed with historical investors and entry of new investors (Irdi Soridec, Cemag Invest, etc.) and conversion of bonds for €3.1m and fundraising of €27.8m at the time of the IPO completed in December (at €14.03/share, including exercise of the over-allotment option completed over Dec. 2017-Jan. 2018)
- 2019 and 2020: Nearly €1.7m raised via the exercise of historical BSPCEs and BSAs (at €3.22/share)
- 2021: Raised €9.4m net via private placement (at €7.14 per share) and 0.3 M€ via exercise of BSPCE and historical BSA (at €3.22/share)

Overall, the company has raised just over €68m since its creation. BPI Investissement, which has supported the company since 2011, is the largest shareholder with 22.6% of the capital at the end of 2021. IXO Private Equity, which had entered the capital in 2011, also followed the pre-IPO and IPO financing rounds, but started to reduce its position from 2020, to hold only 7.7% at the end of 2021. During the pre-IPO and IPO rounds, new institutional investors entered the capital such as Cemag Invest and Irdi Soridec, whose stake in terms of number of shares has remained relatively stable since then, but whose weight in the capital has been reduced through dilution during the fundraising rounds carried out since then to 7.5% and 4.4% of the capital respectively. DNCA became a new shareholder in the July 2021 private placement (1.9% of the capital). Finally, due to managerial changes in recent years, the holdings of certain individuals have been significantly reduced or have even led to a total withdrawal from the company's capital, such as Luc-André Granier (co-founder and CEO), Caroline Roussel (co-founder and former CEO), Ludovic Robin (former CEO) and Françoise Brunner-Ferber (former independent director).

Table 6: Main changes in capital distribution

	31/12/16		Avant IPO		31/12/17		31/12/18		31/12/21	
	No of shares	% capital	No of shares	% capital	No of shares	% capital	No of shares	% capital	No of shares	% capital
BPI Investissement	1 552 800	40,1%	2 083 005	32,6%	2 249 568	28,1%	2 249 568	27,9%	2 249 568	22,6%
Cemag Invest	10 000	0,3%	540 505	8,5%	748 064	9,3%	748 064	9,3%	748 064	7,5%
Irdi Soridec Gestion	-	-	411 140	6,4%	435 511	5,4%	431 947	5,4%	435 511	4,4%
Charlotee Sibley	-	-	0	0,0%	0	0,0%	0	0,0%	0	0,0%
Hege Hellstrom	-	-	0	0,0%	0	0,0%	0	0,0%	0	0,0%
Catherine Guittet	-	-	-	-	-	-	-	-	101 778	1,0%
Nathalie Lemarié	-	-	-	-	1 069	0,0%	1 069	0,0%	-	-
Autres salariés	35 525	0,9%	43 195	0,7%	43 479	0,5%	43 479	0,5%	-	-
Luc André Granier	250 000	6,5%	250 000	3,9%	250 000	3,1%	250 000	3,1%	-	-
Caroline Roussel	140 000	3,6%	146 630	2,3%	146 885	1,8%	146 885	1,8%	-	-
Ludovic Robin	-	-	26 525	0,4%	28 971	0,4%	28 971	0,4%	-	-
Sub Total *	**1 988 325**	**51,4%**	**3 501 000**	**54,8%**	**3 903 547**	**48,8%**	**3 899 983**	**48,4%**	**3 534 921**	**35,5%**
IXO PE	802 280	20,7%	1 310 660	20,5%	1 462 082	18,3%	1 422 082	17,6%	769 802	7,7%
Marie-Odile Humblet	504 590	13,0%	593 965	9,3%	597 249	7,5%	597 249	7,4%	294 755	3,0%
Françoise Brunner-Ferber	218 745	5,7%	319 010	5,0%	317 393	4,0%	317 393	3,9%	104 799	1,1%
DNCA	-	-	-	-	-	-	-	-	191 071	1,9%
Autres flottants	98 540	2,5%	296 440	4,6%	1 351 775	16,9%	1 433 275	17,8%	4 669 567	46,9%
Jean-Pierre Lefoulon	258 800	6,7%	365 990	5,7%	370 650	4,6%	370 650	4,6%	362 332	3,6%
Total free float	**1 882 955**	**48,6%**	**2 886 065**	**45,2%**	**4 099 149**	**51,2%**	**4 140 649**	**51,4%**	**6 392 326**	**64,2%**
Treasury shares	-	-	-	-	-	-	21 712	0,3%	22 904	0,2%
Total	**3 871 280**		**6 387 065**		**8 002 696**		**8 062 344**		**9 950 151**	

* Employees, board members and committee members

Source: Advicenne

Additionally, the group has obtained financing in the form of:

