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EQUITY RESEARCH

PHAXIAM THERAPEUTICS

INITIATION OF COVERAGE

BUY

TP 8.5€

Ambition of a global leadership in phage therapy

Research partially paid by the Issuer

Thanks to the Erytech - Pherecydes merger, PHAXIAM Therapeutics will be able to accelerate its developments in the field of phages and the fight against antibiotic resistance, offering patient solutions for those in therapeutic limbo.

PHAXIAM was created in mid-2023 from the merger between Erytech and Pherecydes and specializes in phage therapy. Phages are natural viruses that attack bacteria, a specialty driven by the need to respond to antibiotic resistance concerns, notably through the development of alternative solutions. The group's goal is to develop individualized therapeutic treatments targeting the most resistant human infections.

The group has already developed an in-vitro analysis tool that can be used to test the sensitivity of a patient's bacterial strains, enabling only phages that are genuinely active for the bacteria in question: the Phagogramme. While treatment is individual, the targeted phages are standardized and sourced from a tightly knit collection based on criteria of efficacy, purity and production.

Technological advances, targeted indications and the experience gained from the use of phages for healthcare have enabled the group to treat over 90 patients to date with PHAXIAM phages (ATU or AAC). The initial results are the impetus for further clinical research, launched in mid-2022 for phases I/II: PhagoDAIR for prosthesis osteoarticular infections (results expected in mid-2024). The design of phase IIb/III is underway, with discussions with the FDA and EMA soon to begin. A 2nd phase I PK should be launched by the end of the year for infectious endocarditis. Management also announced its intention to conduct studies for other indications (urinary tract infections, respiratory infections), in addition to hospital-led projects.

The company's phage technology and know-how could also be the subject of licensing agreements with 3rd parties for in vitro diagnostics, outside human health, in related sectors, or for indications not covered by the company's own development, thus enabling it to generate revenue (up-front, milestones, or royalties), before the first marketing authorization, scheduled for 2028 according to our scenario. However, until such agreements are reached, the company will need to raise new external financing to pursue its R&D efforts: an estimated €60m over the next 3 years (only in equity in our scenario).

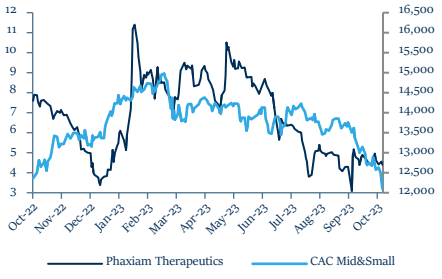
Given the pipeline's maturity, the combined research and clinical and regulatory skills of the Erytech and Pherecydes teams, the newsflow should accelerate and contribute to the stock's rebound. Therefore, we are initiating our company coverage with a Buy rating and a price target of €8.5 per share.

Key data	
Industry	Heathcare
Ticker	PHXM-FR
Shares Out (m)	6.075
Next event	CA 2023

Ownership (%)	
Go Capital	7.8
Auriga / Elaia	13.3
Pool Guy Rigaud	3.7
Tikehau	7.8
Free float	62.3

EPS (€)	12/23e	12/24e	12/25e
Estimates	-4.28	-1.90	-1.36
Change vs previous estimates (%)	na	na	na

Performance (%)	1D	1M	YTD



TP ICAP Midcap Estimates	12/22	12/23e	12/24e	12/25e
Sales (m €)	0.0	0.0	0.0	0.0
Current Op Inc (m €)	-2.8	-25.9	-20.1	-20.6
Current op. Margin (%)	na	na	na	na
EPS (€)	-0.07	-4.28	-1.90	-1.36
DPS (€)	0.00	0.00	0.00	0.00
Yield (%)	na	na	na	na
FCF (m €)	-31.8	-26.3	-20.3	-20.8

Consensus FactSet - Analysts:3	12/23e	12/24e	12/25e
Sales	0.0	0.0	na
EBIT	-18.9	0.0	na
Net income	-16.5	0.0	na

Analyst
Claire Deray - Sponsor Finance for TPICAP Midcap

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Description

Phaxiam Therapeutics was born in July 2023 from the merger between equals of Erytech and Pherecydes Pharma. The merger of the two companies should make it possible, thanks to the know-how and cash of Erytech (support functions, clinical, regulatory, support functions, etc.) to accelerate the developments carried out by Pherecydes in the fight against resistant bacterial infections, responsible for many serious pathologies. The technology deployed is based on the use of natural phages and on a precision therapy with the in vitro analysis of the phages effectively active on the infections which concern a given patient, chosen on the basis of a restricted collection of phages (a few phages per targeted bacterium).

SWOT Analysis

Strengths

- Phage technologies and know-how
- Mastery in CMC processes (Chemistry, Manufacturing and Control)
- Clinical and regulatory skills (Eur. and US)
- More than 90 patients treated

Weaknesses

- Still no product on the market
- No major partnership agreements
- Research still in prgogress which requires recourse to external funding

Opportunities

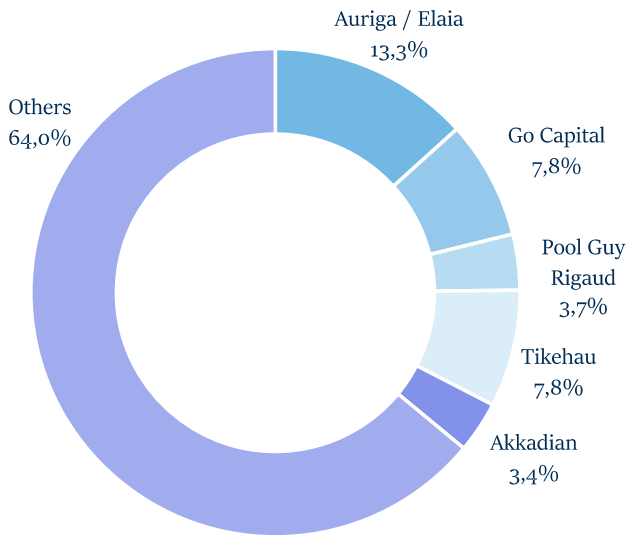
- Product marketing authorizations
- Partnership agreement / technology licensing
- Supply of the project pipeline

Threats

- R&D failures
- Delayss in marketing products
- Difficulty in finding external financing

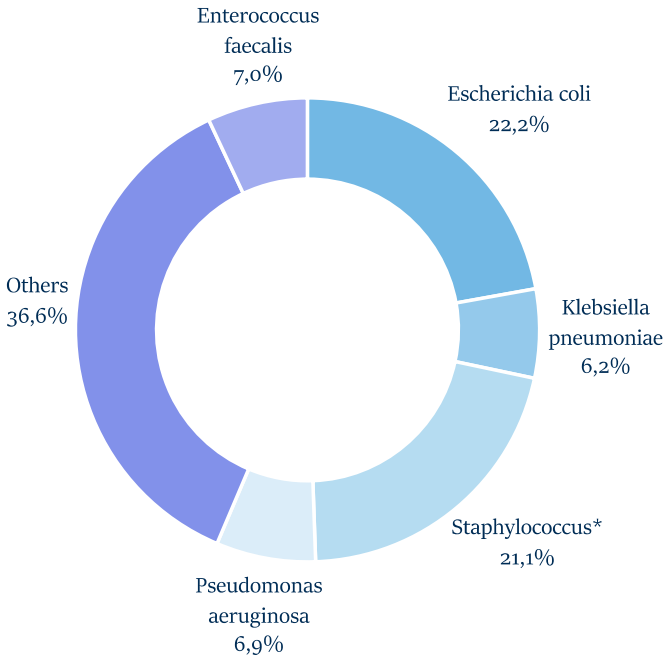
Overview

Post-merger shareholding



Source : company and threshold crossing declaration

Relative share of micro-organisms in nosocomial infections in France (data for 2022)



Source : Santé Publique France

PHAXIAM aims to pursue the research initiated since 2006 by Pherecydes Pharma, a biotechnology company specializing in phage therapy, i.e. the development of treatments based on phages (or bacteriophages), viruses that infect only bacteria. In effect, each phage targets a specific bacterial species to inject its DNA, reproduce there, then destroy the bacteria by releasing new phages and replicate this operation until the bacteria disappear. Through this cycle, phages have a unique mode of action which is highly targeted (specificity), rapid (less than 45 min) and effective (self-repeating until the last bacterium is killed).

The discovery of bacteriophage dates to the end of the 19th century. Since the beginning of the 20th century, phages have been used to combat bacterial infections throughout the world, but have since been progressively abandoned, except in certain Eastern European countries, in favor of antibiotics, which are more stable and easier to use. Since the 2000s, with the growing awareness of antibiotic resistance, phage therapy has been the subject of renewed interest since it offers an alternative solution for treating infections caused by antibiotic-resistant bacterial strains. This occurs by either eliminating bacteria or by weakening them sufficiently for the patient's immune system or antibiotics to take over and overcome them. What's more, since phages are active on a particular bacterial species, they preserve the flora and microbiota of those treated (one of the undesirable side-effects of certain antibiotic treatments). Bacteriophages thus represent a serious avenue for the discovery of sustainable treatments for bacterial infections.

After a decade of collection, analysis and characterization to build up a bank of natural phages, research into phage purification and duplication, the possibility of using genetically modified organisms (challenging concerning health regulations), or a phage cocktail, , is the group's focus though the use of:

1) **restricted phage collections**: a few phages per targeted indication selected based on criteria of efficacy, purity and production capacity.

2) **phage production outsourcing**: transfer of know-how to a Czech subcontractor since 2020, equipped with a GMP site, which can support the planned ramp-up at competitive production costs.

3) **precision phage therapy**: development of a "Phagogram", an in-vitro analysis of phage activity on the bacterial strain collected from a patient, enabling only those phages active on the strain of bacteria causing the infection to be retained (CE marking as an in-vitro diagnostic test obtained in Sept. 2022). Analysis process historically carried out at Pherecydes' Nantes site, and now at the new combined ex-Erytech site in Lyon.

4) **targeting bacteria responsible for most human infections**. To date, work is targeting four of the main nosocomial infections, namely: 1) staphylococcus aureus (two active phages selected), 2) pseudomonas aeruginosa (four phages selected), 3) escherichia coli (four phages selected), and 4) Klebsiella pneumoniae (work initiated in mid-2023).

5) **serious indications for bacterial infections**, for which practitioners find themselves at a therapeutic impasse, and which can lead to the patient's death, such as osteoarticular infections on prostheses and infectious endocarditis (infection of the heart lining) caused by staphylococcus aureus, or urinary tract infections caused by escherichia coli.

Due to the pathologies addressed and the decline in the use of phages in healthcare (established non-toxicity and tolerance criteria), the phages selected by the group via the use of the Phagogram could quickly be used to treat patients. To date, more than 90 have been identified within the framework of ATU (Temporary Authorizations for Use) / or AAC Authorization for Compassionate Access (new name of ATU since 2021) in various indications without having yet completed the clinical studies. If treated patient samples are not sufficiently representative in clinical data, the results obtained make it possible to guide research programs, and to offer some assurance on their potential for success.

The product of the research efforts carried out since 2006 should quickly materialize with the first results of the PhagoDAIR study, in the field of osteoarticular infections for prosthesis, expected by mid-2024 (sixty patients targeted, followed until the end of 2025). With the support of teams from Erytech, clinical newsflow should accelerate. The teams have already made progress on the design of the IIb/III study, allowing discussions to be initiated with the competent American (FDA) and European (EMA) authorities before the end of 2023, to be ready to launch the study. in H2 2024, with the results of phase I/II of PhagoDAIR in support of the project. At the same time, the protocols for the phase I Pharmacokinetic (PK) study targeting infectious endocarditis have been finalized, which should make it possible to recruit the first patient probably before the end of FY 2023 (12 patients targeted, 4 centers in France) and to be able to publish results before the end of 2024. Finally, the progress of the preparatory stages of the phase I/II study which targets urinary infections caused by escherichia coli, should make it possible to launch patient recruitment in early 2024 (with results in 2025).

As part of Hospital Clinical Research Programs, other phase I/II clinical research should be launched in France for which PHAXIAM brings its know-how and technology (Phagogram use to target the phages to be used and sourcing of phages from of the Czech service provider): 1) PhagOS which targets osteoarticular infections on prosthesis caused by staphylococcus aureus whose promoter is the Bordeaux University Hospital (launch H1 2024), 2) PhagoPied which targets diabetic foot infections caused by staphylococcus aureus whose promoter is the Nîmes University Hospital (launch H1 2024), and 3) PyoPhaNeb which targets respiratory infections caused by pseudomonas aeruginosa whose promoter is the APHP (launch 2024).

Beyond clinical studies, the group continues its investments in technology: 1) phages: collection / analysis / selection to complete coverage and conduct constant monitoring of bacteria already targeted, and to address other bacteria for which practitioners find themselves in a therapeutic impasse (antibiotic-resistant bacteria), which concern indications already targeted or complementary areas, and which could be treated by the use of phage therapy, 2) for precision phage therapy with the objective of developing a new generation Phagogram as part of the PhagECOLI project carried out in partnership with the CEA (2022-2024 project), faster, automated and scalable (financing of €2m from BPI), and 3/ in related sectors such as endolysins (proteins released by phages), with different mechanisms of action, which could make it possible to address other market segments, and which benefits from Erytech's know-how in the field of proteins.

Given the progress of the research programs, PHAXIAM should not record significant revenue linked to the commercialization of its phages for several years (1st Marketing Authorization expected for 2028 in our scenario), with revenue limited to subsidies and research tax credits (a few €M per year). In the short-term, thanks to the current state of developments, management is aiming to commercialize products and solutions in the form of licensing of technology and know-how, which could generate up-front revenue, milestones, or royalties beyond human healthcare (for example, in animal health, agri-food or cosmetics), in related sectors, or for indications which would not necessarily have been developed on their own (microbiome). However, as it is difficult to anticipate such agreements, therefore our scenario does not include them.

The group has a unique positioning that targets unmet therapeutic needs for serious conditions. This strategy should probably allow the group, as for PhagoDAIR, to benefit from lighter clinical protocols limiting the costs of phases I/II to €4-5m, and that of phases IIb/III to €10-20m. In view of the development pipeline, the group should carry out two or three phase I/II studies in parallel, and one or two phase IIb/III studies, to which are added the regulatory stages. We estimate that the group could thus devote €12m per year in R&D costs, to which are added general, administrative and commercial costs, leading to operational losses estimated at €20-25m per year. Thus, there is the need to find external financing: capital increase of €20m per year between 2024 and 2026 has been retained in our scenario (possible grants and non-dilutive financing, projects currently under review).

