Spexis AG

Switzerland / Biotechnology
SIX Swiss Exchange
Bloomberg: SPEX SW
ISIN: CH0106213793

Initiation of coverage

RATING	**BUY**
PRICE TARGET	**CHF 1.80**
Return Potential	328.6%
Risk Rating	High

DRUG CANDIDATES FOR RARE DISEASES WITH HIGH MEDICAL NEED

Spexis AG is a biotech company with a clinical-stage product pipeline focused on rare diseases and oncology. Spexis is the result of the merger of the rare diseases specialist EnBiotix Inc and the listed cancer and infectious diseases biotech Polyphor AG. Spexis' proprietary discovery technology generates drug candidates from a new class of drugs called macrocycles. At present, Spexis focuses on two inhaled drug candidates for the treatment of chronic, even lifelong infections in patients with the rare disease cystic fibrosis (CF). I) Murepavadin is a macrocyclic drug candidate which recently demonstrated safety in phase I trials in Europe. II) ColiFin®, the lead drug candidate for treating CF infection, was in-licensed with worldwide rights ex-Europe from PARI Pharma GmbH, a global specialist in nebulised therapies. The product has been approved in Europe since 2010 and is the market leader in the region. Spexis has obtained approval for its phase III protocol from the US registration agency FDA. The FDA has also granted ColiFin® orphan drug and fast-track designations and 12-year US market exclusivity. Preparations for the phase III study are underway, with the beginning of the pivotal study planned for H2 2023. We estimate ColiFin®'s sales potential in the US/Canada at >USD 250m. Spexis intends to build up its specialised sales force, in order to maximise ColiFin®'s value through effective marketing. Opinion leaders expect the product to become the leading treatment of infections in CF patients in the US. Given that the product has European approval with more than 15k administrations to date, the upcoming phase III study is substantially de-risked. In our view, the publication due in 2023 of positive headline results from the first part (COPILOT) of the phase III trial should add substantial value to Spexis and positively impact the share price. We initiate coverage of Spexis with a Buy rating and a CHF 1.80 price target.

ColiFin®, currently Spexis' most valuable asset, is backed by the US Cystic Fibrosis Foundation The US Cystic Fibrosis Foundation invested USD 2.4m in a stake in Spexis during the most recent financing round which raised USD 12.8m. Moreover, it intends to support the clinical development of ColiFin® by providing access to its network of >130 centres across the US and Canada during the phase III study. (p.t.o.)

FINANCIAL HISTORY & PROJECTIONS

	2020	2021	2022E	2023E	2024E	2025E
Revenue (CHF m)	0.05	0.00	0.62	12.20	2.20	0.00
Y-o-y growth	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
EBIT (CHF m)	-1.22	-4.25	-15.38	-9.50	-32.80	-37.83
EBIT margin	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Net income (CHF m)	-1.85	-11.86	-15.56	-9.66	-32.79	-37.82
EPS (diluted) (CHF)	-0.14	-0.82	-0.32	-0.13	-0.29	-0.27
DPS (CHF)	0.00	0.00	0.00	0.00	0.00	0.00
FCF (CHF m)	-0.77	-1.14	-11.29	-8.92	-32.32	-37.71
Net gearing	n.a.	n.a.	n.a.	n.a.	-26.3%	3.2%
Liquid assets (CHF m)	0.29	14.37	1.75	12.29	9.59	1.36

RISKS

Risks include, but are not limited to development, regulatory, competition and financing risks.

COMPANY PROFILE

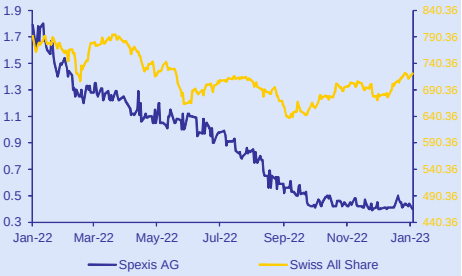
Spexis is a biotech company focused on the research and development of new drugs based on its proprietary macrocycle technology platform to treat rare diseases and several types of cancer. The company is based in Switzerland and currently has two advanced drug candidates for cystic fibrosis, ColiFin® which is ready to start phase III clinical trials in the US, and murepavadin in phase I in Europe.

MARKET DATA

As of 24 Jan 2023	
Closing Price	CHF 0.42
Shares outstanding	48.69m
Market Capitalisation	CHF 20.45m
52-week Range	CHF 0.39 / 1.80
Avg. Volume (12 Months)	12,391

Multiples	2021	2022E	2023E
P/E	n.a.	n.a.	n.a.
EV/Sales	n.a.	25.6	1.3
EV/EBIT	n.a.	n.a.	n.a.
Div. Yield	0.0%	0.0%	0.0%

STOCK OVERVIEW



COMPANY DATA

As of 30 Jun 2022	
Liquid Assets	CHF 7.00m
Current Assets	CHF 9.08m
Intangible Assets	CHF 10.27m
Total Assets	CHF 40.00m
Current Liabilities	CHF 7.90m
Shareholders' Equity	CHF 26.61m

SHAREHOLDERS

Jeffrey Wager/Apeiron Holdings	18.6%
RLG Business Corporation	12.5%
Vectura Group Limited	8.8%
Trustees of Boston University	4.4%
Freefloat and other	55.7%

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INVESTMENT CASE

Spexis resulted from a reverse merger of two complementary biotech companies; it has two clinical-stage lead drug candidates for the rare disease cystic fibrosis (CF), both of which have therapeutic potential in non-CF bronchiectasis and chronic obstructive pulmonary disease (COPD) Spexis AG was created in December 2021 through the reverse merger of the two complementary life science specialists, the publicly listed Swiss firm Polyphor AG and the privately held US company EnBiotix Inc. The company's lead drug candidate, ColiFin®, is a phase III-ready inhaled formulation of colistin, a broad-spectrum antibiotic that has shown outstanding efficacy in the treatment of *P. aeruginosa* infection in the rare disease CF. This bacteria represents the most significant threat for CF patients leading to higher exacerbation rates, loss of lung function and death. The second lead candidate, inhaled murepavadin, is a highly selective macrocyclic antibiotic compound undergoing phase I studies for the same CF indication.

Spexis is ready to start a single phase III registrational study of inhaled ColiFin® once funding is secured; the US FDA has granted it orphan drug, qualified infectious disease product (QIDP) and fast-track designations allowing for a 12-year period of market exclusivity Spexis has obtained the green light from the US registration agency FDA to initiate a single international pivotal phase III study (COPA) of ColiFin® in CF. Prior to this trial, Spexis will conduct a small European open-label pilot clinical trial (COPILOT) with a 28-day treatment period, comparing once-a-day (QD) dosing against the original twice-a-day (BID) dosing of ColiFin®. If, as expected, COPILOT shows comparable safety and tolerability, the COPA study will be immediately initiated with QD dosing. The QD version is anticipated to substantially reduce the treatment burden of people with CF without compromising efficacy. Spexis had a cash position of CHF 7m at end H1 2022, which should be sufficient to fund operations into Q1 2023, plus an equity-linked financing line of CHF 15m as back-up. The company is currently looking for funding to carry out this study which we estimate will cost >CHF 60m (plus >CHF 15m to establish its own US marketing and sales organisation if the product is approved). Provided that the required funding can be secured, management anticipates the phase III COPA study initiation in H2 2023.

ColiFin® is the leading first-line treatment for CF patients with *P. aeruginosa* lung infection in Europe; US/Canada peak sales could exceed USD 250m five years after launch Spexis in-licensed the worldwide rights ex-Europe for ColiFin® from the German-based nebulised medical devices specialist PARI Pharma GmbH in Q1 2019. ColiFin® is approved in Europe and has become the most prescribed drug for front-line therapy in chronic lung infections in CF patients. Hence, having been used to treat more than 15k patients, the product's 12 year track record of safety and efficacy lowers its development risk for US registration in our view. ColiFin® has a superior profile in treating *P. aeruginosa* infections when compared to its main US peer products, TOBI and Cayston. The great advantage of ColiFin® (as observed in Europe) is that it can be prescribed continuously with low risk of resistance. In addition, if ColiFin®'s planned once-daily QD dosing is successfully developed, the product is expected to have better patient compliance, making it more attractive to patients than its peers. The need for alternative antibiotics among the 39k CF patients in the US is so great, that the CF Foundation estimates that ~36% of CF adults with moderate or advanced disease are currently receiving off-label treatment with intravenous colistin (ColiFin®'s active ingredient) solution administered through various nebulisers that were not tested for the administration of colistin. Key CF opinion leaders thus expect ColiFin® to become the front-line therapy in the United States just as it has been in the EU. We estimate that US/Canada approval and a subsequent market launch could occur in 2026, with peak sales five years after launch at USD 255m (CHF 234m).

Inhaled murepavadin, Spexis' second CF drug candidate, is a potent macrocycle antibiotic which proved to be safe in a phase I study The compound has already been studied in nine clinical trials in an intravenous formulation which proved to be generally safe and well-tolerated. On 9 January 2023, the phase I study of inhaled murepavadin in 39 healthy volunteers was successfully completed. The preliminary, blinded data demonstrated that the product was safe and well tolerated at all six investigated single doses, clearing the way for the phase II trials. This study and the upcoming phase II proof-of-concept study in P. aeruginosa infections in people with CF are partly funded by the Innovative Medicines Initiative (IMI) and the US CF Foundation. The further development strategy for inhaled murepavadin will be decided once phase II results are available. The company will compare the efficacy/safety profile of the product with that of ColiFin®, assessing both drug candidates' efficacy in specific populations and the cannibalisation potential (i.e. a drug taking market share from a similar drug). Spexis will then decide whether to continue with phase III development in people with CF, or to switch to indications with more sizable patient populations such as non-cystic fibrosis bronchiectasis (15x larger than CF) or COPD (50x larger than CF). In CF, we expect murepavadin could achieve US and European peak sales five years after launch of >USD 340m (CHF 311m).

Balixafortide is Spexis' clinical-stage macrocyclic drug candidate with therapeutic potential in a variety of solid tumour, haematologic malignancy and rare disease applications The product inhibits the well-validated target CXCR4, which is implicated in the spread and metastasis of several types of cancerous tumours and has also demonstrated stem cell mobilisation in phase II trials. Unfortunately, the drug candidate failed to demonstrate statistically significant efficacy in a phase III study with HER2-negative advanced breast cancer patients. The company is currently analysing preclinical data and undertaking further investigations to determine the most promising indications for future phase II trials. Management expects to publish results of the analysis in early 2023. Since the forward clinical development program for balixafortide is still being formulated, we have not included it in our valuation model, leaving it as upside.

Macrocycle technology platform and further drug candidates will secure future growth Spexis' proprietary technology platform enables the company to generate a new, highly efficient class of molecules called macrocycles. Importantly, this emerging and largely underexploited class of chemical molecules excels through its unique ability to bind to complex and difficult-to-address extra- and intracellular biological targets such as protein-protein interactions (PPIs) with high relevance in several cancer indications. Lonodelestat is a clinical-stage macrocycle discovered through the technology platform. The compound inhibits the enzyme human neutrophil elastase (hNE), which is associated with inflammation and lung tissue damage in CF, bronchiectasis, COPD, acute respiratory distress syndrome (ARDS) and a variety of other lung diseases. This product has been licensed to Santhera and is scheduled to start phase II clinical trials in ARDS in 2023. Spexis is entitled to receive up to CHF 121m in potential development, regulatory and sales milestones for the CF indication, as well as royalties of up to 10% of sales. The company additionally owns several promising preclinical programmes.

Spexis' shares are significantly undervalued in our view. We initiate coverage with a price target of CHF 1.80 and a Buy recommendation In our valuation, we focus on the most advanced drug candidates – ColiFin® and murepavadin. Our proprietary risk-adjusted sum-of-the-parts valuation model suggests a fair value for Spexis of CHF 1.80 per share, representing a return potential of >300% from the current level. Over the past 12 months, we believe Spexis shares have suffered from investors' waning appetite for small-cap biotech companies, which are considered risky against a backdrop of macroeconomic uncertainties and recession fears. However, over the next 12-18 months, we expect positive news from the phase III clinical trials for ColiFin® in CF and from the initiation of phase II development of murepavadin, which will significantly reduce pipeline risk and act as a potential catalyst for a rebound in the share price. We initiate coverage with a Buy recommendation.

SWOT ANALYSIS

STRENGTHS

- **Experienced management team** Mr Jeff Wager, MD, (CEO), Mr Hernan Levett (CFO), Mr Juergen Froehlich, MD (CMO), and Mr Stephan Wehselau (COO) are highly qualified executives with over 100 years of combined experience in the pharmaceutical, biotech, VC and other high tech industries.

- **Lead drug candidate ColiFin® is an approved drug in Europe which has already demonstrated safety and efficacy in CF patients** The product has been approved in Europe since 2010 and has become the market leader for treating CF patients. Thus far, >15k patients have been treated with the drug. The FDA gave the green light for the conduct of a single phase III registrational study, and also granted orphan drug, qualified infectious disease product (QIDP) and fast-track designations, allowing for a 12-year period of US market exclusivity. As a result, the required US phase III trial involves lower-than-average risk in our view.

- **Validated macrocycle technology** The technology enables the company to generate a new, highly efficient class of peptidic and non-peptidic molecules called macrocycles. These have emerged as molecules capable of engaging and modulating tough targets in drug discovery, such as protein-protein interactions (PPIs). Importantly, macrocycles have demonstrated drugability (e.g. drug candidates balixafortide and inhaled murepavadin) with high target specificity and a favourable safety profile. Some 19 macrocycle drugs have been approved by the FDA since 2014.

WEAKNESSES

- **Limited financial latitude** The company closed a USD 12.8m pre-merger financing round in December 2021, which should finance operations through Q1 2023. In July, management secured a new equity-linked financing line which may provide gross proceeds of up to CHF 15.0m over two years. This type of financing is typically negative for the stock price. The proceeds also fall short of the total amount of >CHF60m needed for ColiFin®'s phase III study-related costs.

- **Development setback of cancer product** The drug candidate balixafortide failed to show efficacy in its phase III breast cancer study. Management suspects that the utilised dose was too low and is conducting studies and additional analyses to reposition its development efforts towards the most appropriate indication and dose. The compound's CXCR4 target is generally recognised in bio-pharma circles as a very well-validated target. Spexis has already completed 8 clinical trials involving a total of 501 subjects. However, it may still be challenging to regain investors' trust in the product (at least without additional clinical data and/or external academic/corporate validation such as a strategic alliance).

OPPORTUNITIES

- **Progress shown by ColiFin® in the COPILOT pilot safety phase III results due in H1 2023 may create significant shareholder value** This small open-label COPILOT clinical trial in 38 patients with 28 days of administration will provide valuable safety and efficacy data comparing an improved once-a-day (QD) dosing against the current twice-a-day (BID) dosing version. If COPILOT shows a similar tolerability and safety profile for QD dosing, paving the way for a phase III registration study with QD dosing, ColiFin® would have a substantial commercial advantage against the competing twice-daily or three times daily standard of care products.

- **ColiFin®'s potential market expansion into additional non-CF indications** The potent antipseudomonal properties of ColiFin® suggest potential efficacy in several indications with more sizable patient populations, such as non-cystic fibrosis bronchiectasis (15x larger than CF) and chronic infections in COPD patients (50x larger than CF). These new indications hold out the prospect of significant additional market potential.

- **Additional value upside from further pipeline drug candidates** Due to financing limitations, Spexis is currently focusing its resources on its lead drug candidates ColiFin® and murepavadin. The company has further attractive macrocycle programmes with substantial value-generation potential. Preclinical and clinical data for the drug candidate balixafortide suggests potential use in therapy of various solid tumours and rare diseases. The development strategy for the drug candidate is under review. Once defined, it could enter phase II development if sufficient funding can be secured.