- Reimbursable advances (€276k at the end of 2021): in 2019, the company took out a protection insurance policy with the BPI for prospecting expenses in Germany and the United Kingdom in the amount of €552k, of which €276k was received in H1 2019 (fixed amount of €83k to be reimbursed between Sept. 2024 and June 2025, with additional reimbursements depending on sales from Sept. 2024 onwards, to reach the maximum amount of the insurance policy.
- Of EIB loans (€7.5m at the end of 2021): in July 2019 obtained a loan agreement with the European Investment Bank for a total amount of €20m to finance the development of a portfolio of pediatric treatments for orphan renal and neurological diseases and, more specifically, of the drug candidate ADV7103 in the dRTA and cystinuria indicators. A first tranche of €7.5m was drawn in June 2020 (fixed rate not communicated but below 10%, interest paid partly annually, partly capitalized, repayment at term in 2025). Two other tranches can be drawn: €5m subject to conditions related to the company's activity and financing, and €7.5m subject to conditions specific to the ADV7103 product and its sales. In addition, the Company has undertaken to pay the EIB an additional annual remuneration based on sales starting on 31 January 2021 for a period of 9 years.
- State guaranteed loan (€4.3m at the end of 2021): in October 2021, as part of the measures put in place to enable companies to cope with the consequences of the health crisis, the group obtained two State Guaranteed Loans from BPI France (rate of 2.25%) and BNP Paribas (rate of 0.75%) for a total amount of €4.3m with a maturity of 5 years: first maturity in November 2021, last maturity at the end of 2026.

A still healthy financial situation

As a result of the fundraising, the group had a cash position of €12.7m at the end of 2021 (€7.3m at the end of June 2022). Due to the EIB loan and the EMP obtained in 2020, the net position has been reduced. However, as the maturities are still far away, the group is not faced with a debt wall.

Table 7: Main sources of financing and changes in net position

M€	2015	2016	2017	2018	2019	2020	2021
Cash excess (deficit)	**-2,9**	**0,0**	**-6,1**	**-10,2**	**-10,5**	**-12,3**	**-12,9**
Change in debt	3,0	-0,1	-0,1	-0,2	0,0	11,9	-0,2
Change in equity	0,0	0,0	40,8	0,4	1,0	0,6	9,0
Change in cash	0,1	-0,1	34,6	-10,0	-9,6	0,1	-4,1
Net cash	**-1,8**	**-2,2**	**35,5**	**25,8**	**15,0**	**3,0**	**0,1**
Cash available	1,6	1,6	36,2	26,2	16,6	16,8	12,7

Source: Advicenne

As the group continues its development efforts, we believe that in the coming years, even if revenues are expected to grow strongly, results are likely to remain negative, requiring the use of new external financing.

Results Forecast and Funding Requirements

Given the current structure of the group, and the development strategy (use of CROs, external firms, etc.) and commercial strategy (direct in France and United Kingdom), we estimate that administrative and commercial expenses should increase less rapidly than growth in results.

In terms of R&D, we believe that expenses should remain sustained (€8-9m range) to support ongoing studies (dRTA and cystinuria indicator) but also to continue to feed the product pipeline (epilepsy project, and other research areas).

The growth in revenues should thus enable us to initiate a reduction in losses from 2023 onwards, in our opinion, and to move into positive territory by 2027.

With a tax deferral of €76m at the end of 2021, and expected operating losses for the next few years, the group should not pay taxes for many years.

Table 8: Earnings forecasts

M€	2017	2018	2019	2020	2021	2022E	2023E	2024E	2025E
Sales	**0,6**	**1,0**	**1,7**	**2,1**	**2,7**	**3,4**	**4,2**	**5,7**	**8,0**
Change	**108%**	**73%**	**73%**	**24%**	**29%**	**26%**	**24%**	**36%**	**41%**
Charges	-0,3	-0,5	-0,7	-0,9	-1,0	-1,2	-1,4	-1,8	-2,1
Gross Profit	**0,2**	**0,5**	**1,0**	**1,2**	**1,7**	**2,1**	**2,8**	**3,9**	**5,9**
% of sales	**43,6%**	**50,8%**	**58,4%**	**57,0%**	**63,6%**	**63,8%**	**66,7%**	**68,7%**	**73,8%**
G&A et commercial expenses	-3,3	-4,5	-7,4	-8,4	-6,0	-6,5	-7,0	-7,5	-8,0
R&D expenses CIR excl.	-4,9	-7,1	-8,5	-8,0	-8,8	-8,0	-8,0	-7,5	-7,5
Others revenues	2,0	6,0	0,9	1,5	1,1	0,8	0,9	1,1	33,1
EBITDA	**-5,9**	**-5,2**	**-14,0**	**-13,7**	**-12,0**	**-11,5**	**-11,3**	**-10,0**	**23,5**
Depreciation and amortisation	-0,1	-0,1	-0,2	-0,4	-0,4	-0,4	-0,4	-0,4	-0,4
EBIT	**-6,0**	**-5,3**	**-14,2**	**-14,1**	**-12,4**	**-12,0**	**-11,8**	**-10,4**	**23,0**
Financial result	-0,1	0,3	0,1	-0,7	0,0	-1,0	-1,0	-1,1	-0,8
NP	-6,1	-5,0	-14,2	-14,8	-12,3	-13,0	-12,8	-11,5	22,3