After only five years of deployment of the precision phage therapy strategy for indications with unmet therapeutic needs, Pherecydes launched its first phase I/II study in 2022. The results, expected in 2024, should confirm those obtained under ATU, and thus validate with the scientific community and the authorities, the effectiveness of the phage-based treatments developed by the group. This should facilitate the next steps for the indication in question, but probably also in the other targeted indications. With the support of the Erytech teams, the developments of the new PHAXIAM group, particularly clinical and regulatory, should accelerate, making it possible to feed the newsflow.

Details of the merge operation

The schedule

February 15, 2023: Announcement of the proposed merger via absorption of Pherecydes by Erytech through a share exchange transaction. 15 new Erytech shares for 4 Pherecydes shares, allowing Pherecydes shareholders to hold 49.5% of the capital of Erytech post operation, i.e. a merger between equals. The operation counted on the support of the main shareholders from Auriga Partners and Recordati SpA on the Erytech side and Elaia Partners, Go Capital and a pool of shareholders represented by Mr. Guy Rigaud for Pherecydes. This was unanimously approved by the boards of directors of both entities.

February 20: Pherecydes capital increase of €1.5m reserved for historical shareholders at a price of €2.09 per share, i.e. a discount of 21.4% vs. the last closing price at the time of the operation. The aim was to provide the necessary resources to the company to finance itself until the merger with Erytech is completed.

March 20: Favorable opinion from the CSE (Economic Social Committee) of Erytech on the merger project.

April 14: Declaration of crossing the threshold of 5% of Erytech's capital by Akkadian Partners, a Luxembourg investment fund.

May 9: Declaration of crossing the threshold of 5% of Erytech's voting rights from Akkadian Partners (shareholder with 5.66% of the capital and 5.4% of the voting rights at the time of the announcement, before merger operation). This new shareholder then declared himself firmly opposed to the merger project.

May 15: Contribution in kind of Pherecydes shares to Erytech from Eleia Partners, Go Capital and a pool of shareholders represented by Mr. Guy Rigaud, i.e. 827,132 Pherecydes shares (approximately 10% of the capital), resulting in the creation of 3,101,745 Erytech shares on the basis of the parity proposed for the merger, allowing them to jointly hold 12.1% of the capital of Erytech and 14.4% of the voting rights, and thus to obtain two positions of administrators.

May 16: Submission of the report from Finexsi, contribution commissioner appointed by the Lyon commercial court, ruling on the fair nature of the exchange parity (4 Pherecydes shares for 15 new Erytech shares) proposed in the merger.

May 17: Convocation to the general meetings of the two companies scheduled for 23 June.

May 24: Dissemination of documents relating to the proposed merger of the two companies.

June 5: Launch of a procedure by Akkadian Partners with the aim of obtaining the appointment of a legal expert to evaluate the parity ratio and thus postpone the votes on the merger operation planned during the general meetings of June 23, considering the proposed parity as disadvantageous for Erytech shareholders.

June 14: Rejection by the Lyon commercial court of the request to postpone the AGM. Appointment of an expert to issue a report on the parity proposed as part of the operation within 4 months, the cost of which will be borne by Akkadian Partners, as well as the costs incurred by Erytech and Pherecydes for the procedure's framework.

June 20: New procedure on the part of Akkadian Partners which requests the cancellation of the capital increase carried out on May 15 following the contribution in kind of Pherecydes securities, based on the parity proposed as part of the project fusion.

June 23: Quorum of AGO and EGM reached. Largely favorable vote for all the resolutions from the shareholders who expressed their vote. Erytech Board of Directors validating the merger which becomes retroactive to January 1, 2023 for accounting. The new group thus formed is renamed PHAXIAM Therapeutics, the new board of directors and the new management team are formed.

June 29: PHAXIAM Therapeutics shares admitted to trading under the ticker PHXM (Eurolist C and Nasdaq).

July 3: Settlement and delivery of new shares issued as remuneration for Pherecydes shares. Number of PHAXIAM Therapeutics shares increased to 60,751,054 shares.

July 7: Declaration of threshold crossing and concerted action on the part of Auriga Partners (13.3% of capital and 14.61% of voting rights), the Guy Rigaud shareholder pool (3.7 % of the capital and 3.61% of the voting rights) and Go Capital (7.83% of the capital and 7.64% of the voting rights), which hold, in total, 24.8% of the capital of PHAXIAM Therapeutics and 25.9% of voting rights).

August 1: Declaration of Akkadian Partners crossing the downward threshold following the merger: 3.39% of the capital and 3.3% of the voting rights.

September 18: Consolidation of shares (1 for 10), share capital increased to 6,075,105 shares with a nominal value of €1.

Despite the rebellion led by Akkadian Partners, thanks to the favorable decisions of the Lyon commercial court, the regulatory steps were able to be completed within the initially planned timetable, i.e. in less than six months. The operational merger was able to be launched and should make it possible to deploy, by the end of 2023, the synergies targeted by the merger of the two companies.

The New PHAXIAM Therapeutics

New shareholding

At the end of the various operations (capital increase, contribution in kind, exchange of shares), the number of shares making up the share capital of Erytech, which became PHAXIAM, increased from 31m to nearly 61m (6.1m post consolidation by 10 carried out in September), with a reference shareholder base mainly from the historical shareholders of Pherecydes Pharma, the free float of Erytech being at almost 95% before the operation.

Three shareholders declared themselves acting in concert: Eleia Partners / Auriga, Go Capital and a pool of shareholders represented by Mr. Guy Rigaud, representing 24.8% of the capital of PHAXIAM and 25.9% of the voting rights. Ace, historic shareholder of Pherecydes, also holds 7.8% of the capital. Note that post-merger, Akkadian's participation was reduced to 3.39% of PHAXIAM's capital (based on the number of shares declared by the latter at the beginning of August).

The free float of the new group has thus been increased to more than 50% (vs. less than 25% before for Pherecydes), with a security listed both on compartment C on Euronext Paris and on Nasdaq in the United States, allowing to access a wider panel of investors.

Table 1: Main shareholders

	August 2023**		
	No of shares	% capital	% voting rights
Auriga / Eleia*	807 886	13,3%	14,6%
Go Capital*	475 607	7,8%	7,6%
Pool Guy Rigaud*	224 941	3,7%	3,6%
Total concert	**1 508 434**	**24,8%**	**25,9%**
Tikehau*	471 777	7,8%	7,6%
Patricipations Besancon	91 432	1,5%	1,5%
BVF Partners	9 734	0,2%	0,2%
Akkadian*	205 695	3,4%	3,3%
Others	3 788 033	62,3%	61,6%
Total	**6 075 105**		

*Participation at the time of declaration of threshold crossing, **restated from the share consolidation carried out in September

Source: PHAXIAM Therapeutics

After the share consolidation carried out in September, the number of listed securities was increased to 6,075,105 and the par value from €0.1 to €1, which made it possible to mechanically raise the stock price, placing it above beyond $1 on the American market, one of the conditions for being able to maintain continuous trading on the market in question.

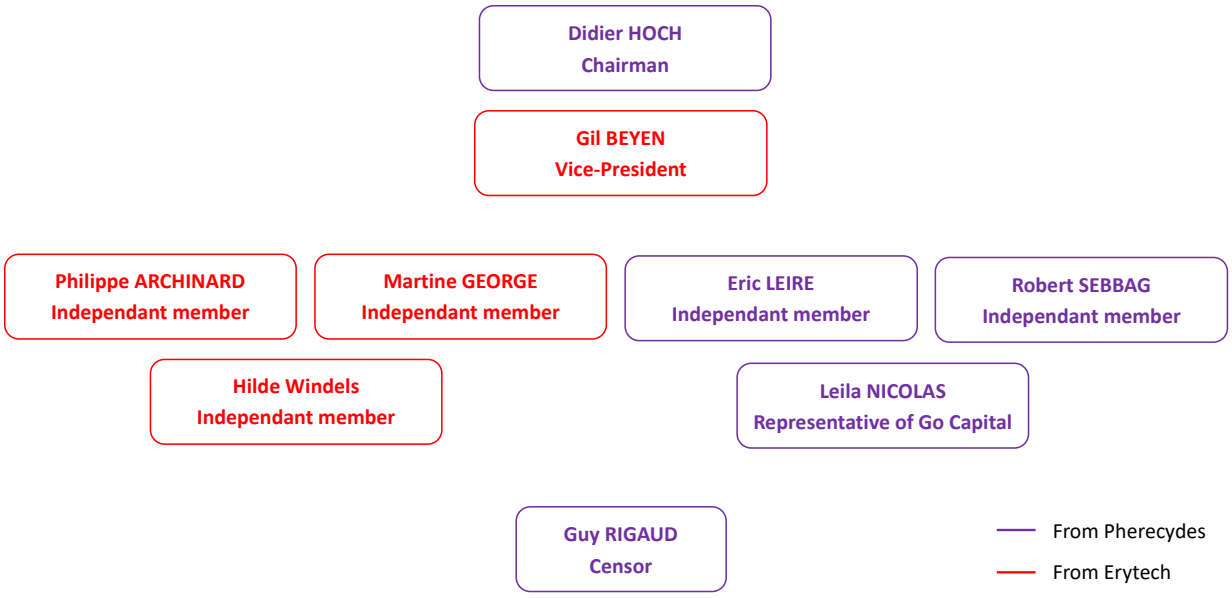
New management and teams

In accordance with the project which was presented in mid-February, on 23 June, the group's governance and management teams were reshuffled, although with the same equity strategy which was deployed on the shareholder side.

Composition of the Board of Directors

The board of directors, in place since 23 June, is now made up of 8 members, in equal numbers from the former boards of directors of Ertyech and Pherecydes and a censor. The board is now chaired by Dider Hoch (former President of Pherecydes) supported by Gil Beyen as Vice-President (former Managing Director of Erytech).

Graph 1: Composition of the PHAXIAM board of directors

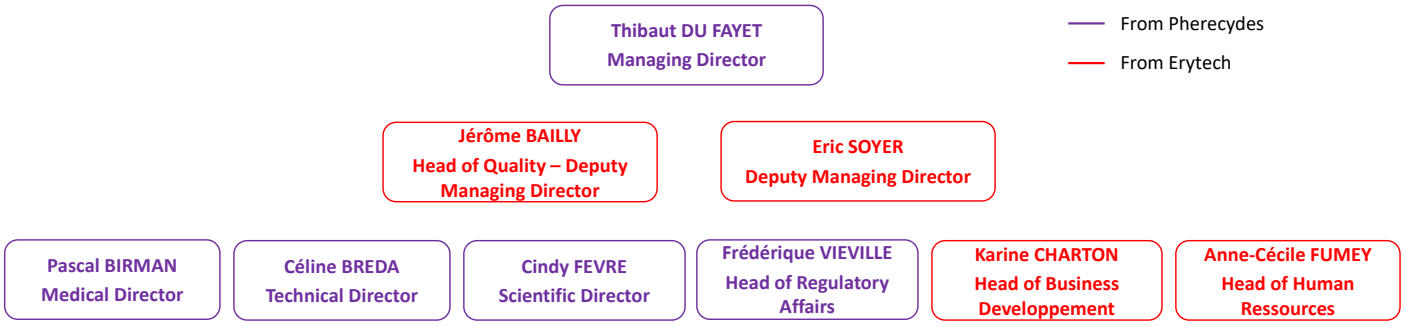


Source: PHAXIAM Therapeutics

Composition of the management team

Management is composed of Thibaut du Fayet (former Managing Director of Pherecydes), the Managing Director of PHAXIAM Therapeutics. Gil Beyen, former Managing Director of Erytech, has taken over. Vice Chairman of the Board of Directors and remained Executive Chairman of Erytech Pharma, Inc., the subsidiary based in the United States. Eric Soyer also remained Deputy Managing Director and Financial Director, positions he previously held at Erytech.

Graph 2: Composition of the PHAXIAM management team



Source: PHAXIAM Therapeutics

A strategic steering committee has also been set up. It is made up of Gil Beyen, Thibaut du Fayet, Eric Soyer and Didier Hoch, and aims to supervise the implementation of the merger, including the operational integration of the two companies.

Team integration

The company's head office was established in Lyon, on the Erytech site. All of the Pherecydes teams, based in Nantes (phage study and phagogram testing site) and Paris (support and R&D functions), 29 people at the end of June 2023, will thus join Erytech (49 people at the end of 2022 and 40 people at the end of June 2023) who notably have know-how in clinical research (up to phase III) and regulatory in France and internationally.

The site was chosen because it is part of a major hub in the fields of infectious diseases in Europe (presence of Bioaster: Institute of Technological Innovation in Microbiology, HCL-CHU, CRIOAC Lyon, etc.), in the heart of target of the new group's research.

PHAXIAM also benefits from the establishment of Erytech Pharma in North America: Erytech Inc., which could, in our opinion, facilitate access to the local market both in regulatory, clinical and investor terms.

The objective is to finalize the integration by bringing the teams' together by the end of 2023. The operational integration and collaboration has already started with the aim of deploying the synergies targeted by the operation.

Pro forma accounts

To serve as a reference base, pro forma IFRS 2022 accounts (unaudited) have been established and show an operational loss of -€14m, and a net loss of -€11.5m for the new entity in the last FY.

Pherecydes' accounts were established under French standards, among the main IFRS restatements. We can cite the taking into account of R&D costs in the expense items and no longer in the asset accounts since the development programs in progress have not yet obtained marketing authorization. Other activity income was thus reduced by nearly €3.2m for FY 2022, and depreciation charges on development costs by nearly €325k. Furthermore, the research tax credit which was included as a product in the tax line under French standards (€1.4m in 2022) is now included in other income within the PHAXIAM scope.

Furthermore, certain exceptional positive and negative elements need to be corrected, in our opinion, to obtain a fairer vision of the performance of the two companies in 2022. In our approach, we have therefore restated the 2022 pro forma accounts of:

- a capital gain of €24.3m realized by the sale of the Erytech production site in the United States at the beginning of 2022
- provisions for depreciation of production assets and provisions for restructuring recorded in Erytech's accounts in H1 2022, for €2.5m and €1.9m respectively
- tax impact linked to the sale of the American site (taxes in H1 of €3.7m, H2 income of €3.2m once tax deferrals have been activated)
- Costs linked to the merger operation amounting to €3.1m

Overall, we obtain a corrected group share of net income of -€27.8m on a pro forma basis for FY 2022, vs. -€11.5m on an unadjusted basis.