- **Potential licensing deals for ColiFin® with pharmaceutical companies in the non-core Asian/Middle East region could lead to attractive up front and milestone payments** We believe management is considering licensing certain less valuable non-core Asian or middle-East territories to access an additional, non-dilutive source of funding. We also see potential for Spexis to transfer partial rights for ColiFin® in areas such as co-development, co-marketing or label expansion studies (i.e. non-CF bronchiectasis, COPD) to partners.

THREATS

- **Financing risks** The company will need to raise funds to finance further development of its R&D portfolio. A difficult financing environment or negative results from clinical trials would impede raising more capital.

- **Development and regulatory risks** Development of the lead drug candidate ColiFin® may progress more slowly than expected. The product may fail to demonstrate safety in the open-label QD vs BID dosing phase III trial (COPILOT) or efficacy in the US COPA pivotal phase III trial (even though European doctors have been prescribing the product to patients for ~12 years).

- **Competitive risks** Spexis' pipeline, particularly the CF lead drug candidate ColiFin®, may face competitive pressure. Several leading pharmaceutical and biotech companies, including Vertex Pharmaceuticals (CFTR market leader), AbbVie, Eloxx Pharma and 4D Molecular Therapeutics are developing innovative CFTR modulators for treating CF. Any unexpected breakthrough by one or more competitors could significantly hit Spexis' potential revenues.

VALUATION

Biotechnology valuation is notoriously difficult since there is a high risk in developing the R&D pipeline, which leads to uncertainty in projecting cash flows. We have assessed Spexis's fair value based on a sum-of-the-parts methodology. We believe this is the most appropriate valuation method for Spexis because it reflects the implicit risk-adjusted value of every drug candidate in the R&D pipeline. Development risks, including clinical and regulatory risks, are considered, as are market size and the expected timing of cash flows post-approval for each project.

We have used a risk-adjusted NPV model for each product line and key indication, namely the inhaled antibiotic drug candidates ColiFin® and murepavadin, for treating *P. aeruginosa* infection in CF patients. We have also estimated milestone payments for outlicensing of non-core programmes/regions. We believe that ColiFin® and murepavadin have value in further indications (e.g. bronchiectasis and chronic infections of COPD patients), and that the third drug candidate balixafortide also has potential in several cancer indications. However, these areas are currently not the company's main focus, and we regard them as upside to our valuation.

During the forecasting process, we adjusted our sales projections and resulting cash flows for estimated success probabilities to obtain risk-adjusted expected values. We base our probability coefficients on statistical sector studies, such as DiMasi et al., and on our own estimates. In this instance, we have derived a 32% probability of success for the drug candidate in phase I (murepavadin) and a 71% success probability for the drug candidate in phase III (ColiFin®) clinical development. At the moment we consider ColiFin® to be the most important value driver for the company by far.

Additionally, using First Berlin methodology, which takes company-specific risk factors into account, we have derived a cost of equity (COE) of 16.4% for Spexis. Based on a debt ratio of 0.0%, we arrive at a WACC of 16.4%, which we have used to discount projected cash flows. Including projected net cash of CHF 85.9m, we value Spexis at CHF 269.2m, which implies a fair value of CHF 1.80 per share on a pro forma fully diluted basis. For the treatment cost, market size and potential sales projections in our valuation model, we have applied an exchange rate of 0.92 CHF per USD. Using our ten-factor risk analysis, we have set a High-risk rating for Spexis. The main risk factors that we have identified are development, regulatory, competition and financing.

Table 1: "Sum-of-the-parts" valuation model

Compound	Project[1]	Present Value	Patient Pop (K)	Treatment Cost (CHF)	Market Size (CHFM)	Market Share (%)	Peak Sales (CHFM)	PACME Margin[2] (%)	Discount Factor (%)	Patent Life[3] (years)	Time to Market (years)
ColiFin®	CF - US	CHF 212.8M	43K	35,780	1,549.3M	12%	233.8M	45%	16.4%	12	3
Murepavadin	CF - US	CHF 62.3M	43K	36,697	1,589.0M	10%	220.0M	45%	16.4%	12	6
Murepavadin	CF - EU	CHF 13.8M	48K	13,761	660.6M	10%	91.4M	24%	16.4%	12	6
PACME PV		CHF 288.8M			3,798.8M		545.2M				
Costs PV[4]		CHF 123.1M									
NPV		CHF 165.7M									
Milestones PV		CHF 17.6M									
Net Cash (Pro forma)		CHF 85.9M									
Fair Value		CHF 269.2M									
Share Count (Pro forma)		148,200K									
Price Target		CHF 1.80									

1) A project typically refers to a specific indication or, where necessary or relevant, a combination between indication and geographic market

2) PACME (Profit After Costs and Marketing Expenses) reflects the company's profit share on future revenues.
This share may be derived in the form of royalties (outsourced marketing/manufacturing) or operating EBITDA margin (in-house model), or some mix of both (depending on the specific parameters of partnership agreements)

3) Remaining patent life after the point of approval

4) Includes company-level R&D, G&A, Financing Costs and CapEx; COGS and S&M are factored into the PACME margin for each project

Source: First Berlin Equity Research

Assumptions on share dilution

To raise the funding required ahead of our projected operating cashflow break-even date in 2027, we have assumed that the company will place 50m shares at CHF 0.40 in Q1/23, 30m shares at CHF 1.00 in FY/24, 25m shares at CHF 1.20 in FY/25, and 16.7m shares at CHF 1.20 in FY/26. In addition, we have taken into count potential dilution of 3.3m shares from the employee option programme, which have conversion prices in the CHF 0.40-1.43 range during the period 2023-2029. Thus, we have projected an overall potential dilution of 125m shares, which have a pro forma present value of 100m.

PRODUCTS – DETAILED ANALYSIS

Estimation of price, sales potential and product value

Inhaled ColiFin® against chronic *P. aeruginosa* infection in CF patients in the US and Canada ColiFin® is an inhaled broad-spectrum antibiotic that has shown potent efficacy in treating *P. aeruginosa* infection in CF patients. This bacteria represents the largest threat for CF patients leading to higher exacerbation rates, loss of lung function and death. The compound is ready to start phase III clinical development for registration in the US and Canada (the company has license rights ex-Europe). Based on statistics provided by CF country registers (see disease chapter of this report), the total number of subjects suffering from CF is estimated at 39k in the US and 4.3k in Canada. According to the US CF Foundation, 3.6k patients do not respond to antibiotic treatment with TOBI/Cayston and are using unapproved intravenous (IV) colistin (colistimethate sodium – CMS) inhaled through generic nebulisers. In our view, ColiFin® could capture this target population immediately upon approval. Furthermore, we expect ColiFin® to progressively take market share from TOBI/Cayston, which are showing growing bacterial resistance.

We have conservatively assumed an average ex-factory drug price per year of USD 6,500 coupled with 25% discounts to insurance providers, which, assuming an average of 8 28-days treatment courses p.a., results in an annualised therapy price of USD 39k. We note that the comparable inhaled treatments TOBI/Cayston have an ex-factory price in the range USD 5.4k-11k (includes generic - so-called copycat drugs - and branded products) per 28d course. Our assumed price is conservative considering the product's advantages, including low rate of antibiotic resistance and expected higher patient compliance due to once-daily administration (QD dosing). This should enable the product to penetrate the market faster.

We have assumed that this segment will increase at a CAGR of 3% by 2040. We expect Spexis to achieve a penetration rate of 12%, leading to peak sales of USD 255m (CHF 234m) five years after launch. We note that TOBI achieved peak sales of USD 387m in 2013 before generics entered the market (source: Novartis financial statement, 2013). ColiFin® will enjoy 12 years of market exclusivity in the US before potential generics can receive approval. We project a potential approval and market launch in H2 2026.

Table 2: Assumptions of ColiFin® in CF in the US/Canada

ColiFin® - US	Present Value	Patient Pop	Treatment Cost	Market Size	Market CAGR	Market Share	Peak Sales	PACME Margin	Discount Factor	Patent Life
Parameters	$232M	43K	$39,000	$1,689M	3%	12%	$255M	45%	16.4%	12

Source: First Berlin Equity Research

We have assumed that Spexis will build up its own sales force of ~40-50 employees to commercialise the drug in the US to maximise profitability and value generation. The company is negotiating contracts with manufacturers to deliver ColiFin®'s colistimethate sodium (CMS) dry powder and PARI for the nebulisers. Spexis will conduct final packaging and distribution. We assume a PACME margin of 45%. These assumptions are in accordance with metrics we have observed in the industry.

Inhaled murepavadin against chronic *P. aeruginosa* infection in CF patients in the US and Canada Similarly to ColiFin®, murepavadin has shown promise in treating CF bacterial infection. However, the compound is at an earlier clinical development stage (phase I vs phase III-ready ColiFin®). The product's advantages include its ability to specifically kill the *P. aeruginosa* bacteria (vs the broad-spectrum antibiotics ColiFin® or other approved inhaled antipseudomonal antibiotics), which could translate into higher efficacy, as well as the lowest *P. aeruginosa* resistance rates among all antipseudomonal antibiotics. Once phase II study results, including the efficacy profile, are available potentially in H2 2024, management will take further development decisions. If the product has a complementary patient efficacy profile to ColiFin®, suggesting a low cannibalisation effect, management will likely continue development in CF. Otherwise, the company may opt to switch development focus to substantially larger airway *P. aeruginosa* infection markets, such as bronchiectasis (15x larger than CF) and chronic infections in chronic obstructive pulmonary disease (COPD) patients (50x larger than CF). The main reason to initially investigate efficacy in CF patients was that the compound could be substantially de-risked, showing proof of concept financed mainly through grants. For the time being, we have assumed that murepavadin is complementary to ColiFin® and captures share chiefly from the older and less efficacious peers TOBI/Cayston. Spexis has worldwide commercial rights for the product. We have estimated that Spexis will initially focus on the two main regions of US/Canada and Europe, where 43,300 and 48,000 CF patients respectively live. We have estimated an average ex-factory price for the drug's one-year treatment of USD 40k in the US/Canada (marginally higher than ColiFin®) and USD 15k in Europe.

Given that the drug candidate has completed phase I, we project a potential approval and market launch in 2029. Based on an anticipated penetration rate of 10%, we expect Spexis to achieve peak sales of USD 340m (CHF 311m) by 2033.

Table 3: Assumptions of murepavadin in CF

Murepavadin - US	Present Value	Patient Pop	Treatment Cost	Market Size	Market CAGR	Market Share	Peak Sales	PACME Margin	Discount Factor	Patent Life
Parameters	$68M	43K	$40,000	$1,732M	3%	10%	$240M	45%	16.4%	12
Murepavadin - EU	**Present Value**	**Patient Pop**	**Treatment Cost**	**Market Size**	**Market CAGR**	**Market Share**	**Peak Sales**	**PACME Margin**	**Discount Factor**	**Patent Life**
Parameters	$15M	48K	$15,000	$720M	3%	10%	$100M	24%	16.4%	12

Source: First Berlin Equity Research

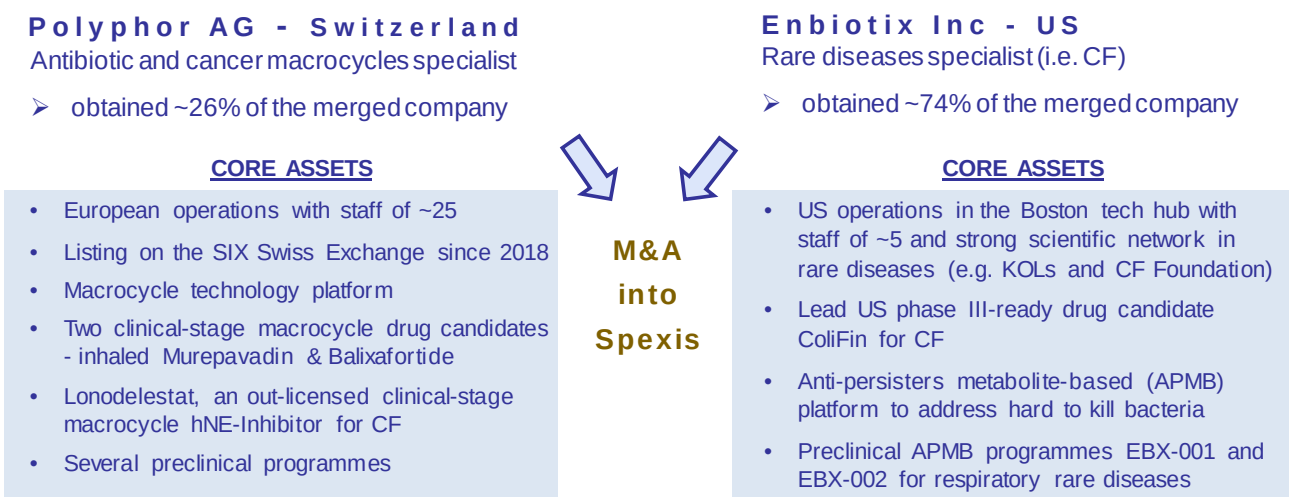
We have assumed that Spexis will commercialise the product with its sales force in the US, generating a PACME margin of 45% (similar to ColiFin®). For Europe, we have assumed that the company will license the product to a pharmaceutical partner, receiving a royalty rate of 24% upon commercialisation. We have assumed that the European partner will fund 50% of the phase III development expenses.

COMPANY PROFILE

OVERVIEW

Spexis AG - Swiss-based biotech company originating from the merger of Enbiotix Inc (US) and Polyphor AG (Switzerland) Spexis AG was created in December 2021 through the reverse merger of the two complementary life science specialists, the publicly listed firm Polyphor AG (founded in Allschwil near Basel, Switzerland in 1996) and the privately held company EnBiotix Inc. (founded in Boston, US in 2012). Polyphor's two lead phase III candidates suffered setbacks in May 2019 and August 2021, and the company began to look for new options to continue operations. Its valuable macrocycle technology platform along with its two development-stage macrocycle drug candidates for cystic fibrosis (CF) and cancer caught the attention of its US peer Enbiotix. The private US company saw a listing opportunity through a reverse merger, thereby expanding its R&D pipeline, scientific staff, regional footprint, and access to an attractive technology platform. Enbiotix had substantial expertise in innovative metabolite-based antibacterial approaches derived from the groundbreaking research of Enbiotix' co-founder and Advisory Board Chairman, Professor James J Collins (https://be.mit.edu/directory/james-j-collins). The company had developed several preclinical programmes of inhaled antibiotics for rare respiratory diseases (e.g. EBX-001 & EBX-002), and also in-licensed ColiFin®, a phase III-ready lead drug candidate in CF. Based on the excellent match, the deal was closed in December 2021, and the combined company was renamed Spexis, taking the Basel location as headquarters. The share split in the new company Spexis AG was respectively ~ 26% / 74% between Polyphor/Enbiotix shareholders. In our view, the lead US phase III-ready drug candidate ColiFin® for CF was the asset with the highest value in the transaction.

Figure 1: Overview of the asset contribution through the Spexis reverse merger transaction



Source: First Berlin Equity Research, Spexis AG

Highly qualified management team Following the merger, Enbiotix' CEO and co-founder, Mr Jeffrey Wager, MD, took over as the new Spexis CEO and Chairman and his former management team colleagues Mr Stephan Wehselau and Mr Juergen Froehlich, MD, joined the new Spexis management team as President & COO and CMO, respectively. Polyphor's Board member, Mr Hernan Levett, MD, became Spexis CFO. The highly experienced management team leading Spexis has over 100 years of combined biotech experience.