Sources: Advicenne, TPICAP Midcap

The estimated operating losses during the period 2022-2024, combined with investments (equipment to produce ADV7103) and the increase in WCR linked to the growth of the activity, should lead to negative FCF of €43m, and thus require recourse to additional financing (debt or capital).

In terms of debt, in view of the research program advances, we estimate that the group could benefit from tranche 2 of the EIB loan, amounting to €5m by the end of the year (possible tranche 3 of €7.5m). The EMP should also start to be repaid from 2022, over a period of 4 years.

For the balance of the financing needs, for reasons of prudence, we have included an exclusively equity financing in our modeling (estimated cumulative €27m), spread over several fundraising rounds over the period 2022-2024. In 2025, the FCF generated by the activity should allow the group to repay the first tranche of the EIB loan.

Table 9: Cash generation / consumption forecasts

M€	2017	2018	2019	2020	2021	2022E	2023E	2024E	2025E
Cash flow	-5,0	-4,5	-13,3	-13,6	-11,8	-12,5	-12,4	-11,1	22,7
Capex	-0,3	-0,1	-0,9	-0,6	-0,3	-2,0	-0,5	-1,0	-1,0
Change in WCR	-0,8	-5,7	3,8	1,9	-0,7	-0,8	-1,2	-1,5	-2,0
FCF	**-6,1**	**-10,3**	**-10,4**	**-12,3**	**-12,8**	**-15,3**	**-14,1**	**-13,6**	**19,7**
Disposals	0,0	0,1	0,0	0,0	0,0	0,0	0,0	0,0	0,0
Financial invesments	0,0	0,0	-0,1	-0,1	-0,1	0,0	0,0	0,0	0,0
Dividends	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
Others	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
Cash excess (deficit)	**-6,1**	**-10,2**	**-10,5**	**-12,3**	**-12,9**	**-15,3**	**-14,1**	**-13,6**	**19,7**
Change in debt	-0,1	-0,2	0,0	11,9	-0,2	4,9	-0,8	-0,8	-8,3
Change in equity	40,8	0,4	1,0	0,6	9,0	9,0	9,0	9,0	0,0
Change in cash	34,6	-10,0	-9,6	0,1	-4,1	-1,4	-5,9	-5,4	11,4
Net cash	**35,5**	**25,8**	**15,0**	**3,0**	**0,1**	**-6,2**	**-11,3**	**-15,8**	**3,9**
Cash available	36,2	26,2	16,6	16,8	12,7	11,2	5,4	0,0	11,4

Sources: Advicenne, TPICAP Midcap

Valuation by Sum of Parts

Summary of dilutive instruments

At the end of 2021, there were several dilutive instruments (BSPCE) that could have led to the creation of a little more than 1m shares representing around 10% of the existing capital. As a certain number of instruments are conditional (sales, development objectives, etc.), we have considered in our valuation approach only the instruments actually allocated, for a little less than 470,000 shares (conversion price between €3.22 for the oldest plans and €11.74), representing a potential fund raising of nearly €3.8m.

Valuation of the dRTA indicator

The ARENA 1 study demonstrated its efficacy on the main biological disorders caused by the disease and confirmed its acceptability for the pediatric target. Sibnayal® (ADV7103) is the only drug approved for the treatment of ARDS in Europe but is also the only drug in advanced clinical development for ARDS in the United States.

Management estimates the number of patients at 30,000 in Europe and 20,000 in the United States. If only 50% of patients are diagnosed, and that the group addresses one-third of patients, we estimate that approximately 6,000 patients could be treated in hours with ADV7103 and 3,500 to 4,000 in the US.

To establish the revenue and outcome potential of commercializing ADV7103 for the treatment of dRTA (distal Renal Tubular Acidosis - ARTd), we based our modeling on several assumptions :

Continued research (ARENA 2 study) and discussions with the authorities for marketing approval in the U.S. by 2024 and commercial launch in 2025, and negotiations with authorities country by country in Europe for sales prices and reimbursement levels (approximately €16m in cumulative investments).