Table 2: Summary of income statements for FY 2022 (unaudited)

€m	Erytech (IFRS)			Pherecydes French GAAP	Phaxiam pro forma IFRS
	H1	H2	FY		
Sales	**0,0**	**0,0**	**0,0**	**0,0**	**0,0**
R&D expenses	17,3	2,6	19,9	6,8	26,8
G&A et commercial expenses	7,9	6,0	13,9	3,1	20,1
Others revenues	25,3	5,7	31,0	3,8	33,0
EBIT	**0,1**	**-2,9**	**-2,8**	**-6,2**	**-14,0**
Financial result	2,6	0,5	3,1	-0,1	3,0
Taxes	-3,7	3,2	-0,5	1,4	-0,5
NP	-1,0	0,8	-0,2	-4,9	-11,5
Corrected NP*	**-17,2**	**-2,4**	**-19,7**	**-4,9**	**-27,8**

* Restated for the capital gain on the sale of the production site net of the tax impact, provisions for depreciation and restructuring and costs linked to the operation

Sources: PHAXIAM Therapeutics, TPICAP Midcap

The total balance sheet of the new group stands at €81m, including €29m in goodwill (linked to the operation, broken down in the H1 2023 reporting between the valuation of PHAXIAM's intangible assets of €17.1 and the balance in goodwill), €4.5m in other intangible and tangible assets, €6m in current assets and €41m in cash. For the main liability items: equity of €49m, financial debt of €13m (including €3m due in less than one year), €17m including rent, a supplier item of €10.5m and other current liabilities and taxes for €4m.

The main restatements of the Pherecydes balance sheet for the transition to IFRS concern R&D costs which were capitalized. Since no development program has resulted in a commercial product, the application of IFRS standards leads to a reduction in the item of intangible assets for asset items by a little more than €9m, and in return to penalizing the reserves and net income recorded in equity for liability items. Furthermore, considering rental obligations leads to the recognition of rights of use on the assets side of the balance sheet and rental debts on the liabilities side for €1.4m (including €300k in the short-term). Note that this modification of rental charges has little impact on the income statement, it in fact reduces operating costs by €40k, but leads to the recognition of additional financial charges of €55k, i.e. a net impact of -€15k on Pherecydes' net earnings.

Table 3: synthetic balance sheets for FY 2022 (unaudited)

€m	Erytech IFRS	Pherecydes French GAAP	Phaxiam pro forma IFRS
Intangible assets	0,0	9,1	0,0
Goodwill	0,0	0,0	29,2
Tangible assets	0,4	0,6	0,8
Rights of use	2,6	0,0	3,2
Others non current assets	0,2	0,2	0,3
Total non current assets	**3,2**	**9,8**	**33,5**
Clients and others	0,1	0,3	0,2
Others current assets	3,8	2,3	6,0
Cash and cash equivalent	38,8	1,0	41,3
Total current assets	**42,6**	**3,6**	**47,6**
Total Assets	**45,8**	**13,4**	**81,1**

€m	Erytech IFRS	Pherecydes French GAAP	Phaxiam pro forma IFRS
Capital	52,1	16,1	80,4
Reserves	-28,4	-3,7	-28,4
Earnings	-0,2	-4,9	-3,3
Total shareholders' equity	**23,5**	**7,5**	**48,7**
Long term provisions	0,4	0,0	0,5
Rights of use (long term)	10,2	2,5	13,1
Total non currentlLiabilities	**10,6**	**2,5**	**13,5**
Short term provisions	0,3	0,0	0,3
Rights of use (short term)	3,3	0,5	4,1
Payables	5,1	1,6	10,5
Taxes	0,5	0,0	0,5
Others current liabilities	2,4	1,0	3,4
Total current liabilities	**11,7**	**3,2**	**18,9**
Total liabilities and shareholders' equity	**45,8**	**13,2**	**81,1**

Sources: PHAXIAM Therapeutics, TPICAP Midcap

Strategy

Motivations for the merger

For Erytech

Erytech was a company based in Lyon, listed on Euronext since 2013 and on Nasdaq since November 2017, which carried out research and clinical studies in oncology on therapies based on red blood cells (encapsulation of drugs in red blood cells via a proprietary Erycaps® technology) in the areas of pancreatic cancer or acute lymphoblastic leukemia. However, despite the investments made (more than €300m raised since the creation of the company, to which are added repayable advances, the research tax credits, etc.) the various clinical studies carried out have not been able to lead to favorable results, the last phase III study in pancreatic cancer having failed in its objectives at the end of 2021.

Since then, the Erytech company has been looking for a strategic partner who would allow it to take advantage of its teams' know-how (R&D, production, regulatory in Europe and the United States), and the capabilities of financing of the company (€38.8m available at the end of December 2022). In parallel with this search for a partnership, a reorganization phase was initiated leading to the sale of the production site in the United States in April 2022 (for $44.5m and takeover of the teams), a reduction in the workforce with maintenance of main R&D teams, quality and support functions (headcount increased from 129 people at the end of December 2021 to 49 people at the end of 2022, including 7 people in the United States).

For Pherecydes

After around ten years focused on the collection, analysis and characterization to constitute a bank of natural phages, carrying out research around the purification and multiplication of phages, in 2017, the group launched a precision phage therapy approach with the development of a technique which makes it possible to test the sensitivity of a patient's bacterial strain to several phages, the "Phagogram", an in-vitro analysis of the activity of phages on the bacterial strain collected which allows only the phages that are truly active on the bacteria in question to be retained (CE marking as an in vitro diagnostic test obtained in September 2022).

The group selected around ten phages among the thousands known to primarily target bacteria which are the cause of a large majority of infections in humans, some of which can take a serious form, for which practitioners are concerned. find themselves in therapeutic impasse, and which can lead to the death of the patient, namely: 1) staphylococcus aureus; 2) Pseudomonas aeruginosa and 3) Escherichia coli. Furthermore, studies have been launched since mid-2023 to carry out this selection of phages for a fourth bacteria: Klebsiella pneumoniae.

Due to the pathologies addressed and the hindsight on the use of phages in human health, the phages selected by the group via the use of the Phagogram could quickly be used to treat patients within the framework of ATU (Temporary Authorizations for Use) / or AAC Authorization for Compassionate Access in various indications. The results obtained made it possible to guide targeted indications for the research programs carried out in-house.

The group has thus launched its first phase I/II clinical study: PhagoDAIR for osteoarticular infections on prostheses caused by the Staphylococcus aureus bacteria (1st patient included in June 2022). Projects have been announced to conduct own studies in other indications: infectious endocarditis (infection of the inner lining of the heart) caused by staphylococcus aureus, and urinary infections caused by escherichia coli.

Management also wanted to continue their investments in phage technology (collection / analysis / selection) and in precision phage therapy with the objective of developing a new generation Phagogram.

Despite the more than promising first results obtained via the AAC, and although there was no shortage of development projects, the managers of Pherecydes were confronted with the company's limited capacity to carry out all its projects simultaneously, whether in terms of workforce. (29 people spread across 2 sites at the end of 2022), as well as in terms of financing capacity (€1m in cash flow at the end of 2022). Management announced its intention to accelerate their partnership strategy, in terms of technology, R&D, clinical and regulatory studies, and even financing.

A consistent rapprochement with joint objectives and complementary profiles

After more than a year of research, Pherecydes was selected to be Erytech's partner as part of its new deployment strategy. The new entity thus formed, named PHAXIAM Therapeutics since the end of last June, benefits from:

- Pherecydes Pharma pipeline: the completion of which could be accelerated (increase in AAC, preparation for commercial launch in early access, bringing forward the study launch date, etc.) and its possible enrichment towards other indications, other bacteria, areas outside human healthcare (on its own or through the establishment of partnerships), or even related sectors such as endolysins (proteins generated by phages).
- Complementary technical platforms: Erytech's know-how in protein engineering could, for example, facilitate the exploitation of endolysins (possible cloning of endolysin genes to produce new anti-infectious agents) or even the know-how in encapsulation technologies could make it possible to explore new formulation approaches or new modes of administration of phage-based treatments.
- More mature processes and infrastructures at Erytech: studies carried out until the end of phase III, management of a production site, quality and regulatory processes, etc.
- Erytech locations: 1) in Lyon, whose site will be the future headquarters of the new group, and which is part of a major hub in the fields of infectious diseases in Europe (presence of Bioaster, HCL-CHU, CRIOAC Lyon, etc.), and which also has GMP infrastructures which could serve as a basis for a future bioproduction unit, and 2) in the United States through the subsidiary Erytech Inc. making it possible to accelerate international developments and access to the various stakeholders to access the local market in regulatory, clinical or investors.
- Erytech's cash flow should make it possible to initiate the acceleration of the R&D and clinical studies processes at Pherecydes (financial visibility extended by a few months).
- Erytech's dual European – US listing: expanded float, making it possible to reach a wider range of investors.

Building on the combination of the expertise, know-how, and resources of two companies, management has displayed an ambitious new strategy for PHAXIAM Therapeutics, with the objective of becoming a global player in phage therapy, even a leader, and thus providing solutions in the fight against antibiotic resistance in order to help patients live better and longer.

Les ambitions affichées

Creating a global player in phage therapy: expansion of the clinical portfolio and international development

In 2023 and 2024, PHAXIAM will focus its efforts on the expansion of existing development programs from Pherecydes, in particular on the phase I/II PhagoDAIR trial launched in mid-2022 (osteoarticular infections on prostheses), through the opening of new clinical centers in Europe. The teams will also prepare, in collaboration with the authorities, the protocol for phase IIb/III, which could be launched following the publication of the results of phase I/II, i.e. during 2024.

Furthermore, the new group aims to expand the clinical portfolio in phage therapy with two additional phase I/II studies, in Europe but also through collaboration with clinical centers in the United States, to address infectious endocarditis caused by Staphylococcus aureus (launch planned for the end of 2023) and complex urinary infections caused by Escherichia coli (launch planned for 2024).

As part of this international development strategy, the company also intends to capitalize on its establishment in the United States to facilitate access to investors and North American clinical and regulatory players with a view to future clinical developments.

Develop R&D skills

PHAXIAM's teams aim to rely on Erytech's technological platforms and its expertise for its R&D strategy for the formulation or administration of drugs by red blood cells (ERYCAPS®) or vesicles derived from red blood cells. (ERYCEV™) in oncological indications to adapt them to phage-based therapeutic approaches or in derived areas such as endolysins (proteins released by phages), which could broaden the field of targeted indications and markets. addressed such as cosmetics, food or even animal health.

Furthermore, research programs in the collection, selection and production of phages will continue to strengthen the coverage of bacteria targeted for new indications or to address other bacteria (new target: klebsiella pneumoniae announced last September).

Implement a global production strategy

If the group has subcontracted the production of its phages to a single Czech partner since mid-2020 via a transfer of know-how, as part of the ramp-up of the offer and the international development strategy, particularly in the United States, managers are studying the possibility of using one or more other intermediaries in terms of bioproduction, as a back-up or in addition to the first.

Examine opportunities for collaboration and commercialization agreements

The partnership strategy targeted by Pherecydes will be pursued by PHAXIAM, in the field of research and development and in terms of marketing, and indications (beyond antibiotic resistance or outside human health) or specific territories, through for example license co-development partnerships, sublicensing to third parties, the creation of dedicated subsidiaries, or even distribution agreements.

Furthermore, the teams are focused on increasing compassionate use (AAC, several dozen patients already treated with Pherecydes phages) and on preparing commercial launches in early access, which could help accelerate the generation of revenue even before having completed all the clinical and regulatory steps and obtaining marketing authorization.

A promising outlook

Continuation of the strategy in the field of phages

Antibiotic resistance and phages

Antibiotic resistance, a global problem

Antibiotics have significantly reduced mortality associated with infectious diseases during the 20th century. Unfortunately, their massive and repeated use, whether in town, in hospitals, but also for animals, has led to the appearance of bacteria resistant to these drugs. Due to a genetic mutation, spontaneous or favored by exposure to antibiotics, a bacteria can in fact escape the action of an antibiotic. Resistance is then written into its genes, by multiplying, the bacteria will transmit it to its descendants.

Bacterial resistance has thus become a global and worrying phenomenon. Some strains are multi-resistant, resistant to several antibiotics. Others have even become toto-resistant, resistant to almost all available antibiotics. This phenomenon, still rare but constantly increasing, places doctors in a therapeutic impasse, with some patients having no solution to fight the infection.

According to a study by the European Center for Disease Prevention and Control (data observed from 1 January 2015 to 31 December 2015), antibiotic resistance was the cause of 33,110 deaths in Europe (including 5,500 in France), and 671,689 patients developed infections linked to resistant bacteria (including 120,000 in France). The burden of these infections is comparable to that of influenza, tuberculosis and HIV/AIDS combined. Globally, it is estimated that antibiotic resistance causes the deaths of 700,000 people per year and, if nothing is done, could cause the deaths of 10m people per year by 2050 (Source: Antimicrobial Resistance. O'Neill. 2014), and thus become the leading cause of death in the world, ahead of cancer.

National and international health authorities have taken a certain number of measures since the 2000s to assess, monitor and attempt to limit the impact of antibiotic resistance. The main solutions include:

- Reduce the use of antibiotics in human healthcare, but also in animal healthcare to reduce the exposure of bacteria and their resistance, via awareness campaigns or the use of rapid diagnostic tests to determine whether it is necessary to antibiotics.
- Prevent the transmission of infections by acting on the spread of the virus to reduce the number of patients to be treated through hygiene measures (hand washing for example) and safety (physical distancing, wearing a mask, isolation) and vaccination.
- Develop new antibiotics: relaunch of investments since the 2010s for the discovery of new treatments, the antibiotics segment being less profitable than that of medicines, it had been neglected for many years.
- Explore new therapeutic possibilities, with the aim of overcoming the disadvantages of using antibiotics (side effects such as the elimination of bacteria residing in the digestive system of patients) or finding solutions to antibiotic resistance. Research is being carried out on the joint administration of antibiotics and absorbent charcoal or beta-lactase, on the use of fecal transplants to restore a healthy microbiota, on the development of anti-virulence therapies (blocking of the action system of the bacteria) such as the use of antitoxins, or even on a return to the forefront of phage therapy (administration of phages, viruses specifically affecting and killing certain bacteria), therapy used at the beginning of the 20th century before the discovery of antibiotic and still used in certain countries such as Eastern Europe for example.