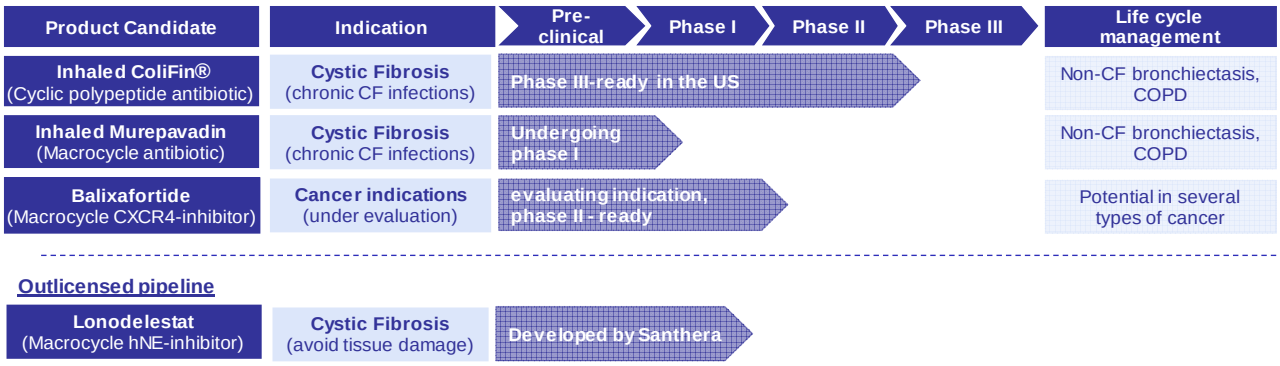
Spexis AG develops therapeutics against the rare disease cystic fibrosis and cancer
The company currently has two drugs in clinical development stage for CF:

1. **Inhaled ColiFin®** is Spexis' lead antibiotic drug candidate. It has obtained the green light from the US registration agency FDA to initiate a single Phase III study in CF. Prior to this trial, Spexis will conduct a small European open-label pilot clinical trial (COPILOT) with a 28-day treatment period, comparing once-a-day (QD) dosing against the original twice-a-day (BID) dosing of ColiFin®. If, as expected, COPILOT shows comparable safety and tolerability, the international pivotal phase III registration study (COPA) will be immediately initiated with QD dosing, which is expected to substantially reduce the treatment burden on people with CF without compromising efficacy. Spexis, through its US subsidiary (Enbiotix), in-licensed the worldwide rights ex-Europe for ColiFin® from the German-based nebulised medical devices specialist PARI Pharma GmbH in Q1 2019. ColiFin® is approved in Europe and has become the most prescribed drug for front-line therapy in chronic lung infections in CF patients. The product has a track record of ~12 years safety and efficacy in >15K patients treated thus far. The US registration agency FDA has granted ColiFin® orphan drug and fast track designations and 12 years of market exclusivity. Provided that the required funding can be secured, management anticipates initiation of the COPA phase III study in H2 2023.
2. **Inhaled murepavadin**, the second drug candidate, is a potent macrocycle antibiotic targeting *Pseudomonas aeruginosa* CF infections, including multi-drug resistant bacterial strains, that recently completed phase I clinical development. The phase I study demonstrated that the product is safe and well-tolerated at all tested doses, clearing the way for a phase II trial.

Balixafortide, is Spexis' third significant drug candidate in clinical development. It has a cancer focus and is a macrocycle inhibiting the well-validated target CXCR4, which is implicated in the spread and metastasis of several types of solid tumours, haematologic malignancies and rare diseases. The company is currently analysing this drug candidate's extensive preclinical and clinical data and undertaking further investigations (e.g. dosing and cancer types, other rare disease indications) to decide on the most promising indications to address in future phase II trials. Management expects to publish results of this analysis in early 2023.

Lonodelestat is a macrocycle inhibiting the enzyme human neutrophil elastase (hNE), which is associated with inflammation and tissue damage in the lungs of people with CF, bronchiectasis, COPD, acute respiratory distress syndrome (ARDS) and a variety of other lung diseases. This product has been licensed to Santhera and is scheduled to start phase II clinical trials in ARDS in 2023. Spexis has received an upfront payment in Santhera shares worth CHF 6.5m and is entitled to receive up to an additional CHF 121m in potential development, regulatory and sales milestones, as well as royalties up to 10% on sales. We give an overview of Spexis' clinical-stage pipeline in figure 2 below.

Figure 2: Snapshot of the clinical stage R&D pipeline focusing on Cystic Fibrosis (CF)



Source: First Berlin Equity Research, Spexis AG

Pre-clinical programmes Thanks to its macrocycle technology platform and metabolite expertise, Spexis has several promising preclinical programmes which secure future supply of additional clinical-stage drug candidates. The more significant ones are:

- EBX-002, a combination of amikacin (AMK) and a potentiator molecule for non-tuberculous mycobacterial (NTM) infections in which preclinical studies to date have shown potential for superior activity compared to ARYKACE;
- SPX CXCR4-inhibitor, a new program focused on orphan, haematological malignancies;
- LptA-OMPTA programmes, a novel class of antibiotics targeting certain hospital-acquired infections caused by drug-resistant bacteria. These programmes are primarily funded through phase I development by the accelerator CARBX, a global non-profit partnership based at Boston University in the US. Some of the main sponsors are 1) the Biomedical Advanced Research and Development Authority (BARDA - part of the US Department of Health and Human Services), 2) the UK's Wellcome Trust and the Government's Department of Health and Social Care (DHSC), 3) Germany's Federal Ministry of Education and Research (BMBF), and 4) the Bill & Melinda Gates Foundation.

Strategy focused on its lead drug candidates The company has established a clear development strategy for the pipeline. The first development priority is conducting and completing the cost-intensive US phase III clinical study over a period of ~3 years for ColiFin®, its lead drug candidate used in treatment of CF. For this purpose, management is working on securing the required funding of >CHF 60m. In addition, management will pursue partnering in emerging markets so as to access non-dilutive funding. Once the drug is approved, the company intends to market the product in the US through its own sales force (would be hired once required). The second priority is conducting the upcoming phase II clinical trials of inhaled murepavadin. Management would still need to raise the required funds of ~CHF 5m. The third priority is establishing the most promising cancer indication for balixafortide, raising the needed funds of ~CHF 15-20m and then conducting a phase II dose-escalating proof-of-concept study. This report focuses on the lead drug candidates ColiFin® and murepavadin in the main CF indication, which are the company's main value drivers.

Swiss Stock Exchange listing and recent funding activities Spexis has been publicly listed on the principal Swiss Stock Exchange SIX since 2018 (as Polyphor), but it began trading as a merged company on the SIX under the new name Spexis AG and symbol "SPEX" on January 3, 2022. Management secured a capital increase of USD 12.8m as pre-merger financing in December 2021. These funds will finance the company into Q1 2023. The main investors in the financing round were:

- Vectura, a leader in inhaled drug development now wholly owned by Philip Morris International, invested USD 7.6m
- the US CF Foundation, invested USD 2.4m
- Sanford Biosciences LLC, invested 1.0m
- "Family & friends" of the company, invested USD 1.8m

In July 2022, the company renewed a previously existing financing contract with the French investor IRIS Capital Investment for an equity-linked financing facility of up to CHF 15m. Spexis can draw down funds when needed, whereas IRIS is committed to buying on a monthly basis 24 tranches of CHF 625k of unsecured zero-coupon mandatory convertible bonds over two years. Each month, IRIS can convert the mandatory convertible bonds into shares that Spexis will issue at a discounted price from the applicable weighted average market price and can sell them at its discretion on the market or as block trades. This type of financing is typically negative for the stock price. It also falls short of the total estimated amount of >CHF80m needed for ColiFin®'s phase III study and the subsequent marketing.

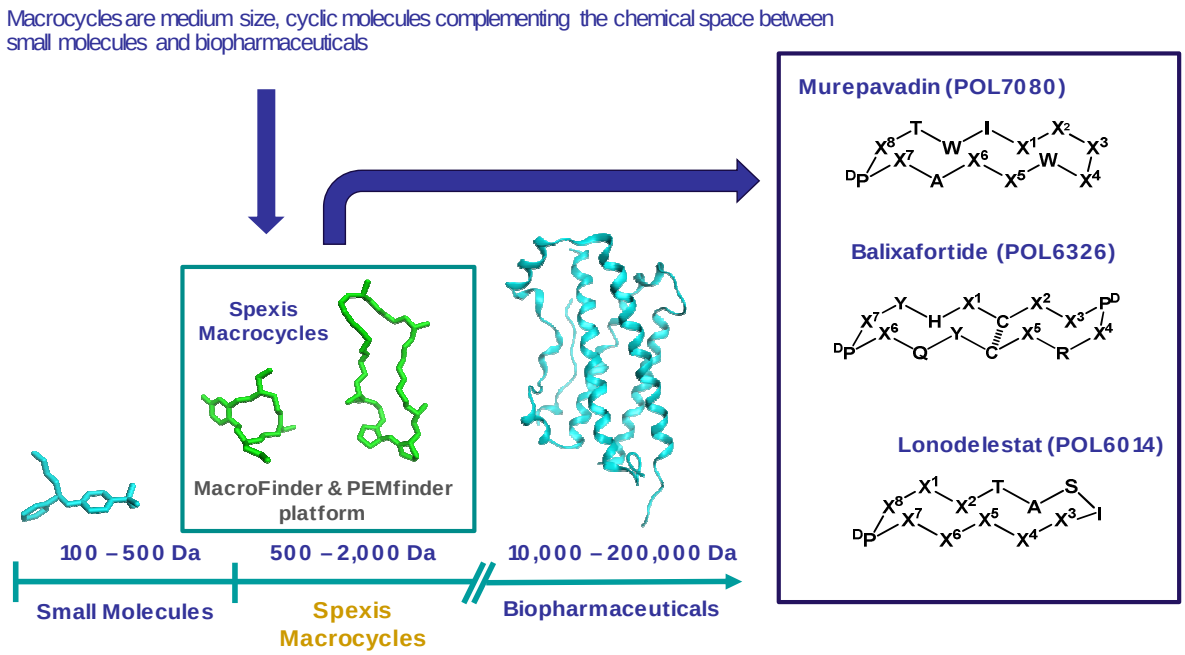
We thus believe Spexis will use these funds only if necessary until a capital increase with committed long-term investors has been completed. By year-end 2021, shares outstanding were 47.6m after the merger completion, and they increased to 48.2m by the end of June 2022. There is further potential share dilution in connection with the IRIS equity-linked financing and ~3.9m shares through exercise of options in the company's current employee ESOP/management programmes.

"MACROCYCLE" TECHNOLOGY PROVIDES A COMPETITIVE ADVANTAGE

Macrocycles – unique molecules capable of addressing difficult targets,… Spexis' proprietary technology platform enables the company to generate a new, highly efficient class of molecules called macrocycles. Importantly, this emerging and largely underexploited class of chemical molecules excels through its unique ability to bind to complex extra- and intracellular biological targets such as protein-protein interactions (PPI's), which would be otherwise challenging to address. PPIs are associated with various diseases (e.g. infectious diseases, cancer, and neurodegenerative diseases) and targeting them offers promise to discover new drugs that can treat them (source: Haying Lu et al., 2020 – Nature).

Macrocycles are medium-sized cyclic molecules with structures that contain one or more rings of at least 12 atoms. They typically have molecular weights (MW) in the range of 500–2000 Daltons (Da), being 3–5 times larger than conventional small-molecule drugs but still substantially smaller than biopharmaceuticals (e.g. monoclonal antibodies). Their "medium" size allows them to reach extra- and intracellular regions, making them quite versatile.

Figure 3: Macrocycles compared with small molecules and large biologics



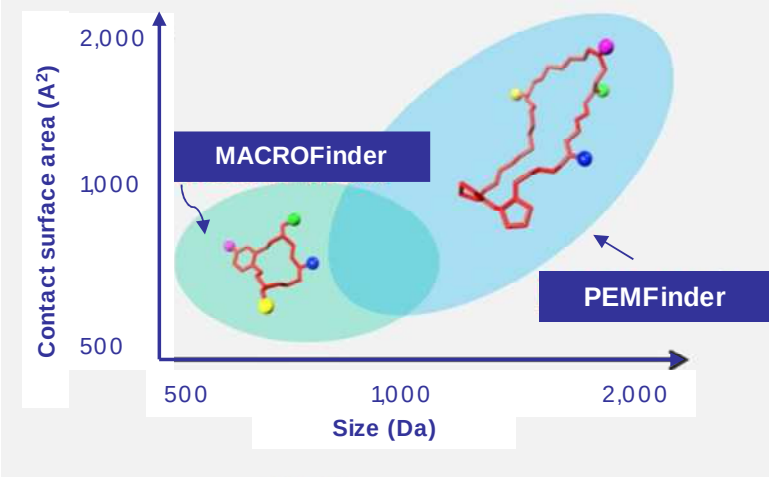
Source: First Berlin Equity Research, Spexis AG

…combining the advantages of small chemical molecules and large biologics In therapeutic use, macrocycles combine the benefits of the two largest drug classes, namely I) large biomolecules (e.g. monoclonal antibodies), which offer high potency, affinity and specificity translating into a favourable side-effect profile, with those of II) small chemical molecules, which offer a) ease of manufacturing, since they can be chemically synthesised,

thereby keeping manufacturing costs at a reasonable level, and b) favourable pharmacokinetic properties such as oral bioavailability, ease of administration and lack of immunogenicity.

Spexis macrocycle technology platform comprises two complementary libraries In collaboration with the University of Zurich, the company has accumulated strong medicinal chemistry expertise and developed a proprietary macrocycle-based discovery platform based on the two complementary technologies PEMfinder and MacroFinder. They consist of two distinct, highly diverse and very well-characterised macrocycle libraries that allow the generation of non-peptidic, cell-permeable and orally bioavailable small molecule macrocycles (MacroFinder), as well as of peptidomimetic macrocycles (PEMfinder). Each library has different applications depending on the targets to be addressed.

Figure 4: Macrocycles compared with small molecules and biopharmaceuticals



Source: First Berlin Equity Research, Spexis AG

Spexis' macrocycle technology platform can efficiently address multiple types of intra- and extracellular targets relevant to a wide variety of diseases. The company's macrocycles have shown encouraging results in accurately addressing these promising targets, particularly intracellular pathways and targets (e.g. PPIs) that are inaccessible to biologic drugs. This underscores the uniqueness of the technology platform. Through it, the company has generated its three clinical-stage drug candidates (murepavadin, balixafortide and lonodelestat), its preclinical SPX CXCR4-inhibitor, and the LptA-OMPTA programmes.

In the past decade, interest in macrocycles has strongly increased, and > 100 macrocyclic drugs and clinical candidates are currently either in drug discovery or in commercialisation (source: Eman et al., 2016). In our view, the main reason for this is the discovery of novel targets such as chemokines or peptide hormones. The challenge of targeting intracellular PPIs has also become a strong driver in research activities' growth on macrocycles. Interest from the pharmaceutical community is growing. Macrocycles possess flexible binding surfaces (i.e. capable of dynamically changing their conformation) and are similar in size to those of PPI interfaces, allowing for a better surface match. Spexis (via its predecessor Polyphor) belongs to the few pioneer biotechs that started researching macrocycles 12 years ago.

THE LEAD DRUG CANDIDATE COLIFIN® SHOWS PROMISE IN CYSTIC FIBROSIS (CF)

PRODUCT PROFILE

Inhaled ColiFin® – European market leader for front-line treatment of CF In Q1 2019, Spexis' US subsidiary (Enbiotix) in-licensed the worldwide rights ex-Europe for the inhaled drug ColiFin® from the German-based medical device specialist PARI Pharma GmbH (PARI). PARI is a global leader in developing and commercialising nebulised medical devices for inhalation therapy and also commercialises ColiFin® in Europe. In 2010, PARI obtained European approval for ColiFin®'s dry powder formulation for treating CF patients with the proprietary PARI eRapid nebuliser system at doses of 1 MIU (~80 mg CMS) and 2MIU (~160 mg CMS) two or three times daily. The product has become the most prescribed drug in the region for front-line therapy of CF patients with chronic lung infections. Since approval, the product has demonstrated a favourable safety and efficacy track record with >15K patients treated with it thus far.