- Progressive increase in the number of patients treated to reach 6,000 in Europe and elsewhere, and 3,600 in the United States ;
- A treatment price of €7,000 per patient in Europe and elsewhere (100 K€ en post ATU 2022), and €25,000 in the United States ;
- Direct sales in France and the United Kingdom, which generate a 75% MB/revenue ratio ;
- The use of distribution agreements for other countries, such as transfer pricing and royalties on sales (sum of revenue at nearly 55% on average at cruising speed) ;
- Setting up of a dedicated structure for marketing in France, steering the sourcing and supply of products, initiating and managing contracts with distributors (€3m per year at cruising speed) ;
- A tax rate of 25% at the end of the period to estimate the normative terminal value ;
- A discount rate of 15%.

Table 10: Forecasted flow chart, dRTA indicator

€m	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031
No. of new patients	100	250	500	700	800	1 100	1 250	1 450	1 650	1 650
O/W Europe and Others	*100*	*250*	*500*	*600*	*650*	*750*	*750*	*750*	*750*	*750*
O/W USA	*0*	*0*	*0*	*100*	*150*	*350*	*500*	*700*	*900*	*900*
Patients in treatment	200	450	950	1 650	2 450	3 550	4 800	6 250	7 900	9 550
O/W Europe	*200*	*450*	*950*	*1 550*	*2 200*	*2 950*	*3 700*	*4 450*	*5 200*	*5 950*
O/W USA	*0*	*0*	*0*	*100*	*250*	*600*	*1 100*	*1 800*	*2 700*	*3 600*
Treatment price Europe (€000s)	*10*	*7*	*7*	*7*	*7*	*7*	*7*	*7*	*7*	*7*
Treatment price USA (€000s)	*25*	*25*	*25*	*25*	*25*	*25*	*25*	*25*	*25*	*25*
Total sales dRTA	**1,5**	**2,3**	**4,9**	**10,0**	**17,5**	**28,7**	**44,5**	**64,8**	**90,0**	**117,8**
O/W Europe and others	1,5	2,3	4,9	8,8	13,1	18,0	23,3	28,5	33,8	39,0
O/W France & UK (direct distribution)	1,4	1,7	2,7	3,5	3,9	4,5	5,8	7,1	8,4	9,8
O/W USA	0,0	0,0	0,0	1,3	4,4	10,6	21,3	36,3	56,3	78,8
Transfer price	0,1	0,2	0,8	2,2	4,5	7,9	12,5	18,4	25,7	33,9
Consolidated sales (France and UK and margin on transfer price fo	1,4	1,8	2,9	4,3	5,7	8,0	11,8	16,5	22,2	28,4
Others revenues (royalties)	0,01	0,03	0,13	0,39	0,81	1,45	2,32	3,46	4,89	6,48
Total revenues	**1,43**	**2,00**	**3,82**	**6,88**	**11,07**	**17,35**	**26,62**	**38,34**	**52,86**	**68,78**
Revenues from distributors % of sales	**51,0%**	**51,0%**	**51,0%**	**52,0%**	**52,6%**	**53,2%**	**53,7%**	**54,1%**	**54,4%**	**54,6%**
Sales	1,4	1,8	2,9	4,3	5,7	8,0	11,8	16,5	22,2	28,4
Change	0,4	29%	65%	47%	34%	39%	48%	40%	35%	28%
Gross margin	1,0	1,3	2,2	3,4	4,7	6,9	10,4	14,7	20,1	26,0
% sales		*75,8%*	*76,9%*	*79,5%*	*82,8%*	*85,9%*	*87,7%*	*89,2%*	*90,5%*	*91,4%*
Operational costs	-2,0	-2,0	-3,0	-3,0	-3,0	-3,0	-3,0	-3,0	-3,0	-3,0
R&D costs	-6,0	-5,0	-3,0	-2,0	0,0	0,0	0,0	0,0	0,0	0,0
Others revenues	0,0	0,0	0,1	0,4	0,8	1,4	2,3	3,5	4,9	6,5
Taxes								-1,5	-3,3	-7,4
FCF	**-7,0**	**-5,6**	**-3,6**	**-1,2**	**2,6**	**5,3**	**9,7**	**13,7**	**18,7**	**22,1**
Discounted FCF	**-7,0**	**-4,9**	**-2,7**	**-0,8**	**1,5**	**2,6**	**4,2**	**5,1**	**6,1**	**6,3**
Terminal value	166									
Discounted terminal value	41									
Sum of discounted FCFs	10									
WACC	15%									
Perpetual growth rate	1,5%									
Estimated value of dRTA treatment	**52**									

Source: TPICAP Midcap

According to our model, the value of ADV7103 for dRTA is estimated at €52m.