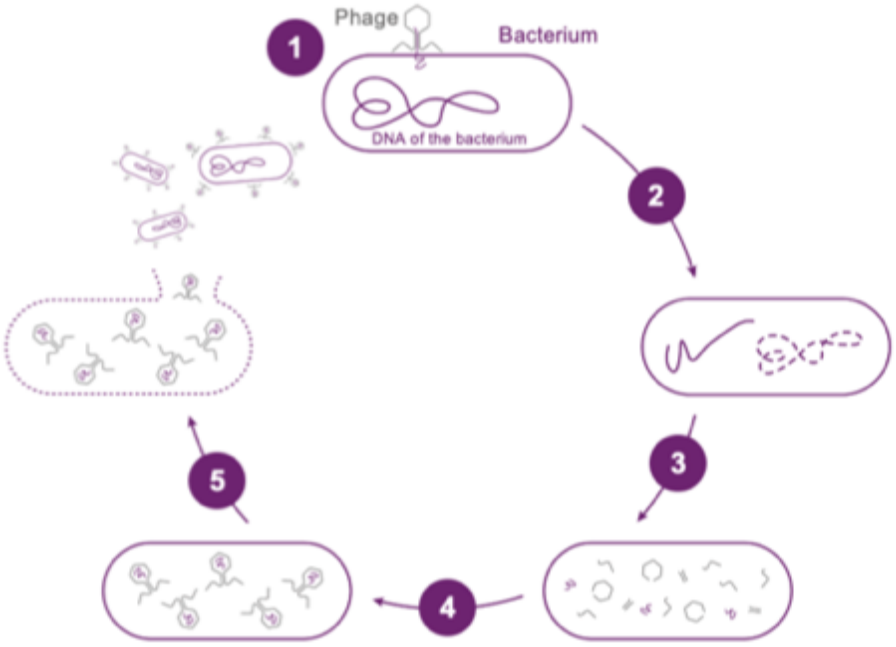
Phages

Bacteriophages or phages are viruses that only infect bacteria. They are omnipresent, they are found everywhere, especially since the environment is rich in bacteria, particularly in significant quantities in excrement, soil and sewer water.

Each phage targets a specific bacterial species to inject its DNA, reproduce there, then destroy the bacteria by releasing new phages and replicate this operation until the bacteria disappear. The infectious cycle of bacteriophages begins with the phage attaching to the bacteria thanks to the specific recognition of receptors located on the surface of the bacteria (phase 1 of the graph below). Secondly, the genetic material (DNA) of the phage is injected into the bacteria (2). Then the infectious cycle continues by hacking the bacterial machinery, in order to produce in large numbers of the genome of the new phages and its structural proteins (3). After an assembly step (4), the new bacteriophages are formed and their evacuation to the outside is carried out by the lysis (destruction) of the bacteria and therefore its death (5). As soon as the cell is destroyed, the newly created phages can find new prey and start the cycle again.

The multiplication of bacteriophages is rapid and always dependent on the presence of the targeted bacteria. Through this cycle, the phages have a unique mode of action which is intended to be very targeted (specificity), rapid (less than 45 min) and effective (self-repetition until the last bacterium).

Graph 3: Infectious cycle of lytic bacteriophages



Source: PHAXIAM Therapeutics

From phages to phage therapy

Bacteriophages were thus used to fight bacterial infections in France from the 1920s, in Germany, then in Georgia, in the USSR, in Poland, in the United States, and finally throughout the world.

In most countries, such as in France, their use and marketing disappeared at the beginning of the 1980s, their effectiveness not being called into question, but their use being less practical than that of antibiotics. However, the use of bacteriophage drugs continued in certain Soviet bloc countries. They are still commonly used in Georgia or Russia for example.

Since the 2000s, and the awareness of the phenomenon of antibiotic resistance, phage therapy has been the subject of renewed interest because it presents a solution for treating infections by bacterial strains resistant to antibiotics. Bacteriophages indeed constitute a serious avenue in the discovery of lasting treatments against bacterial infections.

Phage therapy is thus a form of biological control. It is based on the destruction of pathogenic bacteria by viruses that are fatal for the latter, but incapable of infecting us. With phages, there is no inevitable risk of resistance: if a bacteria mutates and becomes insensitive to a given phage, there necessarily exists another capable of killing it.

Indeed, there are a very large number of phages in nature (several thousand), each of them is specific to a bacterial species or even a particular strain. This means that the treatment of a given infection requires the use of a phage (or a cocktail of phages) effective on the bacteria(s) present in the patient. In short, it is a very personalized medicine, which must adapt the treatment to each particular case. This therefore requires being able to identify the pathogenic bacteria very precisely and having access to a “phage bank” containing a large number of well-characterized viruses to respond effectively to the infection.

In practice, the bacteria causing the infection from which a patient suffers are removed, cultured and placed in contact with a mixture of phages. Those capable of infecting the patient's bacteria will multiply until they rupture (“lysis”) and therefore die. Released into the culture medium, the newly formed phages then infect the still living bacteria and the cycle begins again. When all the bacteria have died, the culture medium contains many phages, which are purified and administered to the patient. The same cycle of infection/destruction then takes place until all the targeted bacteria disappear and the infection is cured. And since there are no longer any bacteria to infect in the patient's body, the phages disappear.

Phage research programs address areas beyond bacterial infections, such as immuno-oncology (adjunctive treatment against bacteria promoting cancer or to locally deliver genes for the expression of associated antigens to tumors), the microbiota (modulation of the microbiome and elimination of bacteria which have been linked to the development and progression of immune-mediated diseases such as inflammatory bowel diseases) or even dermatology (fight against acne or other conditions linked to bacterial attacks such as atopic dermatitis, or infections following burns for example), illustrating the significant potential of phage therapy.

Approach targeted by Pherecydes - PHAXIAM: precision phage therapy

Since its creation in 2006, Pherecydes has developed skills in collecting phages in their natural environment (sewers, etc.), screening, selection and characterization of a large quantity of phages allowing only the most efficient, that is to say targeting a maximum of bacterial strains to best target the targeted infection.

Like the antibiogram for antibiotics, a laboratory test aimed at determining the sensitivity of a bacteria to different antibiotics, Pherecydes has also developed a technique which makes it possible to test the sensitivity of a patient's bacterial strain to several phages: the Phagogram. The Phagogram is an in-vitro analysis of the activity of phages on the bacterial strain collected which allows only the phages that are truly active on the bacteria in question to be retained. Selected phages not only target one species of bacteria, but within that species they target a subset of strains. This ensures maximum effectiveness of the treatment while respecting the patient's microbiota.

On 12 September 2022, the Phagogram developed by Pherecydes Pharma received a first registration as an in vitro diagnostic test according to the EC Directives. The company's laboratory, based in Nantes, is now responsible for carrying out Phagograms for patients involved in ongoing clinical studies and for patients undergoing compassionate treatment.

A new generation of Phagogram 2.0 is being developed in partnership with the CEA, aiming for a faster, automated and scalable tool. The objective is for precision phage therapy to become easily accessible to everyone through large-scale deployment of the solution to other players closer to patients, such as private analysis laboratories or in hospitals. This project is partly financed by BPI as part of the Future Investment Program for €2m, or 50% of the estimated cost of the project (including 80% for Pherecydes Pharma and 20% for the CEA).

If the targeted treatment is individualized, the phages targeted for the treatment are standardized and sourced within a tight collection. Indeed, the company has selected a few phages by indication, targeted based on the criteria of effectiveness, purity and production capacity.

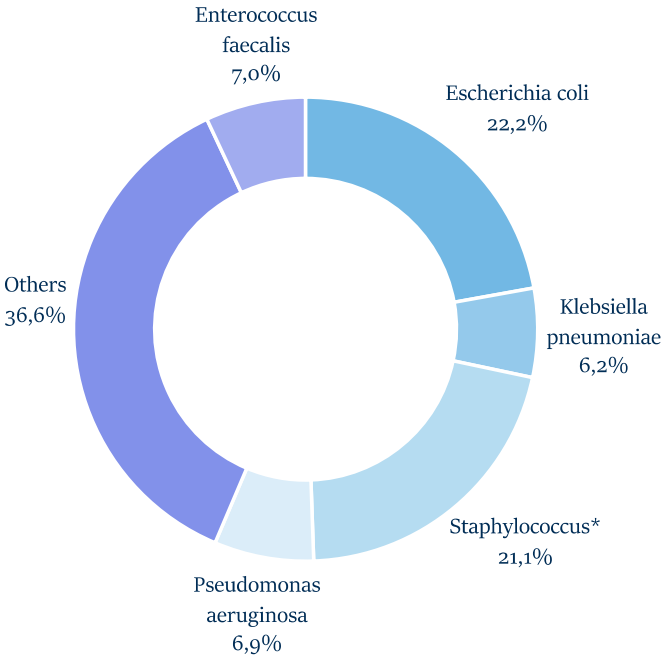
Currently targeted bacteria / indications

Thanks to the developments carried out, the company is currently targeting four types of bacteria: 1) staphylococcus aureus (2 selected active phages), 2) Pseudomonas aeruginosa affecting the respiratory tract (4 selected phages), and 3) Escherichia coli causing complex infections of the urinary tract in particular (4 selected phages), classified among the most frequent in terms of nosocomial infections, and since September 2023 klebsiella pneumoniae (launch of the collection/selection/characterization phase).

Since 1996, France has conducted a national survey of the prevalence of nosocomial infections (infections contracted while in a healthcare establishment) every 5 years, which provides a good idea of infections by category and the evolution of these infections. (Source: Sant é Publique France).

In the survey carried out in 2022, the results of which were made public in May 2023, the ranking of infections contracted in hospitals has changed little. Escherichia coli remains the most common bacteria in nosocomial infections in France in 2022 (22.15%), followed by staphylococci (21.1% including staphylococcus aureus (12.2%) and staphylococcus epidermidis (5.5%), enterococcus faecalis (7.0%), pseudomonas aeruginosa (6.9%) and klebsiella pneumoniae (6.2%). Through its research, the target group accounts for almost half of nosocomial infections.

Graph 4: Relative share of microorganisms in nosocomial infections in France (2022)



*dont *staphylococcus aureus* à 12,2% et *staphylococcus epidermidis* à 5,5%

Source: Santé publique France

The work carried out by Pherecydes has already obtained promising results in the context of the various compassionate treatments carried out since 2017, and in the context of pre-clinical programs on the three bacteria concerned by the historical studies.

Graph 5: Characteristics and performance of the selected phages

Targets	Selected phages	Reference panel coverage*	Activity on clinical strains
Staphylococcus aureus	2	78%	98%
Pseudomonas aeruginosa	4	98%	80%
Escherichia coli	4	91%	Na

*Panels used: staphylococcus aureus: CNR Staphylococci, Pseudomonas aeruginosa: De Soyza, Escherichia coli: Donamur – national reference center for enterobacteria

Source: PHAXIAM Therapeutics

In September 2023, management announced extending the group's research to infections caused by Klebsiella pneumoniae (pneumonia, urinary tract infections, bacteremia, and liver abscesses). The phage selection process is underway, the objective is to establish initial proofs of concept. The first tests on humans will, as for other indications, probably take place in the form of AAC, but not before 2026, in our opinion.

The progress made and the targeted indications

Staphylococcus aureus

Characteristics of the bacteria

The bacterium Staphylococcus aureus, or Staphylococcus aureus, has been recognized by the WHO as a priority pathogen for the research and development of new antibiotics (global priority number 2 out of 3: "high").

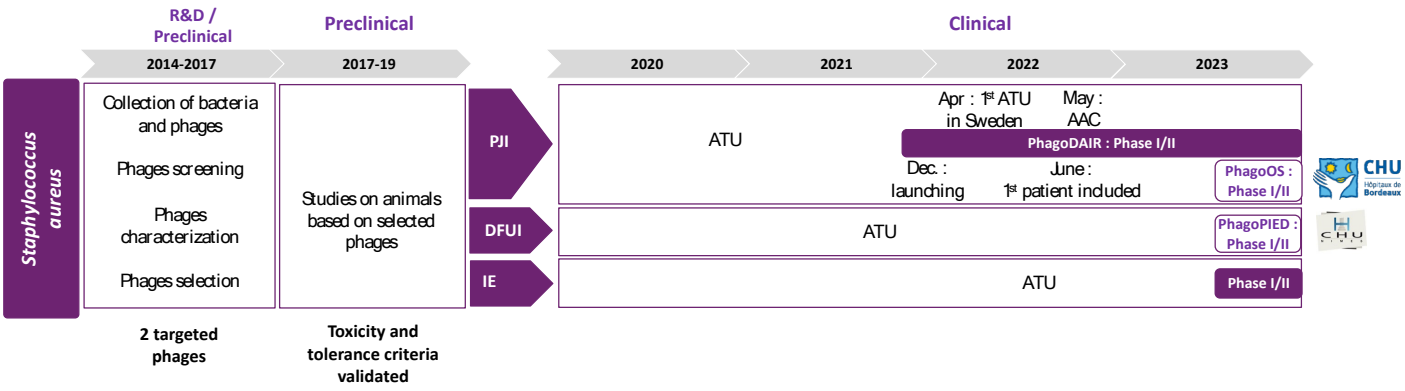
In the French national survey on the prevalence of nosocomial infections published in 2023 (based on 2022 data), staphylococcus aureus represented 12.2% of nosocomial infections. However, Staphylococcus aureus has a strong adaptive power and has thus developed different mechanisms of resistance to antibiotics. Among the patients infected with staphylococcus aureus in the study published on 2017 data, 27.2% were infected by strains resistant to methicillin, for example. Affecting patients who are most often weakened, this bacteria induces a high mortality rate.

According to the CDC, in 2019, 323,700 Americans developed resistant infections (RMSA) linked to staphylococcus aureus, in healthcare establishments and in cities, and 10,600 died. The associated health costs were estimated at $1.7b in 2017.

The developments on staphylococcus aureus carried out by Pherecydes come from a preclinical program, launched in 2014 and co-financed by the public authorities, called PHOSA, which made it possible to select 2 active phages which act alone or in combinations, on a wide variety of strains of staphylococcus aureus. The production of these phages, entrusted to MB Pharma (GMP label), makes it possible to provide the phages used in the context of ATU: more than 40 patients have been treated under ATU/AAC, the vast majority intended for patients with osteoarticular infections on prostheses, but also patients with osteitis-bone infections, diabetic foot infections, or even endocarditis-infection of the inner wall of the heart.

The research carried out internally and by partners targets three indications in the field of Staphylococcus aureus: Osteoarticular Infections on prostheses (OAI), Infectious Endocarditis (infection of the inner layer of the heart) and diabetic foot ulcer (DFU).

Graph 6: Historical developments in the field of staphylococcus aureus



Source: PHAXIAM Therapeutics

1st targeted indication for the staphylococcus aureus bacteria: osteoarticular infections on prosthesis (OAI)

Target market

No clinical development has been successful to date for this indication. Management believes that phage therapy is particularly well suited to IOA infections by staphylococcus aureus given a treatment applied directly to the infection, in the context of a closed site.

In the United States, in 2020, the number of prostheses installed on patients was estimated at 498,000 for hip prostheses and 1,065,000 for knee prostheses, with a high expected growth rate for the next 20 years (doubling by 2030). In Europe, it is estimated that 711,736 hip prostheses and 538,806 knee prostheses were installed in 2017.

Osteoarticular infections (OAI) affect between 1% and 2% of hip prostheses, and between 1.5% and 3% of knee prostheses, and are serious complications. The protocol applied in the event of infection following knee or hip prosthesis installation, called DAIR (Debridment, Antibiotics and Implant Retention) is cumbersome and restrictive (high dose of systemic antibiotics, new surgeries, etc.), fails in 50% of cases present a high risk of reinfection (60%), amputation (around 11%), or even patient death (25% at 5 years), and is relatively expensive ($150k in the United States and €50k to €70k in Europe).