Figure 5: Colifin CF product commercialised by PARI in Europe

Source: Pari Pharma GmbH, German package

Product description and mode of action (active substance colistimethate sodium) ColiFin® is a macrocycle antibiotic (i.e. cyclic polypeptide) used in the treatment of infections caused by strains of gram-negative multidrug-resistant bacteria such as *Pseudomonas aeruginosa (P. aeruginosa)*. The product's active ingredient is colistin which is administered in the form of colistimethate sodium (CMS), a prodrug that is transformed in the body to colistin to reduce the toxic side effects of active colistin. Colistin, also known as polymyxin E, can be typically injected into the vein (IV), into the muscle or inhaled. Colistin is a surface active agent which penetrates and disrupts the bacterial cell membrane leading to leakage of intracellular contents and bacterial death.

ColiFin® excels by not generating significant drug resistance CMS' different mechanism of action compared to the other approved inhaled antibiotics enables it not to exhibit cross-resistance with the other classes, and therefore existing bacteria is largely not ColiFin®-resistant. It is also believed that difficult-to-kill bacteria such as multidrug-resistant *P. aeruginosa* cannot modify colistin's binding site at the organism, the lipid A, which is a key component of lipopolysaccharide (LPS) elaborated by this organism to promote its survival and trigger virulence. Therefore, *P. aeruginosa* is susceptible to being killed by colistin. This represents a significant advantage of the substance. In 2010, the World Health Organisation (WHO) stated that antibiotic resistance is one of the three greatest threats to human health. CF patients are particularly threatened by multidrug-resistant gram-negative bacteria, including *P. aeruginosa*, due to the long-term adaptation of bacterial strains in the lung (source: Emerson et al., 2010). Resistance rates have been demonstrated to be quite high for some antibiotics commonly used for *P. aeruginosa* treatment, but they are still very low for colistin (sources: Valenza et al., 2010; Pit TL et al., 2003).

Inhaled colistin has a positive safety profile, despite toxicity shown by intravenous (IV) administration Colistin was discovered in 1947, being therapeutically used in the 1950s mainly as CMS. However, the IV administration of colistin increasingly showed renal toxicity and neurological problems, and use of the drug largely stopped in the 1960s and 1970's (source: Vaara et al., 2019). The growing worldwide prevalence of infections with multidrug-resistant (MDR) Gram-negative bacteria has renewed interest in colistin in the last two decades. The most recent studies still indicate colistin IV has a renal toxicity incidence of about 36%, recommending it as a last-line agent against multi-resistant strains (source: Eljaaly et al., 2021). Inhaled colistin, on the other hand, has the advantage of achieving high drug concentrations directly in the respiratory tract leading to high efficacy against hard-to-kill bacteria whilst avoiding systemic adverse effects due to negligible systemic bioavailability. The product has shown slight side effects only related to airway reactivity, such as a short-term decline in forced expiratory volume in one second (FEV1 – measured in pulmonary function test) and cough directly after inhalation, throat irritation and abnormal taste in 35% to 49% of treated patients, which are comparable to its main competitor product Tobramycin (source: Hodson et al., 2002). A recent study using data from the UK CF Registry from 2014-2018 determined that inhaled CMS dry powder has a similar safety profile to other inhaled antibiotics (source: Kaplan et al., 2020).

Small studies conducted thus far largely suggest good efficacy of inhaled CMS Unfortunately, CMS lacks large randomised controlled studies investigating colistin versus placebo. However, a meta-analysis conducted by Mukhopadhyay et al. related to treatment with inhaled antibiotics in chronic pulmonary CF lung infection arrived at the conclusion that treatment with inhaled colistin is beneficial. CMS improves lung function and reduces pulmonary exacerbations. This opinion was also shared by Touw et al., who reviewed all studies investigating the benefits of inhaled antibiotics published between 1965 and 1995. According to this review, most studies revealed that inhaled CMS triggered a reduction in hospital admissions and improved lung function without showing severe side effects such as renal- or ototoxicity (source: Mukhopadhyay et al., 1996; Touw et al., 1995). A more recent meta-analysis conducted in 2013, which reviewed randomised controlled trials for the three main inhaled antibiotics approved worldwide for CF (tobramycin, CMS, and aztreonam lysine) concluded that all substances had proven efficacy compared to placebo. The authors confirmed that the three compounds have a proven effect on lung function and exacerbation rate, but they could not reliably determine the superiority of any of the compounds (Maiz et al., 2013). At present, the competing product tobramycin has the most comprehensive data on efficacy in chronic pulmonary infection in CF. We thus believe that the conduct of a sizeable pivotal study for ColiFin® is highly relevant.

PLANNED US PHASE III TRIAL OF COLIFIN® IN CF PATIENTS

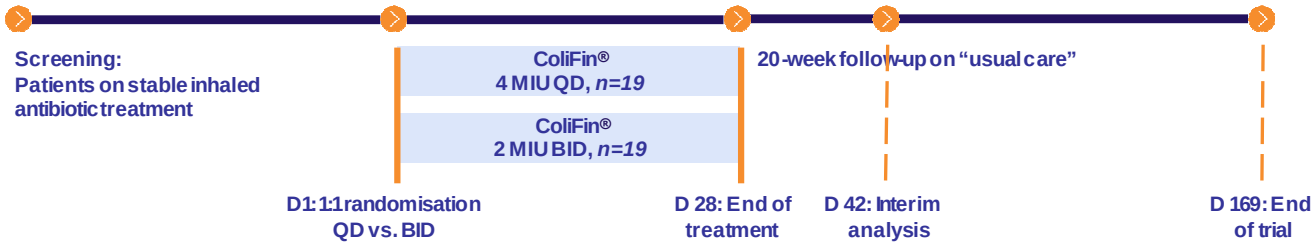
A two-stage confirmatory US phase III trial programme Prior to the formation of Spexis, EnBiotix received a "Study may Proceed" letter from the US Food and Drug Administration (FDA) to initiate a single two-stage phase III trial of inhaled ColiFin® in adult and adolescent CF patients with chronic *P. aeruginosa* lung infection. The FDA granted ColiFin® the Orphan Drug, Quailfied Infectious Disease Product (QIDP) and Fast Track Designations for treating lung infection in patients with CF. The phase III programme comprises two trials:

1. a small European open-label pilot clinical trial (COPILOT) with a 28-day treatment period, comparing tolerability and safety of once-a-day (QD) dosing against the original twice-a-day (BID) dosing of ColiFin®;

2. registrational COPA trial in 480 patients investigating ColiFin®'s efficacy and safety based on the dose established in the COPILOT trial.

COPILOT pilot European trial aims to demonstrate the safety of the new once-a-day (QID) ColiFin® against the established twice-a-day dose (BID) The study protocol entails a European multi-centre, open-label, phase III pilot trial comparing once daily (QD) 4 MIU dose with twice daily (BID) 2 MIU dose administration in chronic CF patients with chronic *P. aeruginosa* lung infection. The study will be conducted in Central and Eastern Europe in 38 patients. The patients will be treated for 28 days and undergo a 20-week follow-up on usual care.

Figure 6: ColiFin® COPILOT pilot safety phase III trial comparing QD vs BID dosing

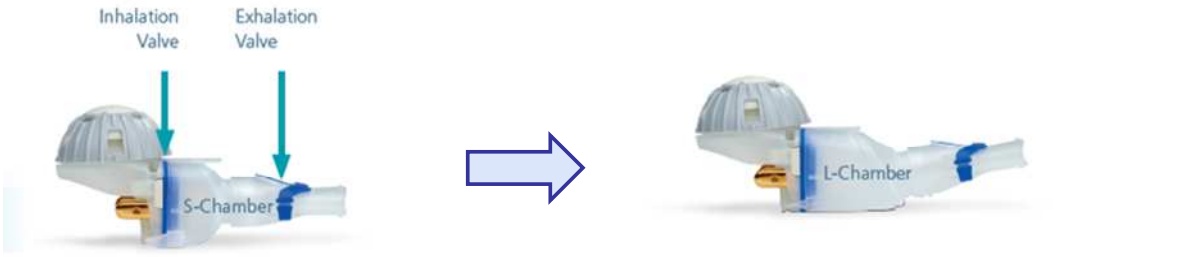


Source: First Berlin Equity Research, Spexis AG

COPILOT is due to start in H1 2023; preliminary data should be available by mid-2023 and the final data by Q1 2024 The primary endpoint of the COPILOT study will be the tolerability and safety of inhaled ColiFin®. The secondary endpoints will include efficacy established through an assessment of pulmonary function (ppFEV1). Spexis intends to start this pilot study of ColiFin® in H1 2023 and preparations for this study are underway. The COPILOT trial will complete its follow-up period by Q2 2023. The company will report interim data after 42 days of treatment, approximately by mid-2023. If the data shows QD's safety and positive signs of efficacy, the company will immediately start preparations for the COPA study with the preferred QD administration. The COPILOT final data analysis will be published by Q1 2024.

QD dose would be a significant competitive advantage for Spexis. Chances of success of the QD dose in the COPILOT study seem good The type of nebuliser used is critical to the efficiency of inhalation and deposition of the drug in the respiratory tract. On behalf of Spexis, the German inhaled therapy specialist PARI has developed the modified eFlow nebuliser system, which is an improved, more efficient version of the previous reliable eRapid system. The optimised eFlow nebuliser handset has a modified medication reservoir and a larger nebulisation chamber particularly designed to administer Colifin at the targeted double dose of 2MIU once daily (see figure 7 overleaf). The eFlow technology at the aerosol head enables short nebulisation times. These features significantly reduce the patients' burden of care, making the product much more attractive compared to the current standard of care alternatives. The remaining device's technical characteristics are the same as the proven eRapid nebuliser. Laboratory studies have successfully demonstrated that the new device achieves a higher dose delivery and reduces the treatment time of ColiFin® per inhalation session, while maintaining similar aerosolisation performance. These measurements suggest that the eFlow device will be able to reach the same ColiFin® 2MIU dose delivered to the lung in one daily administration as the previous device with two daily 2MIU doses.

Figure 7: The optimised eFlow rapid nebuliser allows for faster delivery of a higher dose



Existing eRapid device

The reliable established device uses a class 40 aerosol head, a 4ml medication reservoir, and a residual volume of about 1 ml in a small aerosol chamber

Optimised eFlow rapid device

New aerosol chamber and more efficient reservoir gives better delivered dose – best balance between efficacy and size. eFlow head technology enables short nebulisation times. The new device can deliver the same amount of drug in a shorter time with no residual volume

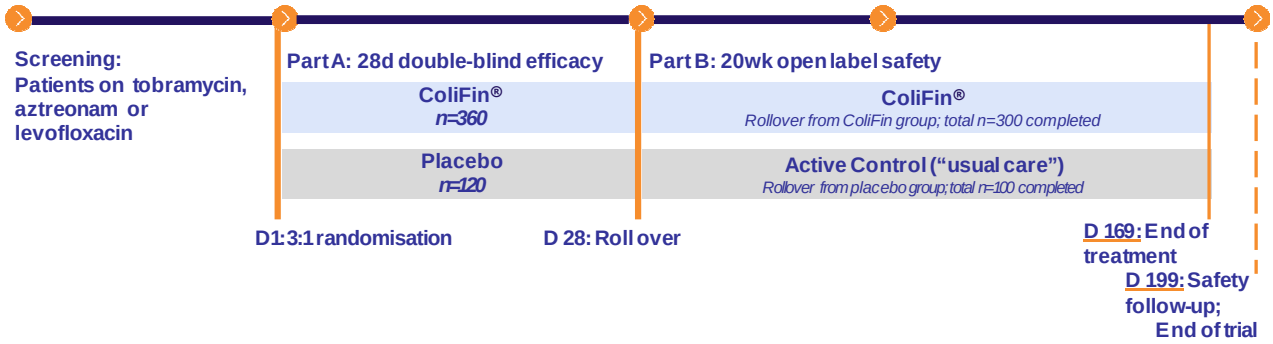
Source: First Berlin Equity Research, Spexis AG

Phase III international COPA clinical trial with 480 CF patients The approved protocol foresees a multi-centred, double-blind, pivotal phase III clinical trial evaluating the safety and efficacy of the QD-inhaled ColiFin® dose in 480 adult and adolescent patients with chronic CF and *P. aeruginosa* lung infection. The international study will take place in the US, supported by the CF Foundation's development network of >130 centres, in European countries and in Australia/New Zealand. The study will be conducted in two parts:

A. An initial period entailing a randomised, double-blind Part A efficacy study over 28 days (4 weeks) comparing ColiFin® against placebo for assessment,

B. A follow-up period whereby the patients will enter an open-label Part B safety study over 20 weeks. In Part B, patients administered ColiFin® will continue with ColiFin®, but placebo patients will be switched back to their prior administered inhaled antibacterial therapy (tobramycin, aztreonam or levofloxacin). Part B intends to compare the safety of ColiFin® against their previous treatment. The complete COPA study runs over 24 weeks (6 months).

Figure 8: Overview of the planned pivotal COPA phase III trial to evaluate the efficacy and safety of inhaled ColiFin®



Source: First Berlin Equity Research, Spexis AG

The COPA study is scheduled to start in H2 2023; it could be completed by H2 2025, leading to a potential approval and market launch in H2 2026 The primary endpoint of the study will be the mean absolute difference in lung function measured as per cent predicted forced expiratory volume in one second (ppFEV1) compared to baseline at Day 28. FEV1 represents the volume of air that the patient can forcibly blow out through a spirometer in one second after full inspiration. The magnitude of lung function improvement of ppFEV1

is expected to be ≥3%. Key secondary endpoints over the six months will be evaluation of exacerbations including severity and duration; consistency of treatment response; the Cystic Fibrosis-Questionnaire-Revised (CFQ-R) respiratory symptom score; microbiology in sputum assessing *P. aeruginosa* density, and resistance development based on the distribution of minimal inhibitory concentration (MIC). An Independent Data Monitoring Committee (DMC) will conduct an interim efficacy analysis after 288 patients (60% of the total) have completed 28 days of treatment. The company currently anticipates that the COPA study will initiate in H2 2023. Assuming normal recruitment progress, the DMC would be able to review the interim results by H2 2024. Completion of the COPA study is planned by H2 2025. Based on these timelines, we anticipate the NDA submission in H1 2026, which given the FDA priority review designation (FDA decision within six months) could lead to a market launch in H2 2026.

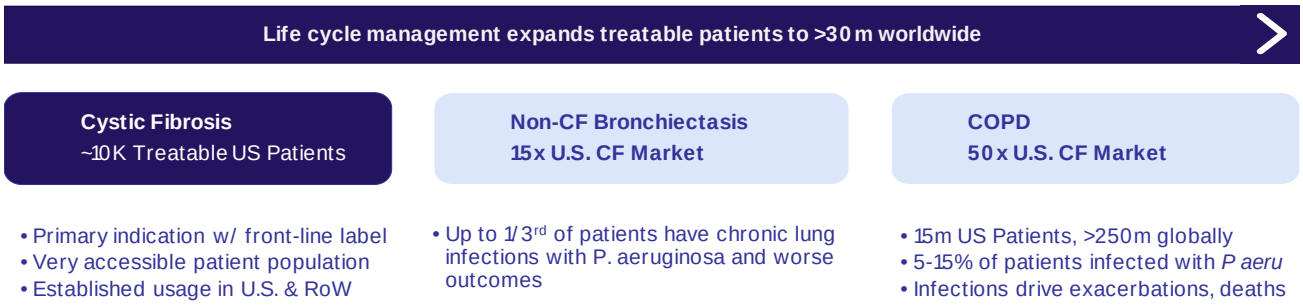
Given successful drug approval, Spexis aims to commercialise ColiFin® itself to maximise sales potential and profitability Assuming a positive outcome of the phase III trial and US approval of the drug, the company intends to build up its own sales force and conduct its own product commercialisation. This path would allow the company to capture a higher margin and maximise sales potential and profitability. CF is a small niche market, and patients are largely treated in specialised centres. We estimate that there are about 200 CF centres in the US, and >130 are part of the CF Foundation development network. For this indication, the company would require a small sales team of ~40-50 reps. Furthermore, the company's close relationship with the CF foundation, one of its main shareholders and a key US clinical development supporter, has enabled Spexis to engage a strong team of 4-5 key opinion leaders (KOLs). KOLs play a fundamental role in creating awareness among CF specialists, thereby supporting product launch and market penetration. Therefore, we believe having an own sales team would be advantageous in marketing the product.