Valuation of the Cystinuria indicator

In the field of cystinuria, the group obtained orphan drug designation from the EMA for ADV7103 in December 2019 (dossier in progress for orphan drug designation in the United States), which should accelerate the research and regulatory phases (less costly development).

Although the Coral 1 and 2 studies (ADV7103 for cystinuria) are less advanced than the dRTA projects, they nevertheless benefit from the results of the latter, particularly in terms of side effects (almost non-existent), which could, if successful, offer real alternatives to patients suffering from cystinuria, given the cumbersome nature of the current therapeutic solutions and the sometimes very serious side effects of the treatments, particularly for children.

The leaders estimate the number of patients at 40,000 in Europe and 20,000 to 30,000 in the United States. If only 50% of patients are diagnosed, and that the group addresses half of the patients, we estimate that about 10,000 patients could be treated in hours with ADV7103 and 14,000 in the US.

To establish the potential revenue and results of commercialising ADV7103 for the treatment of cystinuria, we based our modeling on several assumptions:

- Continued research (CORAL I and CORAL study) and discussions with authorities for marketing approval in Europe by 2024 (commercial launch in 2025) and in the United States by 2025-26 (commercial launch in 2026-27), negotiations with authorities on a country-by-country basis for the sales price and the level of reimbursements (approximately €25m in total) ;
- A gradual increase in the number of patients treated to reach approximately 10,000 in Europe and elsewhere, and 15,000 in the United States ;
- A treatment price of €7,000 per patient in Europe and elsewhere, and €25,000 in the United States ;

- Direct sales in France and in the United Kingdom, which allow us to generate an MB/revenue ratio of 75% ;
- The use of distribution agreements for other countries, such as transfer pricing and royalties on sales (sum of revenue at nearly 55% on average at cruising speed) ;
- Setting up a dedicated structure for marketing in France, managing product sourcing and supply, initiating and managing contracts with distributors (€3m/year at cruising speed) ;
- A 25% tax rate at the end of the period to estimate the normative terminal value ;
- A 15% discount rate.

Table 11: Predictive flow chart, cystinuria indicator

€m	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031
No. of new patients	0	0	0	250	550	1450	3000	5000	6500	7000
O/W Europe	*0*	*0*	*0*	*250*	*550*	*1 200*	*2 000*	*2 000*	*2 000*	*2 000*
O/W USA	*0*	*0*	*0*	*0*	*0*	*250*	*1 000*	*3 000*	*4 500*	*5 000*
Patients in treatment	*0*	0	0	250	800	2 250	5 250	10 250	16 750	23 750
O/W Europe	*0*	*0*	*0*	*250*	*800*	*2 000*	*4 000*	*6 000*	*8 000*	*10 000*
O/W USA	*0*	*0*	*0*	*0*	*0*	*250*	*1 250*	*4 250*	*8 750*	*13 750*
Treatment price Europe (€000s)			*7*	*7*	*7*	*7*	*7*	*7*	*7*	*7*
Treatment price USA (€000s)			*25*	*25*	*25*	*25*	*25*	*25*	*25*	*25*
Total sales Cystenuria	**0,0**	**0,0**	**0,0**	**0,9**	**3,7**	**12,9**	**39,8**	**103,8**	**211,5**	**344,3**
O/W Europe	0,0	0,0	0,0	0,9	3,7	9,8	21,0	35,0	49,0	63,0
O/W France & UK (direct distribution)	0,0	0,0	0,0	0,7	2,0	3,9	6,3	8,8	12,3	15,8
O/W USA	0,0	0,0	0,0	0,0	0,0	3,1	18,8	68,8	162,5	281,3
Transfer price	0,0	0,0	0,0	0,1	0,6	3,0	10,8	29,8	61,6	100,9
Consolidated sales (margin on transfer price)	0,0	0,0	0,0	0,7	2,2	5,1	11,5	25,1	48,4	76,7
Others revenues (royalties)	0,00	0,00	0,00	0,01	0,10	0,54	2,01	5,70	11,96	19,71
Total revenues	**0,0**	**0,0**	**0,0**	**0,8**	**2,9**	**8,7**	**24,3**	**60,6**	**122,0**	**197,3**
Revenues from distributors % of sales				**51,0%**	**51,0%**	**52,7%**	**53,8%**	**54,6%**	**55,1%**	**55,3%**
Sales	0,0	0,0	0,0	0,7	2,2	5,1	11,5	25,1	48,4	76,7
Change					222%	135%	124%	118%	93%	58%
Gross margin	0,0	0,0	0,0	0,5	1,7	4,2	9,9	22,9	45,4	72,8
% sales				*75,8%*	*76,9%*	*80,9%*	*86,3%*	*91,3%*	*93,7%*	*94,9%*
Operational costs	-1,0	-1,0	-2,0	-2,0	-3,0	-3,0	-3,0	-3,0	-3,0	-3,0
R&D costs	-3,0	-5,0	-5,5	-6,0	-3,5	-2,0	0,0	0,0	0,0	0,0
Others revenues	0,0	0,0	0,0	0,0	0,1	0,5	2,0	5,7	12,0	19,7
Taxes								-2,6	-8,1	-22,4
FCF	**-4,0**	**-6,0**	**-7,5**	**-7,5**	**-4,7**	**-0,3**	**9,0**	**23,1**	**46,2**	**67,1**
Discounted FCF	**-4,0**	**-5,2**	**-5,7**	**-4,9**	**-2,7**	**-0,2**	**3,9**	**8,7**	**15,1**	**19,1**
Terminal value	505									
Discounted terminal value	125									
Sum of discounted FCFs	24									
WACC	15%									
Perpetual growth rate	1,5%									
Estimated value of Cystinuria treatment	**149**									