However, it is estimated that 30% to 50% of these infections are due to the resistant Staphylococcus aureus bacteria, i.e. approximately 11,508 osteoarticular infections per year in the United States, and approximately 8,576 in Europe (France, France, France, France, France).), or a total of around 20,000 infections each year.

Phase I/II study: PhagoDAIR

Between 2017 and 2021, the company treated, under Temporary Authorization for Use (ATU), a dozen patients with Staphylococcus aureus infection via the application of its phages. These treatments made it possible to test the feasibility, tolerance and effectiveness criteria relating to the phage therapy developed by the group (publication in November 2020 in Frontiers in Medicine).

After promising initial results, the group obtained the green light from regulatory authorities to launch a phase I/II clinical study in December 2021: PhagoDAIR. The first patient was included in June 2022 at the Hospices Civils de Lyon. The study also carried out in other European countries (France, Netherlands, and France), plans to include 64 patients suffering from an infection of the knee or hip joint due to staphylococcus aureus, distributed between the phage therapy treatment group and the control group which will receive placebo, in addition to the reference treatment.

Patients treated with phage therapy receive anti-Staphylococcus aureus phages active on their strain, selected using the Pherecydes Phagogram. The standard treatment consists of the DAIR surgical procedure (Debridement, Antibiotics, Implant Retention) associated with suppressive antibiotic therapy. The evaluation is done 12 weeks after the application of the phages and patient monitoring is planned for 24 months.

The first results of the PhagoDAIR study are expected in 2024 and monitoring of patients will continue until the first half of 2025. Given the results obtained on patients who have already benefited from this treatment protocol (more than 90 to date under AAC or as part of the clinical study), management has already announced that they have initiated the design work for the Phase Iib/III study (multicenter, randomized, comparative, double-blind) which will be launched once the preliminary results of the PhagoDAIR study are known (possibly H2 2024). Interactions with regulatory authorities (FDA and EMA) will thus be launched before the end of 2023.

Development continues

In April 2022, the group announced the authorization of a first international compassionate treatment. The Swedish regulatory agency (SMPA – Swedish Medical Products Agency) has given its approval to treat a case of osteoarticular infection on a prosthesis with anti-staphylococcus aureus phages from Pherecydes Pharma.

In May 2022, Pherecydes Pharma obtained Compassionate Access Authorization (AAC) from the ANSM for its anti-Staphylococcus aureus phages, intended for patients who have failed antibiotic therapy. To date, Pherecydes Pharma had treated around 40 patients with anti-staphylococcus phages. Aureus in the compassionate framework under the supervision of the ANSM, but outside the AAC regime (in the form of ATU). These phages, administered by different routes (intra-articular, intravenous, broncho-alveolar nebulization, etc.), have demonstrated excellent tolerance, with no reported side effects. Thanks to the green light from the authorities, the group can now make these categories of phages available to patients in therapeutic impasse and thus market its products for the first time.

After several years of implementing the protocol, the Bordeaux University Hospital should launch a phase I/II study in osteoarticular infection on a prosthesis sponsored in the framework of a PHRC (Hospital Research Program) in 2024: PhagOS. Pherecydes will provide the phages that will be used in this study.

2nd targeted indication for the staphylococcus aureus bacteria: Diabetic Foot Ulcer

Target market

Diabetic foot ulcers (UPD in French and DFU in English for Diabetic Foot Ulcer) are among the most common complications among patients. Staphylococcus aureus is the organism most often responsible for diabetic foot infection.

The incidence of diabetic foot ulcers is increasing given the constant increase in the number of diabetics recorded in the world (463m diabetics in 2019 worldwide and 700m diabetics by 2045 according to the IDF – International Diabetes Federation).

In the United States NCBI (National Center for Biotechnology Information), 15% to 25% of patients with diabetes can develop DFU. NCBI estimates that approximately 5% of patients with type 2 diabetes (90% of those with diabetes) develop foot ulcers each year and 1% end up requiring amputation.

Company research advances

For this indication, whose study the company did not a sponsor, financed within the framework of a Hospital Clinical Research Program (PHRC), will study the tolerance and effectiveness of PHAXIAM phages in the treatment of infections of Diabetic Foot Ulcers. The promoter of this study called PhagoPied is the Nîmes University Hospital and the company will provide the phages. After several years, the study protocol is being finalized, which should make it possible to start the study in early 2024.

The main objective of the study is to compare the effectiveness of standard treatment associated with a cocktail of topical anti-staphylococcal bacteriophages compared to standard treatment plus placebo for diabetic foot ulcers infected by Staphylococcus aureus. This effectiveness will be measured via the relative reduction in the surface area of the wound.

3rd targeted indication for the staphylococcus aureus bacteria: infective endocarditis

Target market

Endocarditis is an infection of the endocardium (inner layer of the heart), heart valves (90% of cases) or the aorta. This infection is most often caused by bacteria, mainly Staphylococcus aureus. When it is localized on the valve, the lesions caused by the infection affect their tightness and the functioning of the heart is hampered, sometimes severely. Endocarditis can thus be complicated by cardiac or vascular disorders, or even by a generalized infection.

Although rare, infectious endocarditis is a serious illness that leads to the death of the patient in 15 to 20% of cases, particularly when it appears in people already suffering from heart problems, for example those who have prosthetic or deficient valves: mortality of around 30-40% for this type of patient when it is the staphylococcus aureus bacteria which is the cause of the infection.

Each year in France, around 2000 cases of infective endocarditis are diagnosed. In 60% of cases, this infection appears in a person who already has a history of heart disease (for example, in whom a prosthetic valve has been fitted). However, 40% of endocarditis appears in a healthy heart.

Company Research Advances

Following feedback from the two ATUs carried out on patients with endocarditis (phages administered intravenously), the company announced, in March 2022, the launch of tests on porcine models of its anti-staphylococcus aureus phages, in partnership with Navarrabiome, a Spanish biomedical center.

The promising results obtained on animal models have led management to schedule the launch of a phase I/II study in this area in 2023, with the first patient to be included before the end of the year.

Pseudomonas aeruginosa

Characteristics of the bacteria

The Pseudomonas aeruginosa bacteria has also been recognized by the WHO as a priority pathogen for the research and development of new antibiotics (global priority number 1 out of 3: “critical”).

In the French national survey on the prevalence of nosocomial infections published in 2023 (based on 2022 data), pseudomonas aeruginosa represented 6.9% of nosocomial infections. It is one of the most difficult bacteria to treat clinically. The mortality rate reaches 50% in vulnerable (immunocompromised) patients. According to Opatowski, around 10.9% of infections are resistant, or nearly 4,500 patients per year in France, only for infections linked to hospitalization.

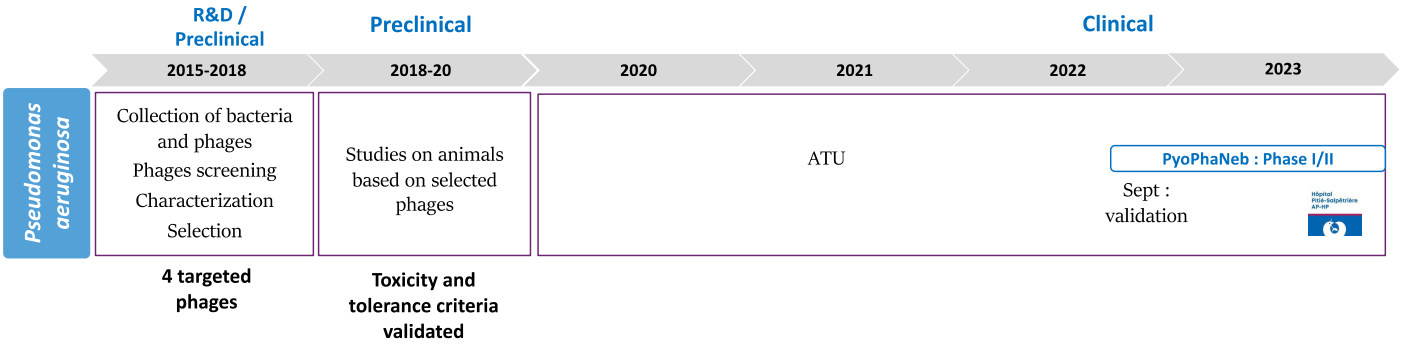
Most often the bacteria causes respiratory tract infections (RTI). This type of infection is largely responsible for ventilator-acquired pneumonia (VAP), a frequent and serious complication of assisted ventilation in intensive care units and intensive care units (in intensive care, approximately 90% of nosocomial pneumonias are VAP).

Launched in June 2015, the Pneumophage research project, carried out in partnership with the CEPR (Center for the Study of Respiratory Pathologies, joint INSERM/University of Tours academic laboratory) and the company DTF (company specializing in the development of new adapted medical devices to the nebulization of drugs), aimed to demonstrate the interest of inhaled phage therapy for treating pseudomonas aeruginosa respiratory tract infections. Several tests have been carried out on pigs. It was determined that the phages used significantly reduced the bacterial load related to pseudomonas aeruginosa in the infected lung lobe.

The combined results of these programs made it possible to arrive at a selection of 4 phages active on the pseudomonas aeruginosa bacteria, the production of which was entrusted to MB Pharma (GMP label), and makes it possible to supply the phages used within the framework of ATUs. : more than 40 patients have been treated with ATU/AAC for indications such as osteoarticular infections on prostheses, osteitis-bone infections, lung infections, endocarditis-infection of the inner wall of the heart, bacteremia – infection present in the blood, or more infections on burns.

Among respiratory tract infections, the company has identified a priority indication to initiate the clinical development of anti-pseudomonas aeruginosa phages: Ventilator-Assisted Pneumonia (VAP).

Graph 7: Historical developments in the field pseudomonas aeruginosa



Source: PHAXIAM Therapeutics

Targeted therapeutic areas: respiratory tract infection

Ventilator-associated pneumonia

PVA are the most common nosocomial infections in intensive care. They generally occur after 48 hours of mechanical ventilation. Mortality is high (20%) and it prolongs the duration of mechanical ventilation and hospitalization in intensive care. This indication is now the main target of the developments followed by the group for anti-pseudomonas aeruginosa phages.

The action of the phages selected by the group on respiratory infections is promising and could lead to the deployment of the group's know-how for other indications in this therapeutic area.

Advancement of research programs

In the context of pre-clinical studies (on animals) and ATU, the selected phages administered by nebulization, nasal instillation or intravenous, have demonstrated a significant reduction in the pulmonary bacterial load, non-toxicity with high tolerance, including with intravenous injections, as part of compassionate treatment. The preclinical phase was completed in 2020 and the objective is now to evaluate it in humans, as part of a clinical trial (phase II, 180 patients).

This study is not sponsored by the company but funded as part of a Hospital Clinical Research Program (PHRC), launched in September 2022. It studies the tolerance and effectiveness of phages in the treatment of pneumonia associated with mechanical ventilation caused by pseudomonas aeruginosa. The promoter of this study, called PyoPhaNeb, is AP-HP and the company provides the phages (upstream tests, including toxicity completed, launch of the study planned for early 2024).

Escherichia coli

Characteristics of the bacteria

The escherichia coli bacteria has also been recognized by the WHO as a priority pathogen for the research and development of new antibiotics (Enterobacteriaceae family, global priority number 1 of 3: “critical”).

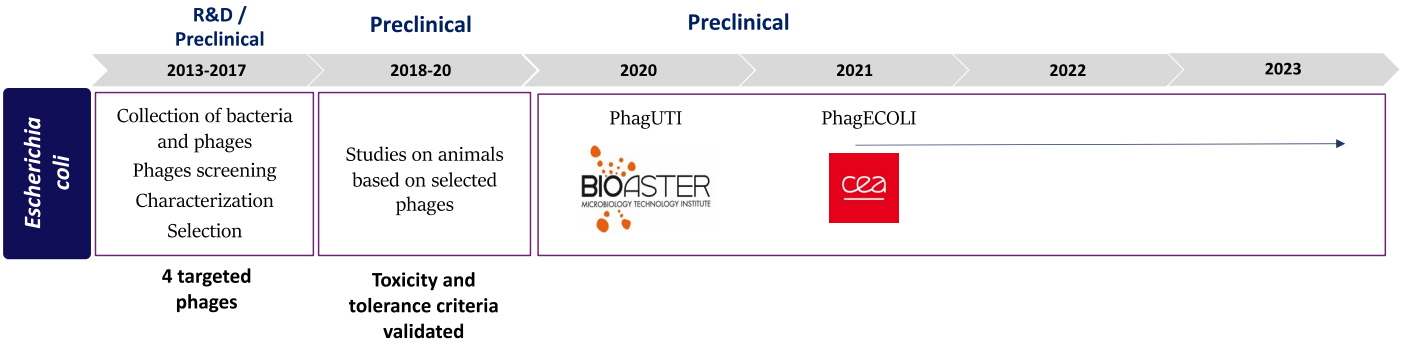
By microorganism, Escherichia coli was the most common bacteria in nosocomial infections in France in 2022 (22.2%). Escherichia coli represents 80% of the bacteria in our digestive tract. This bacteria is harmless in the majority of cases. However, certain strains turn out to be pathogenic and can be complicated by extraintestinal infections and generate urinary tract infections (primary causative agent in women).

According to Opatowski, around 14.4% of infections are resistant, or nearly 30,000 patients per year in France, only for infections linked to hospitalization. According to data from the European Center for Disease Prevention and Control (ECDC), resistant E. coli infections represent the most common infections in Europe in hospitals with more than 163,000 cases per year. The CDC estimates that 197,100 Americans developed resistant infections linked to escherichia coli in 2019, in health care establishments and in cities, and 9,100 died.

The key indications targeted for clinical development are complicated urinary tract infections (UTIs), infections that are among the most common bacterial infections, affecting 150m people worldwide, including nearly 2m in France. In 2017, in the United States alone, according to the same source, there were an estimated 10.5m consultations for urinary tract infection symptoms and 2m to 3m visits to emergency rooms. Additionally, urinary tract infections are a significant cause of morbidity in infants, men, and women of all ages.

The pathogen most often responsible for these urinary infections, whether simple or complicated, is Esherichia coli. According to the ECDC, in Europe in 2019, more than half of samples are resistant to at least one group of antibiotics. Pherecydes' research focuses primarily on complicated urinary tract infections, particularly catheter-associated urinary tract infections and pyelonephritis.

Graph 8: Historical developments in the field of *escherichia coli*



Source: PHAXIAM Therapeutics

Targeted therapeutic areas: urinary tract infection

In 2019, Pherecydes and BIOASTER, the French Institute for Research in Microbiology and Infectious Diseases, entered into a collaboration agreement as part of a project called PhagUTI aimed at exploring the use of phage therapy in the treatment complicated urinary tract infections caused by escherichia coli (ITU in French and UTI in English). The group is now aiming to launch a phase I/II study conducted internally in this indication during 2024 (36 patients targeted, administration of phages locally, inside the bladder).