FDA's decision on the requirement for additional toxicity studies is still pending The FDA requested the conduct of a Good Laboratory Practice (GLP) compliant, 6-month repeat dose inhalation toxicity study in an appropriate species. The company will carry out preliminary toxicity studies to select the appropriate species and optimal dosing. After review of all available toxicology studies and available clinical safety data, the FDA may still require the conduct of 9-month, non-rodent toxicology and carcinogenicity studies. Spexis can run these studies in parallel to the COPILOT and the COPA studies without causing any delay to the phase III program.

FURTHER POTENTIAL IN LARGER INDICATIONS SUCH AS BRONCHIECTASIS AND COPD

Life cycle management into larger markets can expand the potential patient population to >30m worldwide ColiFin® is believed to also have strong therapeutic potential in non-CF bronchiectasis (nCFBE) and chronic obstructive pulmonary disease (COPD). These patients also suffer from chronic *P. aeruginosa* infections without having a proven inhaled standard of care. These two markets are 15x and 50x the size of the US CF market (source: Spexis). Nebulised colistin can currently be prescribed for patients with nCFBE in Europe after the failure of a previous eradicating attempt with oral ciprofloxacin and/or an intravenous (IV) cycle with two antipseudomonal antibiotics (Hill et al., 2011; Blanco-Aparicio et al., 2019), but an inhaled front-line antibiotic therapy has not been approved for this indication to date. The Italian company Zambon is conducting a registrational phase III study in nCFBE patients with mixed results so far. Regarding COPD, Bruguera-Avila et al., 2017, showed in a small study with 36 patients that nebulised colistin may be associated with a substantial decrease in the number and duration of hospitalisations due to exacerbation in COPD patients and infection with P. aeruginosa, but more extensive studies are required to prove efficacy. We give an overview of inhaled ColiFin®'s life cycle management opportunity in figure 9 overleaf.

Figure 9: Life cycle management potential of inhaled ColiFin®



Source: First Berlin Equity Research, Spexis AG

CYSTIC FIBROSIS (CF)

CF IS A DISEASE WITH HIGH UNMET MEDICAL NEED

Description of CF Cystic fibrosis (CF) is a rare inherited genetic disease causing severe damage to multiple organ systems, including the lungs and the digestive system. The most serious and common CF complication is problems with the lungs. CF chiefly affects the cells that produce mucus, sweat and digestive juices. These secreted fluids are normally thin and slippery, acting as lubricants. However, in people with CF, mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene cause the CFTR protein to become dysfunctional. As a consequence, cells in various organs cannot attract water to the cell surface, and mucus becomes sticky and thick, obstructing ducts and passageways, particularly in the lungs and pancreas.

In the lungs, the mucus congestion does not allow the patient to effectively clear inhaled germs (e.g. bacteria), often leading to infections, inflammation (i.e. CF patients show excessive inflammatory response to pathogens up to 10x higher than normal according to Davies et al.), respiratory failure, and other complications. Many patients experience chronic lung infections, with *P. aeruginosa* being one of the major pathogens. CF is a progressive condition whereby chronic respiratory infections lead to lung function decline. These infection episodes, accompanied by irreparable lung damage and worsening symptoms such as increased cough, sputum production and shortness of breath, are known as acute pulmonary exacerbations (PEx). PEx are associated with increased loss of lung function, hospitalisations, reduced quality of life and death. For this reason, managing PEx is a top priority in CF treatment (sources: Mayo Clinic; CF Foundation; Simon et al., 2022).

Incidence of CF and life expectancy Cystic fibrosis is a common genetic disease within the white population in the United States and Europe. The condition is estimated to affect 1 in 3,000 to 6,000 white newborns. In other ethnic groups, CF is less common, affecting ~1 in 17,000 African Americans and 1 in 31,000 Asian Americans. The incidence of CF appears to be decreasing in most countries and patient survival has improved substantially, with an estimated median age of survival of ~50 years today (sources: Scotet et al., 2020; UK, US and Canadian CF Registry Annual Data Report from 2018). The prognosis of CF patients has substantially improved in recent decades. As a result, the proportion of adult patients has increased, currently exceeding 50% in most countries and even 60% in Canada. This growth is expected to continue, as illustrated by a study based on the European CF Registry, which predicted that the number of adult patients living with CF in Europe would increase by 75% between 2010 and 2025 (source: Burgel et al., 2015). Many factors are responsible for these significant advances, such as improvements in care through the management of patients in specialised centres multidisciplinary teams and better, more proactive control of

pulmonary infections with the administration of new inhaled antibiotic therapies, particularly a better control of *P. aeruginosa* colonisation (source: Stephenson et al., 2017). According to the US CF Foundation and CF Europe, close to 40,000 children and adults live with CF in the US, ~4,300 in Canada, ~48,000 in Europe, and an estimated 105,000 people have been diagnosed with CF across 94 countries worldwide. The mean annual health care cost for treating CF has been estimated at USD 15,571, which depending on the severity of the disease can range between USD 10k and 34k. The lifetime CF-related cost of care is ~USD 306k based on a 3.5% discount rate, with the majority of the expenses being used for hospital inpatient and drug treatment (source: Van Gool et al., 2013).

Diagnosis In the US, all 50 states conduct newborn screening for CF to diagnose the disease as early as possible. Doctors usually diagnose CF in children or in older patients through blood tests for high levels of immunoreactive trypsinogen (IRT). In the cases of positive tests, if the doctors suspect that the patient may have CF based on symptoms or family history, they will undergo a sweat test for high salt and chloride content, which indicates CF. In addition, genetic testing capable of identifying the CFTR mutations typically associated with CF can be used to confirm a positive initial test with an elevated IRT or high sweat chloride. Many laboratories can test for the 30–96 most common CFTR mutations, which can identify over 90% of people with CF. Once the diagnosis is confirmed, doctors evaluate the patient's condition with a chest x-ray, chest or abdominal CT or MRI.

TREATMENT OF CF

Treatment and main products There is no cure for CF, and treatment is focused on controlling symptoms and slowing down disease progression. Therapeutic treatment for CF is tailored to specific symptoms and disease severity, typically consisting of drugs to maintain and improve lung function, fight infections, clear mucus, help to breathe, and work on the faulty CFTR protein. These drugs can be classified into one of the following five core groups:

- **Antibiotics** to prevent or treat lung infections and improve lung function. Inhaled antibiotics, i.e., colistin, tobramycin, aztreonam lysine and levofloxacin, are the main antibiotics used as maintenance treatment for CF patients.
- **Anti-inflammatory** drugs, such as ibuprofen or corticosteroids, reduce inflammation. Inflammation causes damage to lung tissue that can be irreversible. Ibuprofen is especially beneficial for children, but side effects can include kidney and stomach problems. Corticosteroids are also used to stop inflammation quickly. Nevertheless, corticosteroids show limitations in the case of long-term administration, inducing severe side effects such as bone damage, diabetes, hypertension, weight gain and eye disorders (Ethgen et al., 2013; Curtis et al., 2006).
- **Bronchodilators** help keep the airways open by relaxing the muscles around the bronchial tubes. The most commonly prescribed bronchodilators for CF are inhaled short-acting beta-agonists (SABAs), including Albuterol (Ventolin, Proventil, Proair) and Levalbuterol (Xopenex).
- **Mucus thinners,** such as inhaled hypertonic saline, to help the patient cough up mucus from the airways.
- **CFTR modulators** improve the function of the impaired CFTR protein. They improve lung function and help prevent lung problems and other complications. There are currently four CFTR modulators approved for people with specific CFTR mutations. They are I. ivacaftor (Kalydeco, approved in 2012); II. lumacaftor/ivacaftor (Orkambi, 2015); III. tezacaftor/ivacaftor (Symdeko, 2018); IV. elexacaftor/tezacaftor/ivacaftor (Trikafta, 2019 US / 2020 EU).

Treatment of chronic infections with *P. aeruginosa* represents a significant challenge for CF A compromised immune response in CF patients' airways against inhaled microbes leads to persistent bacterial infection and inflammation. *P. aeruginosa* is considered one of the most hazardous pulmonary pathogens and the predominant cause of exacerbations and mortality in CF. *P. aeruginosa* is highly virulent and well-equipped to overcome host defences and competition with other bacteria. Over time, these pathogens also can form a biofilm, making them capable of surviving antibiotic treatment administered at high doses. The majority of currently used antibiotics can kill some of the bacteria settled in biofilms. Still, they cannot wholly eradicate the biofilms, and relapses occur, leading to chronic infections (Fernandez-Barat et al., 2017). More than 70% of CF patients can be chronically colonised by *P. aeruginosa* by age 25 (Okoliegbe et al., 2021). According to the CF Foundation Patient Registry, in approximately 18% of US patients with positive *P. aeruginosa* culture, the isolated strains were multi-drug resistant, which are even more difficult to kill. Typically, CF patients' cumulative lifetime treatment with antibiotics leads to the development of multidrug-resistant strains. So far, aggressive early treatment with inhaled antibiotics is the cornerstone of CF clinical care in patients with infections.

Three main EU-approved inhaled antibiotics against *P. aeruginosa* infection, but only two in the US… The three main inhaled antibiotics approved in the EU for CF with a track record of proven safety and efficacy are tobramycin (TOBI / TOBI Podhaler from Viatris, formerly Mylan), CMS (Colistin/Colomycin), and aztreonam lysine (Cayston from Gilead Sciences Inc), followed by the more recently approved antibiotic levofloxacin (QUINSAIR from Chiesi Farmaceutici, approved only for adult use). CMS has become a front-line therapy and the most prescribed drug for chronic lung infections arising from CF in Europe, but it has not been approved in the US yet, creating a substantial market opportunity. In the US, TOBI is the most widely used product for this indication, closely followed by Cayston. QUINSAIR did not receive US approval due to poor phase III results.

…inhaled CMS (ColiFin®) has a competitive profile against its peers for a potential US commercialisation CMS (ColiFin®) has a competitive profile against the two approved antibiotic therapies in the US. Its positive safety and efficacy track record over its ~12 years of commercialisation and its leading market position in Europe reflects its optimal profile in treating *P. aeruginosa* infections. Chronic pulmonary *P. aeruginosa* infection in CF requires lifelong treatment. The risk of developing *P. aeruginosa* resistance (i.e. multi-drug resistant strains) to the commonly used antibiotics is a relevant problem and plays a crucial role in antibiotic treatment decisions. CMS's significantly lower resistance rate against *P. aeruginosa* compared to the two other inhaled antibiotics makes CMS a preferred treatment option for the US. Continuous alternating treatment with inhaled antibiotics is considered an important strategy to improve the clinical outcome and avoid drug resistance. In the US, TOBI and Cayston are typically prescribed alternating on a monthly basis (on/off regimen). CMS/ColiFin® has the advantage of being prescribed continuously with a low risk of resistance (as in Europe). In addition, if ColiFin®'s planned one-daily formulation is successfully developed, the product will have a superior patient compliance profile, more attractive to patients than their peers. Treatment burden is critical since patients usually take multiple inhaled daily therapies to manage all CF symptoms. According to CF Foundation estimates, the US need for alternative antibiotics is so big that ~12% of CF adults and ~36% CF adults with moderate or advanced disease are currently receiving off-label treatment with IV colistin solution administered through an unapproved standard nebuliser. Key CF opinion leaders (KOLs) members of the CF Foundation development network thus expect that once approved, ColiFin® has the potential to become US front-line therapy as it is in the EU.

Table 4: Favourable competitive position of inhaled CMS/ColiFin® against its two peers in the US

	Tobramycin (TOBI) / aztreonam lysine (Cayston)	CMS(ColiFin®)
Mechanism of action	Binding to specific bacteria sites to block relevant functions and provoke cell death. Leads to resistance development.	Disrupts the bacterial cell membrane. Difficult for *P. aeruginosa* to mutate around
Resistance Development	It is increasing, up to 40% in some regions	Rarely exceeding ~5%
Safety	TOBI has significant ototoxicity concerns	Latest EU post-marketing safety analyses show favourable safety profile of ColiFin®
Efficacy	Decreased efficacy over time	Front line agent in Europe over TOBI®/Cayston
Dosing	Continuous alternating therapy (CAT: by repeating cycles of 28d Rx on TOBI b.i.d, followed by 28d on Cayston t.i.d.)	At present continuous b.i.d. dosing (twice-a-day) without CAT alternation. Phase III development plans for q.d. dosing (once-a-day)
28d AWP Pricing	Between ~USD 5,400 – 11,000 (generics - branded)	Targeting ~USD 8,000

Source: Spexis AG

CFTR modulators represent a breakthrough in CF treatment The US biotech company Vertex Pharmaceuticals is changing the CF treatment paradigm with its four commercialised disease-modifying CFTR modulators. Following the first CFTR approval (Kalydeco) in 2012, these four drugs are transforming patients' lives with sustained and long-term benefits, including a reduction in sweat chloride to normal levels, lowered frequencies of pulmonary exacerbations, slower deterioration and even improved lung function (FEV1) at six months post-treatment initiation, in some cases less frequent detection of *P. aeruginosa* and other common pathogens, and improved quality of life. Trikafta offers the most significant disease-modifying impact, with lung function improvements of up to 14% and partial rescue of CFTR activity up to 60% of physiological values. The triple combination Trikafta also boosted the eligible CF patient population to 90% from the 50% that the three previous drugs were able to address. Trikafta proved beneficial even in patients with advanced lung tissue damage, suggesting that early treatment with this product could prevent airway changes and lung function decline. A recent real-world study on more than 16k US patients showed that the drug led to an 87% reduction in risks of a lung transplant, 77% fewer pulmonary exacerbations and a 74% reduction in risk of death. Trikafta has been approved for people with CF ages 6 and older. As a weak point, the product carries warning label regarding liver injury. (McKone et al., 2014; Heltshe et al., 2015; Quittner et al., 2015; Frost et al., 2019, Middleton et al., 2019; McGarry et al., 2021, Fajac et al., 2021, Fierce Biotech, 2022).

CFTR modulator administration is complementary to the other symptomatic therapies CFTR modulator administration has been added to the additional symptom-related therapeutic treatment of eligible patients rather than replacing these therapies. Despite some positive signs of infection frequency improvements, the potential positive effect of CFTR modulators on chronic infections is still to be proven. The long-term bacterial load of *P. aeruginosa* does not seem to be affected by this treatment (source: Waters et al., 2021). In several studies, either the *P. aeruginosa* burden following treatment with the CFTR modulator ivacaftor/Kalydeco remained unchanged (e.g. 6-year follow-up study from Duckers et al., 2021), or the initial reduction was followed by a rebound at the pre-treatment levels (sources: Einarsson et al., 2021; Saluzzo et al., 2022). The development pipeline of CFTR modulators is growing, and some recent programs have also been pursuing the identification of modulators for less common CF-causing mutations, which could, over time, lower the CF population not yet benefiting from these treatments. We give an overview of the main CFTR therapies commercialised or in clinical development in table 5 overleaf.