Source: TPICAP Midcap

According to our modeling, the valuation of ADV7103 for cystinuria is estimated at €149m.

Valuation of In & out licenses, and other indicators

For the other indicators, we have grouped together all sources of revenue (sales of licensed products, royalties on the Primex distribution agreement, etc.) and expenses (R&D, structural costs, capex, etc.). As we have not included new indicators, expenses are limited in our model, and generated revenue, in particular the balance of the Primex contract, should more than compensate for operating expenses over the period observed, leading to a value of nearly €16m for distribution agreements and licenses granted.

Table 12: Forecasted flow chart of licenses and other indicators

M€	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031
Sales	2,0	2,4	2,8	3,0	3,3	3,4	3,6	3,7	3,7	3,8
Change		*20,0%*	*15,0%*	*10,0%*	*7,0%*	*5,0%*	*4,0%*	*3,0%*	*2,0%*	*2,0%*
Gross Margin	1,1	1,4	1,7	2,0	2,1	2,2	2,3	2,4	2,4	2,5
% Sales	*56,0%*	*60,0%*	*60,0%*	*65,4%*	*65,4%*	*65,4%*	*65,4%*	*65,4%*	*65,4%*	*65,4%*
REBIT	**-1,0**	**-0,1**	**0,7**	**31,7**	**0,5**	**0,5**	**0,5**	**0,5**	**0,6**	**0,6**
Margin	*-50,5%*	*-5,8%*	*26,3%*	*1042,3%*	*15,0%*	*15,0%*	*15,0%*	*15,0%*	*15,0%*	*15,0%*
Others revenues	0,8	0,9	1,0	32,7	1,0	1,0	1,0	1,0	1,0	1,0
EBIT excL others revenues	-1,8	-1,0	-0,3	-0,9	-0,5	-0,5	-0,5	-0,5	-0,4	-0,4
FCF	**-1,0**	**-0,1**	**0,7**	**31,7**	**0,5**	**0,5**	**0,5**	**0,5**	**0,6**	**0,6**
Discounted FCF	**-0,9**	**-0,1**	**0,4**	**15,8**	**0,2**	**0,2**	**0,2**	**0,1**	**0,1**	**0,1**
Sum of FCF	16,2									
Terminal Value	0,6									
Equity method	0,0									
EV Licence in & out and others	**16,8**									

Source: TPICAP Midcap

Valuation summary and market rating

Given the MA already obtained in Europe for dRTA, the ongoing study in the United States, and the absence of a treatment for this rare disease, we are confident in the company's ability to deploy ADV7103 in this indicator. However, as it is difficult to control the regulatory advances (US marketing authorization, pricing and reimbursement levels, etc.) and the pace of diffusion of the product on the market (mainly indirect distribution), we are applying a 30% discount rate to the value obtained in our modeling (amounting to €36m).

In the field of cystinuria, studies are less advanced, even if the orphan disease status could accelerate developments in Europe. As a precautionary measure, we have chosen to apply a significant discount to the valuation obtained for this indicator in our valuation approach (80% discount, for a valuation of €20m for this indicator).