Following the work carried out in the pre-clinical phases, the group selected 4 phages active on the escherichia coli bacteria, the production of which was entrusted to MB Pharma. The GMP label should be obtained before the end of 2023, which should make it possible to supply the phages for the phase I/II study carried out internally planned for 2024.

In 2021, the group launched the PhagECOLI project based on the complementary expertise and experiences of the company and the CEA. This three-year project aims to offer new treatments for difficult-to-treat or resistant Escherichia coli infections. The project notably includes the development of a new generation Phagogram with the aim of measuring the effectiveness of anti-Escherichia coli phages on the patient's bacterial strain. In January 2022, the PhagECOLI project received a €2m grant from BPI as part of a call for projects on the theme “Emerging infectious diseases and new radiological, biological and chemical threats”.

In March 2022, the group announced a new research collaboration with BIOASTER, called Phagebac, to treat bacteremia (blood infections) caused by escherichia coli bacteria, but also by staphylococcus aureus and pseudomonas aeruginosa, with phages (intravenous administration).

Bacteremia, defined as the presence of pathogenic bacteria in circulating blood, represents the second cause of bacterial infection in the world with approximately 1.5m deaths associated with this pathology per year. In the United States alone, the CDC estimates that up to 1.7m people develop bacteremia each year. Staphylococcus aureus, escherichia coli and pseudomonas aeruginosa represent the major causes of bacteremia resistant to antibiotic treatments.

The results of this research could lead to completing the indications targeted by the company's teams.

Klebsiella pneumoniae

Characteristics of the bacteria

Klebsiella pneumoniae bacteria has been recognized by the WHO as a priority pathogen for the research and development of new antibiotics (global priority number 1 of 3: “critical”).

In the French national survey on the prevalence of nosocomial infections published in 2023 (based on 2022 data), Klebsiella pneumoniae, the cause of numerous infections, in particular pneumonia, urinary infections, bacteremia and abscesses of the liver, represented 6.2% of nosocomial infections, a doubling in 10 years; the latter only represented 3.1% of nosocomial infections in 2012.

It is estimated that in Western countries, around 3 to 5% of pneumonias are linked to an infection caused by Klebsiella pneumoniae. In patients at risk (alcoholics and sepsis), mortality linked to this type of infection is between 50 and 100% (Source: John V. Ashurst; Adam Dawson ET AL., 2022).

Furthermore, if the bacteria mainly infects immunocompromised people, the emergence and spread of hypervirulent and multi-resistant strains have recently broadened its potential targets to people without health problems. According to the company, the incidence of resistance to Klebsiella pneumoniae is estimated between 90,000 and 100,000 patients in the United States and in the 5 main European countries (France, Germany, United Kingdom, Spain and Italy), and mainly concerns urinary and pulmonary infections.

Advancement of research programs

To respond to this unmet therapeutic need, and with their historical expertise, management announced in September 2023 the launch of pre-clinical work to select phages and test their effectiveness in pulmonary, blood and urinary infections caused by Klebsiella pneumoniae.

The objective is to develop a fourth family of phages, which could make it possible to launch the first trials on humans, if AAC is obtained, by 2026, in our opinion. This new target could provide new addressable indication in the years to come, and thus serve as a relay in the pipeline of products in development, and ultimately in terms of marketed products.

Thanks to collaborative programs and public financing (mainly research tax credits), with around €30m raised in capital since the creation of the company before the merger with Erytech, Pherecydes has succeeded in deploying a pipeline of promising projects whether in terms of technological platform (collection, selection, characterization and production of phages, personalized medicine with the development and use of the phagogram, etc.), variety of bacteria and targeted indications particularly exposed to antibiotic resistance, placing many patients in therapeutic impasse, as well as in terms of potential effectiveness of treatments under development (numerous ATU/AAV with promising results). The Erytech merger should make it possible to accelerate the development program and probably enrich the project pipeline, while offering more opportunities in terms of partnerships (technological, R&D, commercial) or source of financing (access to American market).

Acceleration and enrichment of developments

Acceleration of pre-clinical and clinical programs

A positioning which suggests lighter clinical phases and marketing

Possibility of testing phages on humans within the framework of AAC (Compassionate Access Authorization)

The use of pharmaceutical specialties not yet benefiting from a marketing authorization (AMM) and not being the subject of a clinical trial, can be carried out by first obtaining an AAC (Compassionate Access Authorization, formerly ATUn – Temporary Authorization for Nominative Use) from the ANSM. An AAC is issued by the ANSM for a period of 3 years (renewable) under the following conditions:

i) The specialties are intended to treat, prevent or diagnose serious or rare diseases.

ii) There are no appropriate treatments available on the market, with no possibility of inclusion of a patient in an ongoing clinical trial.

iii) The AAC is issued at the request and under the sole responsibility of the prescribing doctor, as long as the medicine is likely to be of benefit to the patient.

Historically, the company had been able to test its phages for pseudomonas aeruginosa and staphylococcus aureus bacteria, on around fifty patients but outside the AAC regime, at the request of practitioners (more than fifteen indications), without real supervision and control. data obtained as part of the treatments, and without the possibility of invoicing for Phagogram and phage supply services.

In May 2022, the group obtained an AAC from the ANSM for its anti-staphylococcus aureus phages intended for the treatment of intra-articular and bone infections (around ten patients since treated under the AAC) , which should make it possible, thanks to this supervised process, to expand the targeted populations and collect more data. The AAC application filed for anti-pseudomonas aeruginosa phages is also currently being examined by the ANSM.

In parallel with clinical studies, the group is in the process of preparing Early Access Authorization (AAP or Early Access) files with the ANSM and the HAS, which will depend on the data collected as part of the clinical studies. in progress.

Early Market Access Authorization (APP) Strategy

Early access is reserved for certain specialties whose effectiveness and safety are strongly presumed in a specific therapeutic indication targeting a serious, rare or disabling disease, without appropriate treatment, for which the implementation of the treatment cannot be deferred, and for which they are presumed to be innovative, subject to a commitment by the laboratory to submit an application for Marketing Authorization within a specified period of two years.

Once the application has been submitted, the ANSM assesses the benefit/risk ratio of the drug. If it issues a favorable opinion, the HAS also evaluates the various criteria and must render its decision within 90 days from the administrative admissibility of the request. In the event of authorization, the laboratory undertakes to submit an MA application within a maximum period of 2 years, and benefits from an Early Access Authorization for a period of one year, renewable for one year.

Medicines benefiting from early or compassionate access are automatically covered 100% by Health Insurance upon granting of authorization. PHAXIAM should thus be able to bill its phages within the framework of AACs or potential AAPs.

Phase I and phase II combined studies and restricted cohorts

Given the long hindsight on the use of phages in the field of healthcare (toxicity and tolerance criteria widely demonstrated), and the natural nature of the phages used in the group's research (no problems linked to the use of GMOs), the safety criteria which are usually the subject of phase I studies are already met, which allows, once the pre-clinical stages have been completed, to directly carry out a phase I/II and to test the effectiveness of the selected phages in the targeted patient indication.

Furthermore, the group primarily addresses potentially serious pathologies and for which practitioners find themselves at a therapeutic impasse, the protocols accepted by the authorities as part of the phase I/II studies address restricted cohorts (64 patients for example for PhagoDAIR or another dozen patients for the study on infective endocarditis, for projects carried out internally), potentially reducing the duration and cost of these studies.

Finally, given the specificity of the targeted indications, the effectiveness of the treatments which will be administered to patients can be quickly measured (12 weeks for PhagoDAIR) making it possible to quickly obtain the first key data, supporting the implementation of the next stages of clinical research.

Management believes that these restricted cohorts and these rapid primary results could also be validated by the authorities for phases II/III or III.

The field of phage therapy and the pathologies addressed make it possible to deploy shorter and lighter clinical research programs, which combined with the financing resources from the Erytech scope, should make it possible to accelerate and multiply the studies carried out internally. However, given the multiplicity of bacteria, therapeutic targets and areas to address, the group will continue its strategy of seeking partnerships in parallel.

Acceleration of clinical research projects

Based on the three targeted bacteria and selected phages (2 for staphylococcus aureus, 5 for escherichia coli, and 4 for pseudomonas aeruginosa), the group is gradually expanding its pipeline of projects in different fields of application, alone or through partnerships. carried out by hospital centers and for which the group provides its know-how in the identification of bacteria and the selection of phages (use of the Phagogram), and in the management of the production of phages which will be administered to patients participating in the studies.

For partnership projects, current projects are based on PHRC (Hospital Clinical Research Program):

- PhagOS project led by the Bordeaux University Hospital which should launch a phase I/II study in osteoarticular infection on prosthesis in 2024.
- PhagoPied project led by the Nîmes University Hospital which aims to study the tolerance and effectiveness of PHAXIAM phages in the treatment of diabetic foot ulcer infections as part of a phase I/II study which should be launched in H1 2024.
- PhyPhaNeb led by AP-HP which targets respiratory infections contracted under assisted ventilation, launch of the phase I/II study planned for 2024.

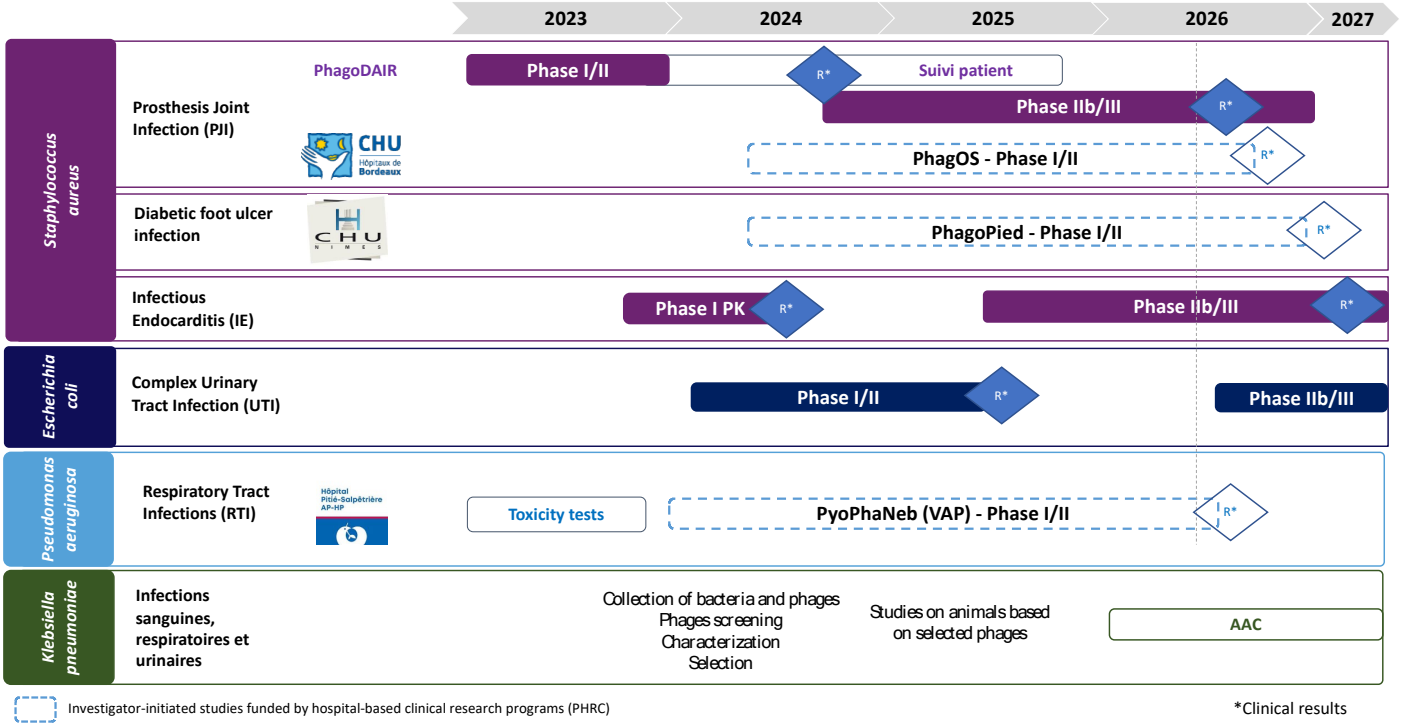
The objective is to continue research partnerships, with hospitals but also other partner companies, for which PHAXIAM would provide the know-how in terms of bacteria identification, phage selection and production management, and the partner would oversee conducting and financing the studies. A first partnership was announced last October with the company Vetophage, a company created in 2017 and based in Lyon, specializing in veterinary phage therapy. The two companies will combine their know-how in phages and derivatives (endolysins) in the fight against microbial resistance. PHAXIAM can thus access the large bank of phages and endolysins discovered by Vetophage and has exclusive licensing options on certain phages and endolysins from the Vetophage platform for human applications.

For projects carried out internally:

- in osteoarticular infections on prostheses:
  - PhagoDAIR phase I/II study. In December 2021, the group obtained the green light to launch the phase I/II study to verify the effectiveness of the selected phages. The first patient was included in June 2022 at the Hospices Civils de Lyon. Thanks to the involvement of teams from Erytech, the study was extended to other clinical centers in Europe (Spain, Netherlands, Austria and Germany), which should make it possible to achieve the objective of 64 patients included in the study, divided between the phage therapy treatment group and the control group which will receive placebo, in addition to the reference treatment. Preliminary results are expected in 2024, and patient monitoring will continue in 2025 (24-month follow-up);
  - The teams are already working on preparing phase IIb/III, then initiating the first exchanges with the American and European authorities before the end of 2023. The study could be launched, in the event of favorable preliminary results from phase I/II, during 2024, with first results planned for the end of 2026.

- Project in infectious endocarditis: following the work carried out with Navarrobiome on animal models during 2022, and the results of ATU, the group aims to launch by the end of 2023 a phase I PK clinical study / 12 targeted patients, in 4 centers in France, and spread over two arms (results expected for 2024), which constitutes a new indication. If successful, phase IIb/III could be initiated as early as 2025, with results targeted for the end of 2026.
- Project in complex urinary tract infections: following the work carried out with BIOASTER (since March 2022), the group could launch a phase I/II study in 2024 on the effectiveness of phages selected by PHAXIAM on urinary infections caused by e-coli, with results planned for early 2025.
- For the klebsiella pneumoniae bacteria, pre-clinical developments have just begun, the first step involves phage screening, characterization, and their selection according to their effectiveness on the targeted indications (blood, respiratory and urinary infections) . Then based on a restricted collection (3 or 4 phages for other bacteria), animal tests will be launched to test the tolerance and possible toxicity of the phages selected. Once these stages have been completed, the group will probably be able, as in its other developments, to benefit from compassionate use authorization even before the launch of potential clinical studies. Considering the experience acquired by the group, we estimate that the time of these preclinical phases could be reduced from 5 to 3 years, making it possible to carry out the first tests on patients by 2026 in our opinion. In the event of convincing results in ATUs, clinical studies could ultimately be carried out on one or more indications for this bacteria.