Table 5: CFTR therapies approved or in clinical development for CF

Company	Drug candidate	Mechanism	Development stage	Comments
Vertex Pharma	Ivacaftor (Kalydeco), oral drug	CFTR potentiator that helps the opening of the chloride channel to allow chloride / salt to move in and out of the cell	Approved in the US / EU since 2012	Long-term benefit, leading to up to 10% improved lung function and 50% reduced pulmonary exacerbations, but applicable to only ~4% of the CF population (Heltshe et al., 2018)
Vertex Pharma	Lumacaftor + ivacaftor (Orkambi), oral drug	Combo of one CFTR protein corrector and one potentiator	Approved in the US / EU since 2015	Slowed decline in lung function by 42% per year (PROGRESS phase III follow-up trial over 2 years)
Vertex Pharma	Tezacaftor + ivacaftor (Symdeko), oral drug	Combo of one CFTR protein corrector and one potentiator	Approved in the US / EU since 2018	Showed an improvement in lung function FEV1 of up to 6.8% (EVOLVE & EXPAND phase III trials)
Vertex Pharma	Elexacaftor + tezacaftor + ivacaftor (Trikafta), oral drug	Combo of two CFTR protein correctors and one potentiator	Approved since 2019 in the US / 2020 in the EU	Showed lung function improvements up to 14%, and rescue of CFTR activity up to 60% of physiological values (phase III study in 403 patients)
Vertex Pharma	VX-561 (deutivacaftor), oral drug	CFTR potentiator, it is an altered form of the potentiator ivacaftor (Kalydeco)	Phase II completed	It seems that Vertex will pursue phase III development only in the triple combo (see next Vertex project)
Vertex Pharma	VX-121 + tezacaftor + VX-561 (deutivacaftor), oral drug	Combo of two CFTR protein correctors and the potentiator VX-561	Phase II completed, Phase III underway	Showed safe and improved lung function FEV1 by 10-14%, depending on the dose. The phase III trials are expected to be completed in 2024
Abbvie	ABBV-2222 + ABBV-576+ ABBV-3067, oral drug	Combo of two CFTR protein correctors and one potentiator	Phase II study of doublet still ongoing/goal is triple combo	Positive phase II results so far of the C1 corrector ABBV-222 and potentiator ABBV-3067 –will be pushed forward in new phase II study for triplet early 2023
Eloxx Pharma	ELX-02, oral drug	Restore CFTR function in people with CF who have nonsense mutations	Phase II underway	Positive topline phase II results proved safe and achieved statistically significant 5.4mmol/L reduction in sweat chloride
4D Molec. Therap.	4D-710, inhaled drug	Gene therapy – AAV vector delivering healthy CFTR gene	Phase I/II underway	First patient (n=~18) was dosed in April 2022. Interim data presented on 3 November suggested safety, no adverse events and clinical activity

Source: First Berlin Equity Research, Cystic Fibrosis Foundation, ClinicalTrials.gov, Companies

Even in the post-CFTR modulator era, we anticipate that *P. aeruginosa* infections will remain a major problem in CF. This challenge may even be accentuated since patients will live longer. Chronic *P. aeruginosa* infection may still remain the leading cause of exacerbations, lung function decline and mortality in CF patients in the future.

COMPETITIVE ENVIRONMENT

Vertex Pharmaceuticals dominates the CF market The global CF market is clearly dominated by the large US-based biotech company Vertex, which has continuously expanded its presence in this niche market for about a decade to consolidate its currently monopolistic position in the CFTR-modulators segment. Traditionally, the anti-infectives segment dominated the global CF market, followed by mucolytics, pancreatic enzyme supplements (PERTs), and bronchodilators. Vertex revolutionised and expanded this market. We thus believe that the company and its four highly priced CFTR-modulators (US list prices between USD 270k and USD 310k per year before discounts) now represent >75% of the CF market. In 2021, Vertex' four-drug CF franchise achieved revenue of USD7.6bn, whereas the blockbuster drug Trikafta, for which ~90% of the CF population will be eligible, generated sales of USD 5.7bn (source: Fierce biotech, 2022). Based on its sound CF product portfolio and promising late-stage development pipeline, this company is poised to comfortably maintain its leading position until at least the end of this decade.

Other relevant CF players standing out with marketed products in other drug classes are:

- The Italian pharmaceutical company, Chiesi, which markets 1) two relevant inhaled antibiotics, Bramitob/Bethkis (tobramycin solution) in the US and top 5 EU countries, and Quinsair (levofloxacin) in the top 5 EU countries, 2) the mucolytic Bronchitol (mannitol) in the US, and 3) the PERT drug Pertzye (pancrelipase) in the US;
- The generic specialist Viatris (formerly Mylan), which commercialises the most popular inhaled antibiotic therapy TOBI (tobramycin solution) and TOBI Podhaler (tobramycin dry powder), which it acquired from Novartis in 2018;
- Nestle HealthScience, which markets two PERT drugs, Zenpep (pancrelipase) and Viokace (pancrelipase);
- Gilead Sciences, which commercialises the inhaled antibiotic (Cayston);
- Pharmaxis, which commercialises the osmotic agent Bronchitol.

AbbVie (triple CFTR-modulating candidate), Eloxx Pharma (non-sense CFTR-modulators and 4D Molecular Therapeutics (gene therapy), are potential new entrants in the field poised to gain significant market share if their promising clinical-stage drug candidates currently in phase I/II or II prove successful in clinical trials.

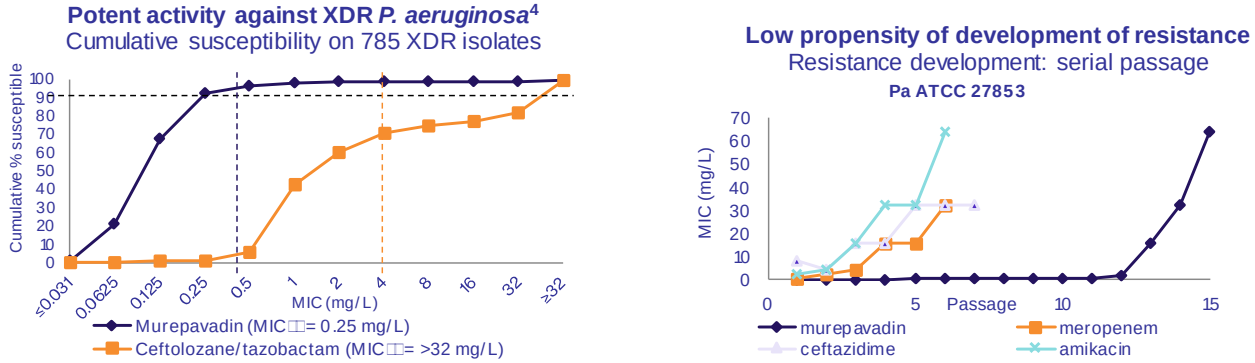
CF market to show a healthy growth dynamic in the period 2021-2027 The global CF drugs market was valued at USD 8.5bn in 2020, and is expected to reach >USD 26.5bn by 2027, expanding at a CAGR of 16.1% in the period (source: Global Market Insights, 2021). CFTR modulators will continue to dominate the CF therapeutics market through the forecast period. This can be attributed to new product launches (i.e. Trikafta), and huge demand for these premium-priced drugs. According to the CF Journal published in May 2022, only 12% of the worldwide 162k CF population has been administered the game-changer CF-modulator Trikafta, leaving substantial upside for growth. The US represents 76% of the world market.

INHALED MUREPAVADIN: A POTENT MACROCYCLIC ANTIBIOTIC FOR THE TREATMENT OF CHRONIC P. AERUGINOSA LUNG INFECTIONS

PRE-CLINICAL DATA SHOW A SUPERIOR PROFILE IN P. AERUGINOSA INFECTION TREATMENT

Profile and mode of action Inhaled murepavadin is Spexis' most advanced drug candidate from a novel class of antibiotics called “Outer Membrane Protein Targeting Antibiotics” (OMPTA). The first-in-class antibiotic peptidomimetic compound was generated with its macrocyclic peptide technology platform. It has a novel mechanism of action by specifically targeting the outer membrane protein LptD of *P. aeruginosa* bacteria. In contrast to widely used broad-spectrum antibiotics, in vitro studies have demonstrated that the macrocycle murepavadin has a lower propensity of provoking drug resistance. This makes it a highly potent drug candidate against *P. aeruginosa*, including most of the resistant strains. The compound has also shown good biofilm activity (in vitro).

Figure 10: Superior in-vitro and in-vivo potency and resistance profile of murepavadin compared to broad-spectrum antibiotics



Source: Spexis AG

Following the discontinuation of the two phase III trials of IV murepavadin in Pneumonia due to concerns of nephrotoxicity, the focus changed to inhaled murepavadin The drug candidate was initially investigated for intravenous administration. Spexis AG (previously Polyphor AG) successfully completed 8 clinical studies (6 phase I and 2 phase II studies) of murepavadin administered intravenous (IV) in healthy subjects and in ventilator-associated bacterial pneumonia patients, demonstrating positive signs of efficacy, good lung penetration and good safety. The company also conducted two phase III studies in hospitalised patients with pneumonia infection caused by P. aeruginosa, which had to be discontinued in May 2019 due to an unexpected elevation of laboratory markers for acute kidney injury in patients who were administered the product. The company decided to cancel both trials due to this safety issue and switch its focus to the inhaled formulation of the product.

INHALED MUREPAVADIN IN PHASE I CLINICAL DEVELOPMENT FOR CF

Inhaled murepavadin unlikely to cause toxicity Preclinical studies showed that locally applied inhaled murepavadin at 1, 5 or 10 mg/kg/day doses did not cause any systemic toxicity after 4 weeks of daily dosing. Moreover, the predicted dose of inhaled murepavadin required for efficacy in *P. aeruginosa* lung infections has low systemic exposure. Thus, it is unlikely to result in any organ toxicity (i.e. kidney damage).

Phase I dose-escalating safety study in healthy volunteers demonstrated that inhaled murepavadin was safe and well tolerated at all dose levels Following Medicines and Healthcare products Regulatory Agency (MHRA) approval of the study protocol, Spexis started subject enrollment of its phase I study evaluating safety and tolerability of single ascending doses (SAD) of inhaled murepavadin in healthy volunteers in Q4 2021. The trial's primary endpoint was safety, including overall and local tolerability of single ascending doses of inhaled murepavadin. The secondary endpoint was the characterisation of pharmacokinetics in the systemic circulation and in bronchoalveolar lavage fluid of murepavadin following inhalation of single ascending doses in healthy adult subjects. The company reported top-line results on 9 January 2023. The primary endpoint was achieved. Inhaled murepavadin proved to be safe and well tolerated at all six tested doses. The company reported no clinically relevant signs of irritation of the upper airways and no serious adverse events. These positive results clear the way for phase II clinical trials in CF patients (or alternatively for non-CF bronchiectasis).

Phase II study in CF patients, partly funded by the US CF Foundation, is expected to start in the second half of 2023 The phase I and phase II studies, up to proof of concept, will be partly funded by the CF Foundation. The main goals of the phase II study will be to investigate the product's safety and its efficacy in CF patients. The results are planned to be available in H2 2024.

Phase III development strategy will depend on phase II data and profile differences with ColiFin® The further development strategy of inhaled murepavadin will be taken after phase II results are available. The company will compare the efficacy/safety profile of the product with that of ColiFin®, assessing both drug candidates' efficacy in specific populations and the cannibalisation potential (i.e. a drug taking market share from a similar drug). Following this analysis, the company will decide whether to continue with a phase III study in CF patients, or to switch to indications with more sizable patient populations such as *P. aeruginosa* infections in non-cystic fibrosis bronchiectasis (15x larger than CF) or COPD (50x larger than CF).

BALIXAFORTIDE – MACROCYCLE FOR POTENTIAL TREATMENT OF SEVERAL CANCER TYPES

TARGETING THE CHEMOKINE RECEPTOR CXCR4

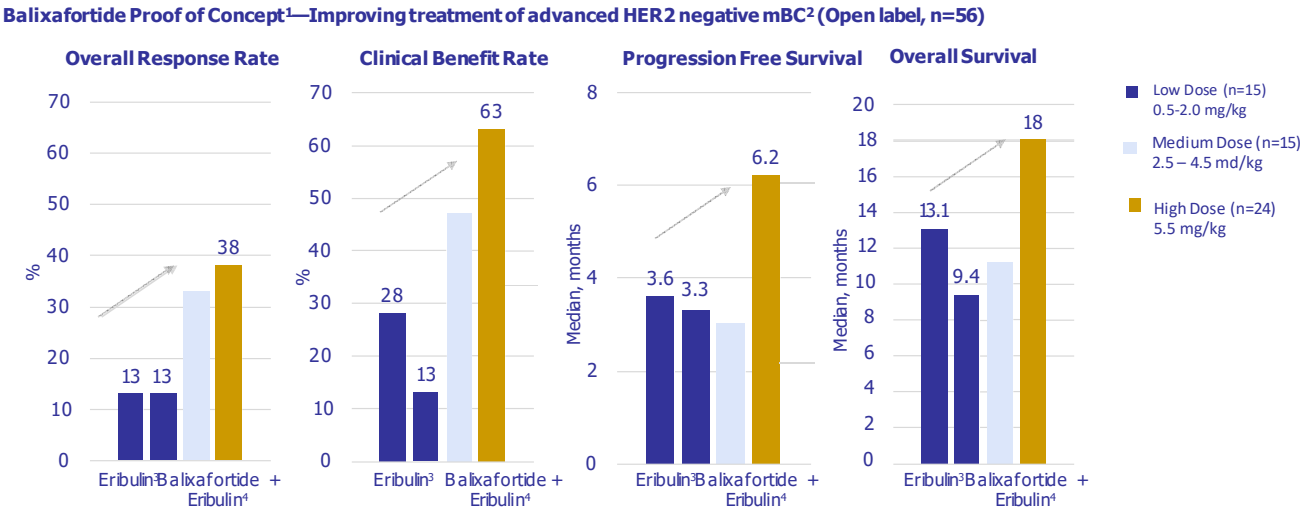
Profile and mode of action Spexis' drug candidate balixafortide, is a macrocyclic peptide that targets a receptor of CXCR4, a key chemokine in the tumour microenvironment (TME) that regulates metastasis, the trafficking and homing of immune cells at tumour sites, thus affecting the specific immune response. balixafortide is a potent and highly selective CXCR4 inhibitor that may potentially deliver best-in-class drug effect compared to other CXCR4 antagonists in development. The chemokine receptor CXCR4 plays a critical role in tumour growth and survival, angiogenesis and metastasis. This makes CXCR4 a promising target for the therapy of hematologic and solid tumours and other non-oncology indications. CXCR4 overexpression has been detected in more than 23 different human cancer types and correlates with a poor prognosis (sources: Santagata et al., 2019; Chatterjee et al., 2014). For example, primary breast cancer cells and breast cancer cells in metastatic sites frequently express high levels of the CXCR4 receptor (source: Muller et al., 2001). Spexis (i.e. Poliphor) therefore chose breast cancer as the previous lead indication.

Preclinical studies demonstrated balixafortide's efficacy in several cancer indications The company conducted in-vitro receptor binding studies, which showed a high affinity of balixafortide for the human CXCR4 receptor, as well as a general lack of significant binding to other potential target receptors. In animal studies, the combination of balixafortide and the chemotherapy Paclitaxel showed a clear synergistic and statistically significant effect in tumour volume against Paclitaxel alone. Preclinical studies demonstrated the efficacy of balixafortide and close analogues in combination with chemotherapy in various haematological and solid malignancies.