Table 12: Summary of our valuation approach

	NPV (€m)	Discount	Retained value (€m)
dRTA	52	30%	36
Cystinuria	149	80%	30
Licence in & out	17	-	17
Others indications	0	-	0
EV			**83**
Net debt at the end of 2021 (€m)			(0,1)
Provisions for retirment (€m)			0,1
Unused tax credit discounted (€m)			17
Equity estimated value (€m)			**99**
Current number of shares			10,0
Induced value per share (€)			**10,0**
Nb. of shares BSPCE			0,46
Cash raided through BSPCE (€m)			3,8
Estimated funds raising 2022-2025 (€m)			27,0
No. of shares after funds raising			6,7
Value per share diluted (€)			**7,6**

Source: TPICAP Midcap

Based on our sum-of-the-parts valuation approach, we obtained an enterprise value of €83m, or an equity value of 10.0/share based on the current share price. However, to achieve these targets, management will need to resort to external financing.

In our model, we have assumed that €27m will be raised over the next few years. Based on the current share price, this corresponds to the creation of 6.7m shares. Additionally, the exercise of outstanding BSPCEs at the end of 2021 could lead to the creation of nearly 500,000 additional shares (for a potential fundraising of €3.8m). On a fully diluted basis, Advicenne's valuation per share stands at €7.6, which is our target price.

After 15 years of growth and development, the group has proven its ability to develop products aimed at unmet needs in orphan diseases and for all patients, from children to the elderly, and to complete regulatory milestones in Europe (AMM in France for Levidcen in 2014, Likozam in 2016, Ozaline in 2018, and in Europe for Sibnayal in 2021) The next steps will be the completion of regulatory steps in North America with the FDA, the extension of indicators, but also the acceleration of the marketing phases which should enable the group to fuel its sales. The clinical, regulatory and operational newsflow should, in our opinion, allow the stock to take off. Our TP offers a potential upside close to 90%. Therefore, we are initiating our coverage of the stock with a Buy rating.

FINANCIAL DATA

Income Statement	12/19	12/20	12/21	12/22e	12/23e	12/24e
Sales	1.7	2.1	2.7	3.4	4.2	5.7
Changes (%)	72.7	24.0	29.5	26.2	23.7	36.3
Gross profit	1.0	1.2	1.7	2.1	2.8	3.9
% of Sales	58.4	57.0	63.6	63.8	66.7	68.7
EBITDA	**-14.0**	**-13.7**	**-12.0**	**-11.5**	**-11.3**	**-10.0**
% of Sales	-842.5	-664.9	-449.8	-342.6	-272.0	-175.4
Current operating profit	**-14.2**	**-14.1**	**-12.4**	**-12.0**	**-11.8**	**-10.4**
% of Sales	-856.8	-685.5	-466.0	-355.4	-282.4	-183.1
Non-recurring items	-0.0	0.1	0.1	0.0	0.0	0.0
EBIT	-14.2	-14.1	-12.4	-12.0	-11.8	-10.4
Net financial result	0.1	-0.7	0.0	-1.0	-1.0	-1.1
Income Tax	0.0	-0.0	0.0	0.0	0.0	0.0
Tax rate (%)	0.0	-0.2	0.1	0.0	0.0	0.0
Net profit, group share	**-14.2**	**-14.8**	**-12.3**	**-13.0**	**-12.8**	**-11.5**

Financial Statement	12/19	12/20	12/21	12/22e	12/23e	12/24e
Goodwill	0.0	0.0	0.0	0.2	0.2	0.2
Tangible and intangible assets	2.1	2.8	2.0	3.4	3.5	4.0
Right of Use	0.0	0.0	0.0	0.0	0.0	0.0
Financial assets	0.3	0.4	0.3	0.3	0.3	0.3
Working capital	-0.5	-2.8	-2.0	-1.2	0.0	1.5
Other Assets	0.0	0.0	0.0	0.0	0.0	0.0
Assets	1.9	0.4	0.3	2.6	3.9	6.0
Shareholders equity group	16.7	3.3	0.3	-3.6	-7.5	-10.0
Minorities	0.0	0.0	0.0	0.0	0.0	0.0
LT & ST provisions and others	0.2	0.1	0.1	0.1	0.1	0.1
Net debt	-15.0	-3.0	-0.5	6.2	11.3	15.8
Other liabilities	0.0	0.0	0.0	0.0	0.0	0.0
Liabilities	1.9	0.4	0.3	2.6	3.9	6.0
Net debt excl. IFRS 16	-15.0	-3.0	-0.5	6.2	11.3	15.8
Gearing net	-0.9	-0.9	-1.7	-1.7	-1.5	-1.6
Leverage	1.1	0.2	0.0	-0.5	-1.0	-1.6