Graph 9: Pipeline of pre-clinical and clinical projects



Source: PHAXIAM Therapeutics

As part of the ATU, the group's phages were tested on other indications, the promising results of which could be the subject of future developments (infections on burns, infection of the aortic prosthesis, etc.), which the group could conduct more internally, at least for the first stages of clinical research, in particular thanks to the know-how of the Erytech teams in research, from the pre-clinical stage to phase III, and in regulatory matters, in Europe, as well as in the UNITED STATES.

Beyond the various regulatory stages to come (North America and Europe) from the first half of 2024, the group should be able to start communicating on the results of the first clinical studies carried out in-house (infectious endorcarditis, PhagoDAIR), communications should accelerate with the progress of the various targeted studies, making it possible to launch the following stages with the first phase IIb/III, the last stage before the Marketing Authorizations. Furthermore, the group is continuing its research programs on phages and associated technologies, targeted bacteria, or even indications which could be the subject of new clinical trials, alone or in partnership, thus continuing to expand the clinical pipeline, and most likely the upcoming newsflow.

Pipeline enrichment

Continue the collection and selection of phages to strengthen the coverage of targeted bacteria, address new indications or new bacteria

If the group has selected around ten phages to address the first three targeted bacteria, and this tight collection makes it possible to address a broad spectrum of strains of these families of bacteria, the group is continuing its work on collecting / analyzing / selecting phages. for these 3 families in order to complete the coverage on the one hand (existing indications and/or new indications) and within the framework of constant monitoring on the other hand (ensuring the performance of the targeted phages, or even the evolve because bacteria themselves are constantly evolving).

Furthermore, if the group has prioritized 4 bacteria which cover a broad spectrum of bacterioresistant infections, there are still many bacteria for which practitioners find themselves in therapeutic impasse and which could be treated by using phage therapy. The group is therefore continuing its research to collect and select phages which could address other resistant bacteria, with high incidence, which may be present in the indications already targeted to date or in other indications.

Target new indications beyond antibiotic resistance or beyond human health

Management discussed the possibility of initiating developments, alone or in partnership, in related sectors or in targeted indications such as the microbiome for example, or even serious skin conditions.

The group could also initiate programs, alone or in partnership, in areas other than human health, in animal health, in the agri-food industry (bacteria present in production sites for example, some of which are difficult to eradicate and dangerous for health). or even in cosmetics (action on bacteria which affect the skin for example).

Investments in technology

Develop related sectors

Beyond the phages themselves, managers continue to invest in the technological platform and are targeting research programs in related sectors such as endolysins which are proteins released by phages, and which have different mechanisms of action. , which are not replicable and which are not associated with a virus, which could ultimately make it possible to address other market segments such as cosmetics for example. Protein engineering know-how from Erytech could accelerate developments in this area.

Develop new formulation approaches

Erytech has developed a technology for encapsulating drugs in red blood cells for the delivery of treatments. This technology, adapted to phages, could provide a new method of administering treatments compared to localized application, injection, or even inhalation, and the development of new formulations, which could better address certain pathologies or open up new areas for the use of phages.

Diagnosis of Phagogram 2.0 program

As part of research programs and ATU/AAC (a little over sixty to date), the group has developed a Phagogram which makes it possible to identify the bacterial strain at the origin of the infection and to test the sensitivity of this bacteria to bacteriophages to select the most active(s), and which received CE marking in September 2022 as an in vitro diagnostic test (staphylococcus aureus and pseudomonas aeruginosa strains). The tests are currently being carried out at the group's site located in Nantes, and should soon be carried out entirely from the new site in Lyon by the end of the year.

The group has now embarked on the development of a second generation Phagogram, as part of the PhagECOLI project in partnership with the CEA (2022-2024 project), faster, automated and scalable (funding of €2m). from BPI, approximately 50% of the project cost, including 80% for PHAXIAM). If this project targets the e-coli bacteria, the Phagogram will ultimately aim to address other bacterial strains. The objective is in fact for precision phage therapy to become easily accessible to all through large-scale deployment of the solution to other players closer to patients, such as private analysis laboratories or in hospitals (by 2026 -2027).

A strategy that aims to establish partnerships

The group aims to pursue the partnership strategy in the field of research and development, but also aims to establish agreements in terms of marketing, in indications (beyond antibiotic resistance or outside human health), in in vitro diagnostics, or for specific territories, for example through license co-development partnerships, sublicensing to third parties, the creation of dedicated subsidiaries, or even distribution agreements, which could generate short-term milestone revenue and longer-term royalties, in addition to revenue that could be generated by the AAC/early access strategy.

However, to date, the group has not yet established such partnerships and has not yet been able to really monetize its technology within the framework of ATU/AAC. Continued investments in technology, in pipeline enrichment, and in the acceleration of clinical programs are likely to continue to weigh on PHAXIAM's operational performance without being able to be offset by significant sources of revenue.

Cash consumption forecasts

Continued significant losses

Revenue which should remain limited in the short and medium-term

Given the maturity of the project pipeline, the group is not expected to generate revenue relating to the commercialization of its phages with a view to therapeutic treatment before 2028. As part of the early access procedures, the regulatory phases could be accelerated, allowing first revenue from 2027 in the indication for osteoarticular infections on prosthesis (conservative scenario retained in our forecasts). The human health alliances that the Group wishes to establish could generate significant revenue from the sale of technology/licensing (up front, milestones, or royalties). But in our opinion, it will most likely be difficult to establish such agreements before the first results of phases I//II, i.e. 2024, or even 2025.

In the shorter term, the group could generate revenue via the marketing of phages within the framework of AAC (AAC in France since May 2022 for its anti-staphylococcus aureus phages intended for the treatment of intra-articular and bone infections) or AAP the where appropriate, using its Phagogram for diagnostic purposes, or through the marketing of know-how and technologies in other segments such as cosmetics, agri-food or veterinary. However, as AACs represent low volumes of patients, the impact on the generation of revenue from compassionate use should, in our opinion, most likely remain low.

Even if the strategy of using partners could generate revenue in the interim period, as no agreement has yet been concluded to date, out of prudence, we are not including such revenue in our scenario.

As in recent years, the group's income should therefore mainly come from subsidies: €0.5m per year at cruising speed (possible more substantial programs to come, files currently being processed) and from the research tax credits (€1.5m in our 2023 forecasts and €2m per year in the following years in view of sustained R&D efforts).

Sustained expenditures

In terms of general and administrative costs, the year 2023 should be marked by 1) the cohabitation of the different teams and structures over a large part of the year, and 2) the costs linked to the merger operation (€3.4m in H1). Despite the continued reduction in structural costs, particularly on the Erytech side, the G&A item should therefore remain significant in 2023: €16m integrated into our scenario, including €2m from the Pherecydes scope (consolidated from the date of the merger i.e. on June 23 in the PHAXIAM accounts), €10m for Erytech and €4m linked to the merger.

In subsequent years, taking into account the synergies generated by the merger such as the grouping of teams on a single site, the control of the workforce at around 50 people (comparable to the workforce of Erytech alone at the end of 2022), and the non-recurrence of costs linked to the merger operation, we estimate that general and administrative expenses could be significantly reduced in 2024, and remain contained in the following years (€10 to 11m integrated into our scenario).

In terms of R&D costs, on the Erytech side with the cessation of clinical studies (another €16.9m in costs linked to clinical studies in 2022), the item continued to reduce with only €3.3m in related costs. for research and development in H1 2023, compared to €13.7m in H1 2022.

Over the whole of 2023, with the consolidation of the Pherecydes scope from June 23, the continuation of the PhagoDAIR study and the probable launch of the study on infectious endocarditis, we estimate that R&D expenses could represent a budget of around €11m.

In the years to come, given the specificity of the positioning (unmet therapeutic needs in serious conditions) the group should probably, as for PhagoDAIR, benefit from lighter clinical protocols limiting, in our opinion, the costs of phases I/II to €4-5m, and that of phases IIb/III at €10-20m. In view of the development pipeline, the group should carry out two or three phase I/II studies in parallel, and one or two phase IIb/III studies, to which are added the regulatory stages, we estimate that the group could thus devote of the order of €12m per year in R&D costs.

Table 4: Income statement forecasts

€m	Erytech	Phaxiam				
	2022	pf 2022	2023E	2024E	2025E	2026E
Sales	**0,0**	**0,0**	**0,0**	**0,0**	**0,0**	**0,0**
R&D expenses	19,9	26,8	11,3	12,0	12,0	12,0
G&A et commercial expenses	13,9	20,1	16,0	10,0	10,5	11,0
Others revenues	31,0	33,0	2,0	2,5	2,5	2,5
EBIT	**-2,8**	**-14,0**	**-25,9**	**-20,1**	**-20,6**	**-21,1**
Financial result	3,1	3,0	-0,1	-0,1	-0,1	-0,1
Taxes	-0,5	-0,5	0,0	0,0	0,0	0,0
NP	-0,2	-11,5	-26,0	-20,2	-20,7	-21,2
Corrected NP*	**-19,7**	**-27,8**	**-22,0**	**-20,2**	**-20,7**	**-21,2**

* Restated for the capital gain on the sale of the production site net of the tax impact, provisions for depreciation and restructuring and costs linked to the operation

Sources: PHAXIAM Therapeutics, TPICAP Midcap

Overall, our forecast calls for an operational loss of -€25.9m for FY 2023 for PHAXIAM (-€12.4m published for H1 the Pherecydes scope consolidated from 23 June), up significantly vs. FY 2022 pro forma level of -€14m (12 months for the two companies), but a clear reduction restated for the proceeds from the sale of the American site for €24.3m for Erytech.

Despite the efforts made for research, thanks to the non-recurrence of charges linked to the merger (€4m estimated for 2023) and the synergies generated by the merger of Erytech and Pherecydes, we anticipate a reduction in the operational loss to €20m in 2024, a loss which should remain at a comparable level in the following years.

Given the expected levels of losses, despite the level of cash displayed at the end of June 2023 (cash of €25.2m), management announced, during the presentation of the half-year results last September, to have visibility until Q2 2024, which suggests recourse to external financing in the short-term, and probably on a recurring basis over the next few years.

Need for external financing

Beyond operational losses, the group should not consume much cash (non-activation of R&D expenses) as WCR should remain limited, the group having not yet entered the commercial phase. Overall, we expect the generation of a negative FCF of €20m to €25m per year on average for the next few years.

Furthermore, the group must amortize part of its debt (€13.1m of short-term and long-term debt accumulated in pro forma as of 12 Dec 2022 excluding rental debts), mainly state guaranteed loans: €10m for Erytech and €2m for Pherecydes.

Overall, we estimate external financing needs at €25m on average per year for PHAXIAM based on our scenario. If the group could benefit from non-dilutive financing of the type grant or bank financing / or public organizations (file currently being processed with the French and European authorities), as it is difficult to foresee this type of envelope, we have not integrated in our modeling only external financing via capital increase.

Considering the cash available at the end of 2022, we estimate that the group could raise €60m in cash over the next few years, which we have equally distributed between 2024 and 2026 in our scenario. Based on the stock price, this corresponds to the creation of a little more than 4.5m additional shares each year (vs. less than 6.1m shares at present).

Table 5: Cash generation/requirement forecasts

€m	2022	2023E	2024E	2025E	2026E
Cash flow	-23,7	-25,4	-19,6	-20,1	-20,6
Capex	-0,1	-0,2	-0,2	-0,2	-0,2
Change in WCR	-8,1	-0,7	-0,5	-0,5	-0,5
FCF	**-31,8**	**-26,3**	**-20,3**	**-20,8**	**-21,3**
Disposals	38,2	0,0	0,0	0,0	0,0
Financial invesments	0,0	0,0	0,0	0,0	0,0
Dividends	0,0	0,0	0,0	0,0	0,0
Others	0,5	0,0	0,0	0,0	0,0
Cash excess (deficit)	**6,9**	**-26,3**	**-20,3**	**-20,8**	**-21,3**
Change in debt	-1,8	-3,5	-3,0	-3,0	-3,0
Change in equity	0,0	0,0	20,0	20,0	20,0
Change in cash	5,1	-29,8	-3,3	-3,8	-4,3
Net cash	**0,0**	**2,2**	**2,5**	**3,3**	**4,6**
Cash available	38,8	11,6	8,3	4,5	0,2

Sources: PHAXIAM Therapeutics, TPICAP Midcap

Valuation and market rating

Sum-of-the-parts valuation approach

In the field of osteoarticular infections on prostheses

Osteoarticular infections (OAI) affect between 1% and 2% of hip prostheses, and between 1.5% and 3% of knee prostheses. It is estimated that 30% to 50% of these infections are due to the resistant bacteria staphylococcus aureus, or more than 20,000 infections each year in the main European countries and the United States (based on 2020 data).

Taking into account growth forecasts for the prosthesis fitting market (doubling over the period 2030, i.e. annual growth of more than 7%), and the prevalence of infections, the target market could exceed 30,000 people per year. year by 2026-2027.

To establish the potential revenue and results from the marketing of PHAXIAM therapeutic solutions in the field of osteoarticular infections on prostheses, we established our modeling on the basis of several hypotheses:

- Continuation of research work: phase I/II completed in 2024 and monitored until 2025 (cost of €2-3m incurred over 2023-2025), launch of phase IIb/III combined US and Europe for 2024-2026 (€15m estimated), a regulatory review in 2027 (US and Europe, €500k per year) and a launch on the market planned for 2028. Note that as part of the early access procedures, the regulatory phases could be accelerated, allowing the first revenue from 2027 (conservative scenario retained in our valuation approach).
- An average treatment price consistent with what was obtained in France within the framework of the AAC (€24k per patient, linked to the cure of the infection, reducing the duration of hospitalization, the probability of having to reoperate on patients, or even in extreme cases avoid the death of the patient).
- A market share which would increase from 0.5% of the target population in 2028 to 15% in 2032.
- At cruising speed, no market share or price erosion considering our cautious scenario, the price in Anglo-Saxon countries 2x to 3x higher than those obtained on the domestic market for example, the treatment being able to address segments other than just hip and knee prostheses for which infection has already been declared, and be distributed in countries outside Europe and the United States.
- A gross margin of 60% of revenue (outsourced phage sourcing).
- A tax rate retained at 25% at the end of the period to estimate the normative terminal value.
- A 15% discount rate.