BALIXAFORTIDE'S CLINICAL DEVELOPMENT IN BREAST CANCER FAILED

Phase Ib study showed efficacy in advanced breast cancer Spexis (Polyphor) conducted eight clinical trials with a total of 462 subjects investigating intravenous (IV) balixafortide either as a single agent or in combination with other drugs. The drug candidate was well tolerated, with no limiting safety events identified at the highest administered dose of 5.5mg/kg. Overall, the clinical studies evaluated its safety and efficacy in the following indications: breast cancer, multiple myeloma, stem cell mobilisation and tissue repair. The company successfully achieved proof of concept in a Phase Ib study of balixafortide in combination with the chemotherapy drug Eribulin in patients with advanced metastatic breast cancer (source: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(18)30147-5/fulltext). The US registration agency FDA granted Fast Track designation.

Figure 11: Proof of concept phase Ib study results of balixafortide + eribulin



Source: Spexis AG, results published in The Lancet and at ASCO Cancer Conference 2017

Pivotal FORTRESS phase III study failed to show statistically significant efficacy; dose was most likely too low The international, multicenter, randomised, active-controlled, open-label phase III FORTRESS study took place between mid-2019 and 2021 in 432 advanced breast cancer patients with metastasis who were HER2 negative. It compared the chemotherapy drug eribulin in combination with balixafortide against eribulin alone. The key primary endpoint was progression-free survival (PFS) at 12 months after the last patient was randomised, and the second primary endpoint was objective response rate (ORR) at 6 months. The drug candidate failed to show a statistically significant difference in ORR or PFS between the treatment arms. The company suspects that the dose was too low, since solid dose-escalating studies to identify the maximum tolerated dose (MTD) were not conducted in early clinical trials.

Further development strategy The company is evaluating potential oncology and non-oncology indications for balixafortide. CXCR4 is a highly validated target. For example, Sanofi's drug Mozobil/plerixafor is a drug that has been approved and marketed since 2008 for mobilising stem cells into the bloodstream for collection and transplantation in patients with Non-Hodgkin's lymphoma (NHL) and multiple myeloma. BiolineRX's CXCR4-inhibitor peptide Motixafortide also recently demonstrated efficacy in the same indication and filed for approval. Additionally, many companies are conducting clinical trials for several indications, including mobilising stem cells, several types of solid tumours, rare neutropenias and B-cell lymphomas. We note that leading pharmaceutical players such as Bristol Myers, Sanofi and Eli Lilly are developing cancer therapies targeting the receptor CXCR4. The company is currently analysing preclinical data and undertaking further investigations to determine the most promising indications to address in future phase II trials. Management expects to publish results of the analysis in early 2023.

FINANCIAL HISTORY AND OUTLOOK

The company's financial statements are prepared in accordance with IFRS accounting standards. The two key relevant historical events to consider to better understand the company's reported figures were: 1) Spexis AG was established in December 2021, through the reverse merger of the two complementary life science specialists, the publicly listed firm Polyphor AG and the privately held company EnBiotix Inc, and 2) Spexis raised pre-merger funds of USD 12.8m (~CHF 12.0m).

FINANCIAL HISTORY

Income Statement FY 2021 – Cost increase in connection with the merger Spexis' financial statement is typical of a development-stage biotech company. The company is generating no revenues and is loss-making. The company's P&L in FY/21 reflects the reverse acquisition dynamic between Polyphor AG and EnBiotix. OPEX increased to €4.2m (FY/20:CHF 1.3m), driven by higher administrative expenses related to share-based compensation totalling €2.5m for its CEO and third-party merger-related consultants. EBIT came in at CHF -4.2m (FY/20: CHF -1.2m). In FY/21, the company saw a significant expansion of financial expenses to CHF 7.6m (FY/20: CHF 0.7m) largely due to fair value changes of derivatives amounting to CHF 6.1m triggered by the reverse merger. Spexis reported a net result of CHF -11.9m (FY/20: CHF -1.9m), which equates to CHF -0.82 per share (FY/20: CHF -0.14).

Table 7: Income Statement FY/21 vs FY/20 and H1/22 vs H1/21 (selected items)

in CHF'000	2021	2020	Delta	H1 2022	H1 2021	Delta
Revenue & other income	0	52	-	616	0	-
Sales & Marketing	70	0	-	420	0	-
General & Administrative	3,302	718	*360%*	2,985	272	*996%*
Research & Development	876	559	*57%*	6,758	313	*n.m.*
OPEX	4,248	1,277	*233%*	10,162	585	*n.m.*
EBIT	-4,248	-1,225	-	-9,546	-585	-
Net income	-11,862	-1,851	-	-9,972	-1,017	-

Source: Spexis AG

H1/22 income statement – expanded development activity with focus on ColiFin® Spexis booked grants of CHF 616k in H1/22 for research reimbursement costs between the former Polyphor and the CARB-X programme. OPEX widened to CHF 10.2m (H1/21: CHF 3.6m) due to higher development expenses of CHF 6.8m (H1/21: CHF 0.3m) and G&A of CHF 3.0m (H1/21: CHF0.3m) chiefly used for the preparation of ColiFin®'s phase III study and the conduction of the ongoing murepavadin's phase I study. EBIT and net result amounted to CHF -9.5m and CHF -10.0m, respectively (H1/21: CHF -0.6m and CHF -1.0m).

Balance Sheet FY/21 and H1/22 The company's FY/21 balance sheet widened substantially due to the reverse acquisition deal and the pre-merger capital increase of USD 12.8m (~ CHF 12.0m). The acquired fixed assets and certain liabilities were newly booked, particularly property plant & equipment of CHF 1.2m, intangible assets of CHF 10.5m (i.e. macrocycle technology platform and murepavadin), goodwill of CHF 18.0m, financial & other LT assets of CHF 1.9m (i.e. leased headquarter premises in Switzerland), pension & other LT liabilities (Swiss staff pension and leasing liabilities). Following the financing measure, the cash position increased to CHF 14.4m at YE/21 (YE/20: CHF 0.3m), which is expected to finance operations into Q1/23. At the end of H1/22, the cash position went down to CHF 7.0m. In July 2022, the company renewed a previously existing financing contract with the French investor IRIS Capital Investment for an equity-linked financing facility of up to CHF 15m. Spexis can draw down funds when needed, whereas IRIS is committed to buying on a monthly basis 24 tranches of CHF 625k of unsecured zero-coupon

mandatory convertible bonds monthly over two years. This type of financing is typically negative for the stock price. It also falls short of the estimated amount of >CHF 80m needed for ColiFin®'s phase III study and the subsequent marketing alone. Spexis thus intends to raise these funds in tranches with committed long-term investors. At YE/21, Spexis's equity position increased to CHF 30.2m from CHF -11.3m at the end of FY/20, going down to CHF 27m at the end of H1/22.

Table 8: Balance Sheet FY/21, FY/20 and H1/22 (selected items)

in CHF'000	2021	2020	Delta	H1 2022	2021	Delta
Cash and cash equivalents	14,368	294	-	6,999	14,368	*-51%*
Accounts receivables	1,652	12	-	1,409	1,652	*-15%*
Other current assets	2,275	2	-	675	2,275	*-70%*
Current Assets, Total	**18,295**	**308**	-	**9,083**	**18,295**	*-50%*
Property plant and equipment	1,177	0	-	819	1,177	*-30%*
Intangible assets	10,496	0	-	10,271	10,496	*-2%*
Goodwill	18,006	0	-	18,079	18,006	*0%*
Financial and other LT assets	1,923	33	-	1,744	1,923	*-9%*
Non-Current Assets, Total	**31,602**	**33**	-	**30,912**	**31,602**	-
Accounts payable	2,460	168	-	1,410	2,460	*-43%*
Other current liabilities	5,750	3,214	*79%*	5,518	5,750	*-4%*
Pension and other LT liabilities	8,282	4,905	*69%*	4,078	8,282	*-51%*
Financial debt ST+LT	3,182	3,323	*-4%*	2,378	3,182	*-25%*
Total Liabilities	**19,673**	**11,610**	*69%*	**13,384**	**19,673**	*-32%*
Equity	30,224	-11,269	-	26,612	30,224	*-12%*
Equity ratio	61%	n.a.	-	67%	61%	-

Source: Spexis AG

Cash Flow Statement FY/21 In FY/21, cash flow from operating activities came in at CHF -1.1m (FY/20: CHF -0.8m). Cash flow from investing activities amounted to CHF 3.4m (FY/20: CHF 0), reflecting the net assets addition of the acquired Swiss-based company Polyphor. Cash flow from financing activities amounted to CHF 11.8m in FY/21 (FY/20: CHF 0.7m); Spexis conducted a capital increase raising net proceeds of CHF 12.0m to finance operations and repaid debt and interests worth CHF 0.2m. Thus net cash flow in FY/21 came in at CHF 14.1m (FY/20: CHF -84k).

Table 9: Cash flow statement H1/18 and FY/20 (selected items)

in CHF'000	2021	2020	Delta	H1 2022	H1 2021	Delta
Operating cash flow	-1,141	-774	-	-7,184	-376	-
Cash flow from investing	3,439	0	-	0	0	-
Cash flow from financing	11,833	691	-	-701	87	-
Net cash flow	14,132	-84	-	-7,885	-289	-

Source: Spexis AG

Cash Flow Statement H1/22 In H1/22, operating cash flow rose significantly to CHF -7.2m (H1/21: CHF -0.4m) due to increased development activity, and there were no investments. Financing cash flow was CHF -700k, reflecting increased debt and lease liabilities repayment (H1/21: CHF 87k). The net cash flow came in at CHF -7.9m (H1/21: CHF -0.3m).

FINANCIAL OUTLOOK

Income Statement Considering that Spexis' lead drug candidate inhaled ColiFin® is ready to enter the phase III development stage, we anticipate first revenues from its potential market launch towards 2026E. We have assumed the potential market launch of the second drug candidate murepavadin would take place in 2029E.

We have assumed that the company will finance further pipeline development until a sustainable breakeven is achieved through a combination of raising funds from investors and upfront payments from licensing non-core regions to pharmaceutical partners (e.g. Asia and Middle East for ColiFin® and murepavadin). We project that the out-licensing of ColiFin® and murepavadin in non-core regions, and of lonodelestat to Santhera, will lead to upfront/milestone payments of CHF 10m in 2023E and further CHF 10m in 2026E. The partner will conduct the phase III development in these regions and receive distribution rights in the CF indication. We also anticipate that Spexis will receive research grants for the CARB-X programme of ~CHF 2.2m p.a. in 2023E and 2024E. We expect that Spexis will complete phase III trials of ColiFin® (US) and murepavadin (US & Europe), which will deliver positive data. We anticipate that Spexis will hire its own sales force to commercialise the products in the US, and will out-license the rights for the commercialisation of murepavadin in Europe.

Our 2022 projections are the baseline for our projections going forward. Considering the company's increased activity with ColiFin®, we project OPEX to rise from CHF16.0m in 2022E to CHF 21.7m in 2023E and CHF 37.8m in 2025E. Our R&D curve assumes that the company will spend CHF 80.5m in research and development in the period 2022E-2025E. In our view, this budget is sufficient to complete phase III clinical trials for ColiFin® and finance the murepavadin development until 2025E. We expect the company to generate its first revenues in 2026E and achieve a sustainable break-even in 2027E due to the marketing of ColiFin® in CF in the US. Spexis had tax loss carried forward (TLCF) of CHF 323.7m at the end of FY 2021, which we expect to lower tax paid. We project that the company will pay no taxes until 2028E, after which we anticipate it to pay a tax rate of 20%. Going forward, we model revenue and net earnings until 2040E. We have taken typical industry development timeframes into consideration.

Table 10: Revenue, EBIT, net income forecasts (selected items)

in CHF'000	2020	2021	2022E	2023E	2024E	2025E
Revenue & other income	52	0	620	12,200	2,200	0
Sales & Marketing	0	70	500	500	500	3,000
General & Administrative	718	3,302	6,000	6,200	6,500	6,825
Research & Development	559	876	9,500	15,000	28,000	28,000
OPEX	1,277	4,248	16,000	21,700	35,000	37,825
EBIT	-1,225	-4,248	-15,380	-9,500	-32,800	-37,825
Net income	-1,851	-11,862	-15,560	-9,660	-32,794	-37,819

Source: First Berlin Equity Research

Balance Sheet We forecast CHF 2.4m of financial debt (venture convertible debt) on Spexis's balance sheet by YE/22E which we anticipate to stay roughly stable going forward. We project cash of CHF 1.7m by YE/22E, expecting it to decline slightly to CHF 1.4m by YE/25E. In Q1/23E, we anticipate that the company will raise CHF 20m to finance the PILOT trial and preparations for the COPA study and look for Spexis to raise a further CHF 30m in FY/24E and CHF 30m in FY/25E. With these funds, the company can adequately fund operations (i.e. development of ColiFin® and murepavadin) until 2025E. Going forward, we project slightly declining property, plant & equipment and intangible assets and stable goodwill. Our forecast does not factor in acquisition activity. We give an overview of the key positions of our balance sheet forecasts for the period 2020-2025 in table 11.

Table 11: Balance sheet forecasts (selected items)

in CHF'000	2020	2021	2022E	2023E	2024E	2025E
Cash and cash equivalents	294	14,368	1,746	12,287	9,595	1,362
Accounts receivables	12	1,652	1,400	1,300	1,200	1,200
Other current assets	2	2,275	650	650	650	815
Current Assets, Total	**308**	**18,295**	**3,796**	**14,237**	**11,445**	**3,377**
Property plant and equipment	0	1,177	807	687	652	722
Intangible assets	0	10,496	10,046	9,596	9,176	8,776
Goodwill	0	18,006	18,006	18,006	18,006	18,006
Financial and other LT assets	33	1,923	1,710	1,499	1,445	1,448
Non-Current Assets, Total	**33**	**31,602**	**30,569**	**29,788**	**29,279**	**28,952**
Accounts payable	168	2,460	1,600	1,700	1,600	1,500
Other current liabilities	3,214	5,750	5,570	5,160	4,950	4,750
Pension and other LT liabilities	4,905	8,282	3,994	3,814	3,643	3,481
Financial debt ST+LT	3,323	3,182	2,350	2,160	2,134	2,021
Total Liabilities	**11,610**	**19,673**	**13,514**	**12,834**	**12,327**	**11,751**
Equity	-11,269	30,224	20,850	31,190	28,396	20,577
Equity ratio	n.a.	61%	61%	71%	70%	64%

Source: First Berlin Equity Research

Cash Flow Statement We expect increasing drug development activity to result in growing negative operating cash flows in the period 2022-2025. We forecast a negative operating cash flow of CHF -11.3m for 2022E, rising to CHF -37.5m for 2025E. We expect Spexis to continue outsourcing the clinical development of its lead programmes and therefore see negligible CAPEX investment in the forecasting period. We estimate cash flow from financing to amount to CHF -1.3m in 2022E, chiefly reflecting debt and lease liabilities repayment. We project financing cash flow to grow substantially over the next years to raise CHF 80m in the forecasting period. We anticipate net cash flow to total CHF -12.6m in 2022E. We provide an overview of our cash flow projections in table 12 below.

Table 12: Cash flow forecasts (selected items)

in CHF'000	2020	2021	2022E	2023E	2024E	2025E
Operating cash flow	-774	-1,141	-11,343	-8,960	-32,230	-37,490
Cash flow from investing	0	3,439	53	41	-85	-217
Cash flow from financing	691	11,833	-1,333	19,460	29,623	29,474
Net cash flow	-84	14,132	-12,623	10,541	-2,692	-8,233

Source: First Berlin Equity Research

NEWSFLOW

In our view, Spexis's stock price will be driven by news about its pipeline as well as by the achievement of financial milestones. We expect the company to make a number of announcements during the coming 12 months which will act as catalysts for the stock. These include:

Pipeline & financing

2023

- Results of the ongoing analysis of balixafortide's pre-clinical and clinical data, and decision on the further development strategy (i.e. new development focus) in early 2023
- Capital increase of CHF 20m in Q1/22 to fund ColiFin®'s COPILOT phase III pilot study and initiation of the phase III pivotal COPA study
- Launch of ColiFin®'s COPILOT study in Q1/23, publication of the headline results by mid-2023 and initiation of the COPA study in H2/23

Further, the company publishes financial results on a half-yearly basis, including detailed updates on the R&D pipeline. Publication of FY/22 results is due in late March 2023.