Cash flow statement	12/19	12/20	12/21	12/22e	12/23e	12/24e
CF after elimination of net borrowing costs and taxes	-13.3	-14.3	-11.8	-13.5	-13.4	-12.2
ΔWCR	3.8	1.9	-0.7	-0.8	-1.2	-1.5
Operating cash flow	-9.4	-12.4	-12.5	-14.3	-14.6	-13.7
Net capex	-0.9	-0.6	-0.3	-2.0	-0.5	-1.0
FCF	-10.4	-12.3	-12.8	-15.3	-14.1	-13.6
Acquisitions/Disposals of subsidiaries	-0.9	-0.6	-0.3	-2.0	-0.5	-1.0
Other investments	-0.1	-0.1	-0.1	0.0	0.0	0.0
Change in borrowings	-0.0	11.9	-0.2	4.9	-0.8	-0.8
Dividends paid	0.0	0.0	0.0	0.0	0.0	0.0
Repayment of leasing debt	0.0	0.0	0.0	0.0	0.0	0.0
Others	1.0	0.6	9.0	9.0	9.0	9.0
Changes in exchange rates	0.0	0.0	0.0	0.0	0.0	0.0
Change in net cash over the year	-9.6	0.1	-4.1	-1.4	-5.9	-5.4
ROA (%)	na	na	na	na	1474.4%	401.2%
ROE (%)	na	na	na	355.1%	171.7%	115.4%

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1. DCF method: discounting of future cash flows generated by the company's operations. Cash flows are determined by the analyst's financial forecasts and models. The discount rate used corresponds to the weighted average cost of capital, which is defined as the weighted average cost of the company's debt and the theoretical cost of its equity as estimated by the analyst.
2. Comparable method: application of market valuation multiples or those observed in recent transactions. These multiples can be used as references and applied to the company's financial aggregates to deduce its valuation. The sample is selected by the analyst based on the characteristics of the company (size, growth, profitability, etc.). The analyst may also apply a premium/discount depending on his perception of the company's characteristics.
3. Assets and liabilities method: estimate of the value of equity capital based on revalued assets adjusted for the value of the debt.
4. Discounted dividend method: discounting of estimated future dividend flows. The discount rate used is generally the cost of capital.
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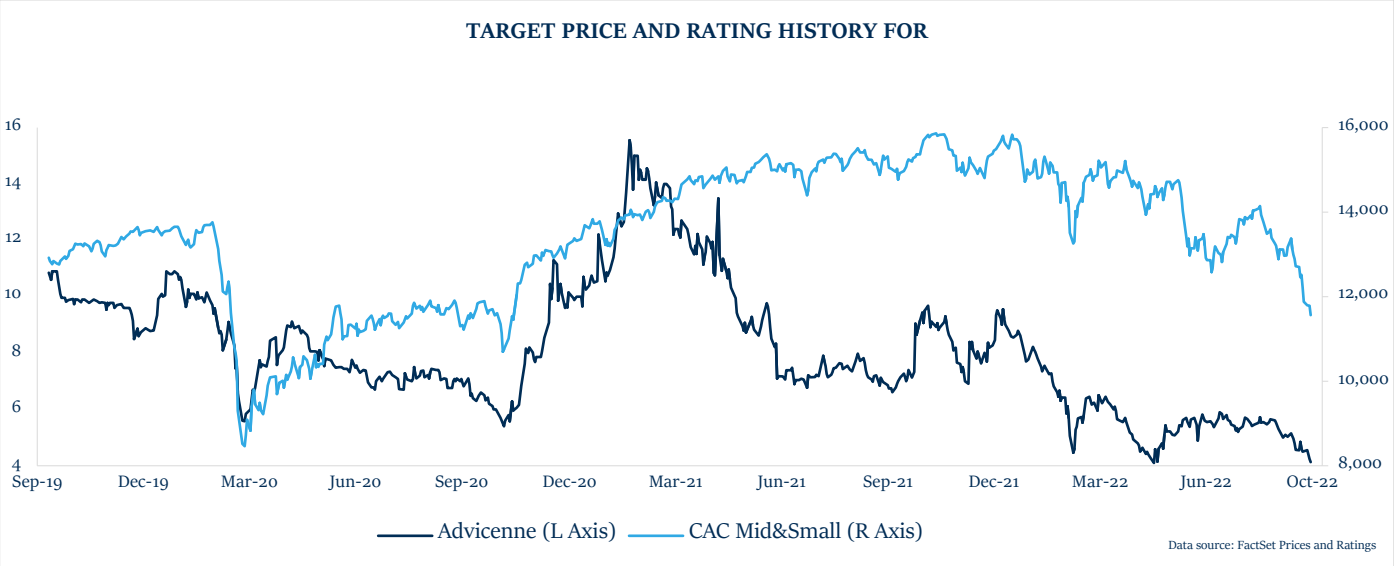
History of investment rating and target price – Advicenne



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Rating	Recommendation Universe*	Portion of these provided with investment banking services**
Buy	86%	64%
Hold	13%	39%
Sell	1%	0%
Under review	0%	

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