Table 6: Forecast flow table, indication for prosthesis osteoarticular infections

€m	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032
No. of patients	**0**	**0**	**0**	**0**	**0**	**172**	**735**	**1 967**	**4 210**	**6 757**
Treatment price (€000s)	*0*	*0*	*0*	*0*	*0*	*24 000*	*24 000*	*24 000*	*24 000*	*24 000*
Sales per year	0,0	0,0	0,0	0,0	0,0	4,1	17,6	47,2	101,0	162,2
Gross margin	0,0	0,0	0,0	0,0	0,0	2,5	10,6	28,3	60,6	97,3
% sales						*60,0%*	*60,0%*	*60,0%*	*60,0%*	*60,0%*
Operational costs					-0,5	-0,5	-0,5	-0,5	-0,5	-0,5
R&D costs	-2,0	-3,5	-6,0	-5,0	-0,5	0,0	0,0	0,0	0,0	0,0
Taxes						-0,2	-1,5	-5,6	-15,0	-24,2
FCF	**-2,0**	**-3,5**	**-6,0**	**-5,0**	**-1,0**	**1,8**	**8,6**	**22,3**	**45,1**	**72,6**
Discounted FCF	**-2,0**	**-3,0**	**-4,5**	**-3,3**	**-0,6**	**0,9**	**3,7**	**8,4**	**14,7**	**20,6**
Terminal value	546									
Discounted terminal value	135									
Sum of discounted FCFs	35									
WACC	15%									
Perpetual growth rate	1,5%									
Estimated value for PJI treatment	**170**									

Source: TPICAP Midcap

The value of phage therapy for osteoarticular infection indications is estimated at €170m.

In the field of infectious endocarditis

If the prevalence of infectious endocarditis is quite low: 3 to 10 per 100,000 people per year, this pathology has recorded strong growth in recent years: more than a doubling during the period 1990-2019, source: frontiersin.org (linked in particular to the increase in cardiac interventions, or even antibiotic resistance). Furthermore, although they remain relatively rare, infectious endocarditis is serious illness which leads to the death of the patient in approximately 25% of cases.

It is estimated that the staphylococcus aureus bacteria is the cause of approximately 30% of infectious endocarditis, which, on the scale of the European and North American markets, could represent a target market exceeding 30,000 people per year by 2027-2028.

To establish the potential revenue and results from the commercialization of PHAXIAM therapeutic solutions in the field of infectious endocarditis, we established our modeling on the basis of several hypotheses:

- For clinical research: phase I/II launched in 2023 and finalized in 2024 (less than €1m), launch of the combined US and Europe phase IIb/III for 2025-2027 (€15m), a regulatory review in 2028 (US and Europe) and marketing planned for 2029.
- Average treatment price estimated at (€25k per patient, linked to recovery from the infection, reducing the length of hospitalization and increasing the probability of patient survival).
- Market share which would increase from 1% of the target population in 2029 to 20% in 2033.
- At cruising speed, no erosion of market share or price considering our cautious scenario, prices in Anglo-Saxon countries being able to be 2x to 3x higher than those obtained on the domestic market for example, the share of market which could be much higher in the event of a significant reduction in mortality rates.
- Gross margin of 62% of revenue (outsourced phage sourcing).
- Tax rate retained at 25% at the end of the period to estimate the normative terminal value.
- A 15% discount rate.

Table 7: Forecast flow table for infectious endocarditis indication

€m	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
No. of patients	**0**	**0**	**0**	**0**	**0**	**0**	**333**	**1 731**	**2 700**	**5 616**	**7 788**
Treatment price (€000s)	*0*	*0*	*0*	*0*	*0*	*0*	*25 000*	*25 000*	*25 000*	*25 000*	*25 000*
Sales per year	0,0	0,0	0,0	0,0	0,0	0,0	8,3	43,3	67,5	140,4	194,7
Gross margin	0,0	0,0	0,0	0,0	0,0	0,0	5,2	26,8	41,9	87,0	120,7
% sales							*62,0%*	*62,0%*	*62,0%*	*62,0%*	*62,0%*
Operational costs						-0,5	-0,5	-0,5	-0,5	-0,5	-0,5
R&D costs	-0,3	-1,5	-5,0	-5,0	-4,0	0,0	0,0	0,0	0,0	0,0	0,0
Taxes							-0,5	-3,9	-10,3	-21,6	-30,1
FCF	**-0,3**	**-1,5**	**-5,0**	**-5,0**	**-4,0**	**-0,5**	**4,2**	**22,4**	**31,0**	**64,9**	**90,2**
Discounted FCF	**-0,3**	**-1,3**	**-3,8**	**-3,3**	**-2,3**	**-0,2**	**1,8**	**8,4**	**10,1**	**18,5**	**22,3**
Terminal value	678										
Discounted terminal value	146										
Sum of discounted FCFs	50										
WACC	15%										
Perpetual growth rate	1,5%										
Estimated value for EI treatment	**196**										

Source: TPICAP Midcap

The value of phage therapy in the infectious endocarditis indication is estimated at €196m.

Valuation Summary and Stock Market rating

Summary of dilutive instruments

At the end of 2022, there were a certain number of dilutive instruments (BSPCE, BSA or AGA) which could result in a total of more than 1,100,000 shares before the consolidation, or 110,000 after the September 2023 consolidation (for those that can be exercised) . However, most of the plans present an exercise price very far from the current stock price of PHAXIAM (weighted average price of the BSPCE exercisable at €122.5 and the BSA at €11.56 restated for the share consolidation), we have chosen to only retain in our valuation approach the dilution that could come from free shares, i.e. 583,721 potential shares, or 58,372 post share consolidation.

Price target

Taking into account the AAC already obtained in France (indication on the price of the treatment), the patients already treated with phages in ATU, and the fact that the phase I/II study is already launched and well advanced, we apply thus a discount of 65% to the value obtained in our modeling for phage therapy for osteoarticular infections on prosthesis caused by the bacteria staphylococcus aureus, to take into account the absence of clinical data to date, the need to carry out a phase IIb/III (possibility of failure), possible schedule uncertainties in the clinical and regulatory phases, and uncertainties linked to the pace of distribution of the product on the market once marketing authorization has been obtained, leading to a value of €59m in our valuation approach.

For phage therapy intended for infectious endocarditis caused by the bacteria- staphylococcus aureus, we apply a discount of 80% to the value obtained in our modeling, because the developments are at a less advanced stage than in the previous indication (phase I/II currently being launched), leading to a value of €39m in our valuation approach.

In other targeted indications, the group not being the sponsor of the studies in certain cases (diabetic foot infection) or having not yet launched phase I/II clinical studies, we have not, at this stage, integrated these areas of research into our valuation of the company.

Furthermore, if the Phagogram or the know-how in terms of phages could be the subject of partnerships, as no agreement has yet been concluded to date, it is difficult to promote the technology developed by the group, we do not We have not integrated it into our valuation.

Table 8 : Summary of our valuation approach

	NPV (€m)	Discount	Retained value (€m)
Prosthesis Joint Infection	170	65%	59
Infectious endocardits	196	80%	39
Urinary tract infections	0	-	-
Respiratory tract infections	0	-	-
Other indcations	0	-	-
Partnerships	0	-	-
EV			**99**
Net debt at the end of June 2023 excl. IFRS 16 (€m)			(10,0)
Equity estimated value (€m)			**108**
Current number of shares			6,1
Induced value per share (€)			**17,8**
Nb. of dilutive tools			0,06
Cash raided through dilutive tolls exercice(€m)			0,0
Estimated funds raising 2023-2026 (€m)			60,0
No. of shares after funds raising (based on current price)			13,6
Value per share diluted (€)			**8,5**

Source: TPICAP Midcap

Based on our sum-of-the-parts valuation approach, we obtain an enterprise value of €99m, or an equity value of €108m or €17.8 per share. However, to achieve their strategy, management will have to resort to external financing.

In our modeling, we have retained fundraising of €60m over the coming years, based on the current price, this corresponds, cumulatively, to the creation of 13.6m shares. On a fully diluted basis, the valuation per share of PHAXIAM comes to €8.5 per share, which constitutes our price target.

Market Rating

After only 5 years of deployment of the precision phage therapy strategy for indications with unmet therapeutic needs, the group has launched its first phase I/II study, and other clinical studies should follow, carried out internally or by hospitals themselves, which should help feed the scientific newsflow. Furthermore, current advances in technology and know-how should allow managers to market them outside the group's scope in the coming months, validating the strategic directions taken and feeding the operational newsflow. We therefore initiate coverage of the stock with a Buy rating.

FINANCIAL DATA

Income Statement	12/20	12/21	12/22	12/23e	12/24e	12/25e
Sales	na	na	0.0	0.0	0.0	0.0
Gross profit	na	na	0.0	0.0	0.0	0.0
EBITDA	**na**	**na**	**1.8**	**-25.3**	**-19.5**	**-20.0**
Current operating profit	**na**	**na**	**-2.8**	**-25.9**	**-20.1**	**-20.6**
Non-recurring items	na	na	0.0	0.0	0.0	0.0
EBIT	na	na	-2.8	-25.9	-20.1	-20.6
Net financial result	na	na	3.1	-0.1	-0.1	-0.1
Income Tax	na	na	-0.5	0.0	0.0	0.0
Tax rate (%)	na	na	177.8	0.0	0.0	0.0
Net profit, group share	**na**	**na**	**-0.2**	**-26.0**	**-20.2**	**-20.7**

Financial Statement	12/20	12/21	12/22	12/23e	12/24e	12/25e
Goodwill	na	na	0.0	13.5	13.5	13.5
Tangible and intangible assets	na	na	0.4	16.1	15.7	15.3
Right of Use	na	na	0.0	0.0	0.0	0.0
Financial assets	na	na	2.6	3.5	3.5	3.5
Working capital	na	na	-4.0	-7.5	-7.0	-6.5
Other Assets	na	na	46.8	25.6	22.3	19.0
Assets	na	na	45.8	51.2	48.0	44.8
Shareholders equity group	na	na	23.5	22.7	22.5	21.8
Minorities	na	na	0.0	0.0	0.0	0.0
LT & ST provisions and others	na	na	0.7	0.8	0.8	0.8
Net debt	na	na	-25.2	2.2	2.5	3.3
Other liabilities	na	na	0.0	0.0	0.0	0.0
Liabilities	na	na	45.8	51.2	48.0	44.8
Net debt excl. IFRS 16	na	na	-25.2	2.2	2.5	3.3
Gearing net	na	na	-1.1	0.1	0.1	0.1
Leverage	na	na	-13.8	-0.1	-0.1	-0.2

Cash flow statement	12/20	12/21	12/22	12/23e	12/24e	12/25e
CF after elimination of net borrowing costs and taxes	na	na	-21.1	-25.5	-19.7	-20.2
ΔWCR	na	na	-8.1	-0.7	-0.5	-0.5
Operating cash flow	na	na	-29.2	-26.2	-20.2	-20.7
Net capex	na	na	-0.1	-0.2	-0.2	-0.2
FCF	na	na	-31.8	-26.3	-20.3	-20.8
Acquisitions/Disposals of subsidiaries	na	na	-0.0	0.0	0.0	0.0
Other investments	na	na	-0.0	0.0	0.0	0.0
Change in borrowings	na	na	-1.8	-3.5	-3.0	-3.0
Dividends paid	na	na	0.0	0.0	0.0	0.0
Repayment of leasing debt	na	na	0.0	0.0	0.0	0.0
Equity Transaction	na	na	0.0	0.0	20.0	20.0
Others	na	na	0.0	0.0	0.0	0.0
Change in net cash over the year	na	na	5.1	-29.8	-3.3	-3.8

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Analyst certifications

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This Report may mention evaluation methods defined as follows:
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.
5. Sum of the parts: this method consists of estimating the various activities of a company using the most appropriate valuation method for each of them, then realizing the sum of the parts.

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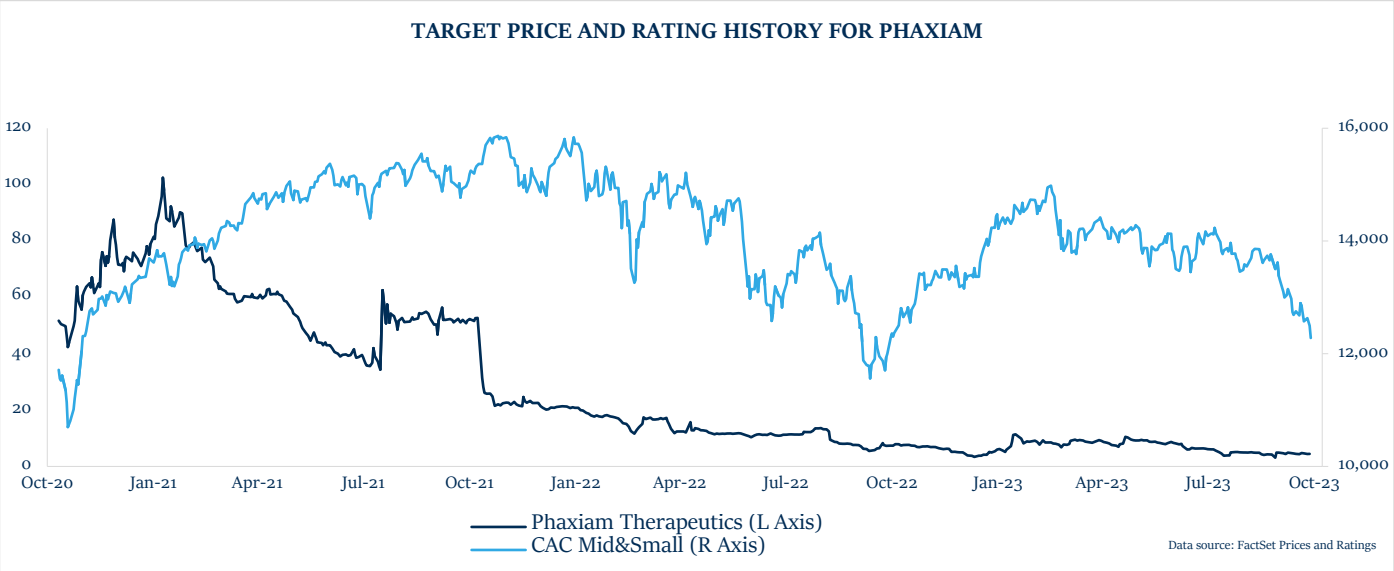
G. Midcap and the Issuer have agreed to the provision by the former to the latter of a service for the production and distribution of the investment recommendation on the said Issuer: Phaxiam Therapeutics

History of investment rating and target price – Phaxiam Therapeutics



Distribution of Investment Ratings

Rating	Recommendation Universe*	Portion of these provided with investment banking services**
Buy	81%	63%
Hold	16%	42%
Sell	2%	0%
Under review	1%	100%

Midcap employs a rating system based on the following:
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Hold: expected performance between -10% and +10% compared to the market over a 6 to 12 months horizon.
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