SHAREHOLDERS & STOCK INFORMATION

Stock Information	
ISIN	CH0106213793
WKN	A2JK4Q
Bloomberg ticker	SPEX SW
No. of issued shares	48,687,779
Country	Switzerland
Sector	Healthcare
Subsector	Biotechnology

Source: Bloomberg, First Berlin Equity Research

Shareholder Structure	
Jeffrey Wager/Apeiron Holdings	18.6%
RLG Business Corporation	12.5%
Vectura Group Limited	8.8%
Trustees of Boston University	4.4%
Sanford Biosciences	4.0%
James J Collins	4.0%
Cystic Fibrosis Foundation	3.1%
Others	44.6%

Source: Spexis AG

MANAGEMENT

MANAGEMENT BOARD

Jeff Wager, MD, CEO & co-founder, Chairman of the Board, USA

Dr Wager is the CEO of Spexis. He co-founded EnBiotix Inc, one of the two predecessor companies of Spexis AG. He is a serial entrepreneur and brings over 30 years of experience in VC & CEO leadership in the biotechnology and pharmaceutical industry to Spexis. Prior to joining Spexis, Dr Wager was co-founder and board member of Grupo Biotoscana SL, a Latin American specialty pharma group financed by Advent International and Essex Woodlands Healthcare Ventures, leading to its USD 1bn IPO in 2017 on sales of ~USD240m and 600 staff in 10 Latin American markets. In 2012, he co-founded the biotech company Proterris Inc, where he is Executive Chairman today. From 2006 – 2010, he was CEO and co-founder of Artisan Pharma Inc, raising USD 53m, building the entire team and running an international Phase 2b/3 study in 750 patients, which ultimately led to Artisan's acquisition by Asahi Kasei Pharma Corporation (Japan) in 2011. In 2000, Dr Wager founded Apeiron Partners, a FINRA-registered (via its affiliate Commonwealth PharmaSecurities LLC) life sciences investment bank focused on corporate spin-outs, M&A, corporate venture capital and principal investments. With this institution, he completed six spin-outs, including Targacept, Inc. (NASD: TRGT), Artisan Pharma (from Asahi Kasei), Biocritica (USD 120m annual revenue Xigris® franchise from Eli Lilly) and KBI BioPharma (acquired by JSR Corporation, Japan). Between 1995-2000, he worked at Medical Science Partners, a Harvard-founded VC fund, forming spin-outs from the Harvard medical system. Dr Wager began his career with a life sciences unit of the Bank of Tokyo, where he led business development. He earned his MD from Rush Medical College and his MBA from the University of Chicago.

Hernan Levett , CFO, Switzerland

Mr Levett joined Spexis AG (former Polyphor AG) in 2019 as CFO. He brings over 25 years of experience as CFO and further financial leadership positions within the pharmaceutical and biotech industry. Besides his position at Spexis, he has been working as part-time CFO for the Swiss NASDAQ-listed company Auris Medical since 2017. Prior to that, he worked as Head of Group Controlling for the pharmaceutical company Acino. From 2011 to 2015, he served as VP of Finance at the biotech company InterMune. Before that he worked for Novartis for 10 years. He started his international career at this pharmaceutical company, assuming increasing responsibility in various countries and regional functions and as CFO for one of its affiliates. Mr Levett holds a CPA degree from the University of Buenos Aires, Faculty of Economics.

Juergen Froehlich, MD, CMO, USA

Dr Froehlich has been the Chief Medical Officer (CMO) of Spexis (former Enbiotix Inc) since 2019. He has over 30 years of experience as CMO & in senior regulatory affairs positions in biotechnology. His expertise covers a broad range of drug development projects and approvals across therapeutic areas such as cerebrovascular, cardiovascular, pulmonary, metabolic, oncologic, genetic and infectious disorders. He has worked with biologics, peptides, small molecules, and RNA therapeutics at companies including Boehringer Ingelheim, Genentech, Quintiles, Bristol-Myers-Squibb, Ipsen, Vertex, Aradigm and Genevant. Since 2005, he has mainly been involved in rare diseases, including bronchiectasis, cystic fibrosis, non-tuberculous mycobacteria infection, acromegaly, neuroendocrine tumours, urea cycle disorders, cervical dystonia and haemophilia. Dr Froehlich was instrumental in obtaining successful marketing authorisations in the US, EMA and other countries for orphan drug designated products in cystic fibrosis, acromegaly and cervical dystonia. As CMO and Head of Regulatory Affairs of Aradigm Corporation, he implemented a Phase III trial program with inhaled liposomal ciprofloxacin in patients with

bronchiectasis and chronic *Pseudomonas aeruginosa* lung infection and was an invited panel member at a US FDA workshop in 2018 for inhaled antibiotics in cystic fibrosis and bronchiectasis. Dr Froehlich is also a Board member of Appili Therapeutics, a publicly traded infectious disease company in Canada. He received his MD from the Medical School at Wuerzburg University, Germany, is a Diplomate of the American Board of Clinical Pharmacology and holds an executive MBA from the Graduate School of Business Administration in Zurich, Switzerland.

Stephan Wehselau, COO, Switzerland

Mr Wehselau is COO of Spexis since January 2022. He is a serial entrepreneur with over 20 years' C-level experience as CFO, COO and CEO, having raised over USD 380m in venture capital and private equity from high-profile international funds in the US, Europe and Asia in the life sciences & IT industries. Mr Wehselau is COO and member of the Advisory Board of Proterris Inc. During the last 22 years, he has been involved in the foundation of the following five Life Science companies, Xantos Biomedicine AG, JenaValve Technology Inc., Spherotec GmbH, Tube Pharmaceuticals GmbH and Granite Bio AG where he has held different executive and non-executive positions. In addition to his life science expertise, Mr Wehselau entered the ICT and Tech industry in 2015. Before he joined Advertima AG in 2020, he was CFO of Censhare AG from 2015 – 2018. Censhare is an agile software company of the next-generation marketing cloud integrating different applications and functions. Mr Wehselau started his career in the pharma industry and worked first for Boehringer Mannheim and later for Roche. Mr Wehselau studied economics and holds a master's degree from the University of Bremen, Germany.

BOARD OF DIRECTORS

Dennis Ausiello, MD, Vice Chairman

Dr Ausiello is the Jackson Distinguished Professor of Clinical Medicine at Harvard Medical School. He is concurrently the Director, Emeritus of the Harvard Medical School's MD/PhD Program. He is also Chair of Medicine, Emeritus, and Director of the Centre for Assessment Technology and Continuous Health (CATCH) at Massachusetts General Hospital and previously served as an editor of Cecil's Textbook of Medicine. Dr Ausiello serves on the board of directors of Alnylam Pharmaceuticals and Seres Therapeutics, Inc. and previously served on the board of directors of Pfizer as its Lead Director, where he currently serves on its advisory board. Dr Ausiello received his B.S. from Harvard College and his M.D. from the University of Pennsylvania School of Medicine. Throughout his career, Dr Ausiello has made substantial contributions to the study of epithelial biology in the areas of membrane protein trafficking, ion channel regulation and signal transduction. He has published numerous articles, book chapters and textbooks.

Dan Hartman, MD, Board Member

Dr Hartman is currently Director, Integrated Development for the Gates Foundation, leading a team that provides technical expertise in product development to other foundation teams and their partners. He joined the foundation in 2012 in his current role and served simultaneously as interim director of the Malaria team from 2016 to 2018. Dr Hartman has extensive management and pharmaceutical experience. Before joining the foundation, he served for four years as president and CEO of Great Lakes Drug Development, a consulting company providing strategic and operational support for early drug development projects. Previously, he served as senior vice president of product development at deCODE genetics, executive director of Pfizer Global Research and Development, and vice president of global clinical development at Esperion Therapeutics, and he held clinical research positions at Eli Lilly & Company. He has also consulted the biopharmaceutical venture capital community

and serves as a member/advisor on several nonprofit boards. He served as a member of the National Institutes of Health's National Center for Advancing Translational Sciences and Cures Acceleration Network advisory board from 2016 to 2019 and was president of the American Society for Clinical Pharmacology & Therapeutics. Dr Hartman has received numerous awards, including Inventor of the Year from the Intellectual Property Owners Association. He received his bachelor's degree from Calvin College and his medical degree from Wayne State University.

Robert Clarke, PhD, Board Member

Dr Clarke has served as CEO and Co-founder of Kinaset Therapeutics since 2020. From 2012 to 2019, he was CEO of Pulmatrix Inc. (NASDAQ: PULM), a clinical-stage respiratory drug delivery company. He successfully brought the company public in 2015. He joined Pulmatrix in 2004 as the first Ph.D.-level scientist and was appointed CSO in 2010. In that role, he was focused on developing Pulmatrix technologies for treating respiratory diseases. During his tenure as CEO, Pulmatrix raised more than USD 50m in public equity, USD 80m in venture capital funding and more than USD 10m in non-dilutive financing to support the company's development programs. Prior to his tenure at Pulmatrix, Dr Clarke was Associate Director, Life Sciences at Alkermes. He holds Board seats at several institutions including Johns Hopkins University and Boston University College of Engineering. Dr Clarke holds a PhD in physiology from Johns Hopkins University and completed his post-doctoral training in respiratory biology at Brigham and Women's Hospital and Harvard University.

Kuno Sommer, PhD, Board Member

Dr Sommer focuses today on active board memberships in the life sciences sector as a non-executive member. He is Chairman of the Board of the Bachem Group, the Sunstar group, TargImmune, PDS Pathology Data Systems AG and Kenta Biotech AG. In his last operational role, he headed the contract research division of Harlan Laboratories Ltd. From 2000 until 2006 he was CEO of Berna Biotech Ltd, which was sold to Crucell NV in 2006 (today Johnson & Johnson). Starting in 1986 at F. Hoffmann-La Roche Ltd he worked in various functions until 1999 and spent four years in the US. In his last position at Roche he became a member of the Executive Committee, responsible for the Flavours and Fragrances division (today Givaudan Ltd). Dr Sommer holds a PhD in Business Administration from the University of Basel as well as an MBA.

Bernard Bollag, MBA, Board Member

Mr Bollag is a senior finance executive with broad experience in corporate finance and capital markets. He was CFO in private equity until 2012, with HomeSun in the UK's Renewable Energy sector and internationally across a broad portfolio of sectors and investments. Before that, he acted as Syngenta's Group Treasurer, leading the company's banking and capital markets funding as it spun off from Novartis and Astra-Zeneca. He established the company's financial risk practice for the group and its international affiliates. Prior to that, he led an international finance career at Unisys, progressing through planning, operations, investments and funding. He is the founder and Managing Director of Beaufort Capital, a boutique supporting High Net Worth individuals with their private equity and alternative investments. Mr Bollag holds an MBA in Finance from the Columbia Business School in New York and a BA in Economics from the Bar-Ilan University of Tel-Aviv.

INCOME STATEMENT

All figures in CHF '000	2020	2021	2022E	2023E	2024E	2025E
Total revenue & other income	**52**	**0**	**620**	**12,200**	**2,200**	**0**
Cost of goods sold	0	0	0	0	0	0
Gross profit	52	0	620	12,200	2,200	0
Sales & Marketing	0	70	500	500	500	3,000
General & Administrative	718	3,302	6,000	6,200	6,500	6,825
Research & Development	559	876	9,500	15,000	28,000	28,000
Total operating expenses (OPEX)	**1,277**	**4,248**	**16,000**	**21,700**	**35,000**	**37,825**
Operating income (EBIT)	**-1,225**	**-4,248**	**-15,380**	**-9,500**	**-32,800**	**-37,825**
Net financial result	-627	-7,614	-180	-160	6	6
Pre-tax income (EBT)	**-1,851**	**-11,862**	**-15,560**	**-9,660**	**-32,794**	**-37,819**
Income taxes	0	0	0	0	0	0
Net income / loss	**-1,851**	**-11,862**	**-15,560**	**-9,660**	**-32,794**	**-37,819**
Diluted EPS (CHF)	**-0.14**	**-0.82**	**-0.32**	**-0.13**	**-0.29**	**-0.27**
Ratios						
EBIT-Margin on total revenue	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
EBITDA margin on total revenue	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Net Margin on total revenue	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Expenses as % of OPEX						
Sales & Marketing	0.0%	1.7%	3.1%	2.3%	1.4%	7.9%
General & Administrative	56.2%	77.7%	37.5%	28.6%	18.6%	18.0%
Research & Development	43.8%	20.6%	59.4%	69.1%	80.0%	74.0%
Y-Y Growth						
Total revenue & other income	n.a.	n.a.	n.a.	n.a.	-82.0%	n.a.
Operating income	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Net income/ loss	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

BALANCE SHEET

All figures in CHF '000	2020	2021	2022E	2023E	2024E	2025E
Assets						
Current Assets, Total	**308**	**18,295**	**3,796**	**14,237**	**11,445**	**3,377**
Cash and cash equivalents	294	14,368	1,746	12,287	9,595	1,362
Accounts receivables	12	1,652	1,400	1,300	1,200	1,200
Inventories	0	0	0	0	0	165
Other current assets	2	2,275	650	650	650	650
Non-Current Assets, Total	**33**	**31,602**	**30,569**	**29,788**	**29,279**	**28,952**
Property plant and equipment	0	1,177	807	687	652	722
Intangible assets	0	10,496	10,046	9,596	9,176	8,776
Goodwill	0	18,006	18,006	18,006	18,006	18,006
Financial and other assets	33	1,923	1,710	1,499	1,445	1,448
Total Assets	**341**	**49,897**	**34,364**	**44,024**	**40,723**	**32,328**
Shareholders' Equity & Debt						
Current Liabilities, Total	**6,705**	**9,846**	**8,120**	**7,760**	**7,550**	**7,250**
Short-term debt	3,323	1,636	950	900	1,000	1,000
Accounts payable	168	2,460	1,600	1,700	1,600	1,500
Accruals	2,077	4,781	4,600	4,200	4,000	3,800
Other current liabilities	1,137	969	970	960	950	950
Longterm Liabilities, Total	**4,905**	**9,828**	**5,394**	**5,074**	**4,777**	**4,501**
Long-term debt	0	1,546	1,400	1,260	1,134	1,021
Pension liabilities	0	4,180	394	394	394	394
Other liabilities	4,905	4,101	3,600	3,420	3,249	3,087
Shareholders Equity	**-11,269**	**30,224**	**20,850**	**31,190**	**28,396**	**20,577**
Total Consolidated Equity and Debt	**341**	**49,897**	**34,364**	**44,024**	**40,723**	**32,328**
Ratios						
Current ratio (x)	0.05	1.86	0.47	1.83	1.52	0.47
Quick ratio (x)	0.05	1.86	0.47	1.83	1.52	0.44
Net gearing	n.a.	n.a.	n.a.	n.a.	-26.3%	3.2%
Book value per share (€)	n.a.	2.08	0.43	0.42	0.25	0.15
Net debt	3,029	-11,186	604	-10,127	-7,461	659
Equity ratio	-3306.4%	60.6%	60.7%	70.8%	69.7%	63.7%

CASH FLOW STATEMENT

All figures in CHF '000	2020	2021	2022E	2023E	2024E	2025E
Net income	**-1,851**	**-11,862**	**-15,560**	**-9,660**	**-32,794**	**-37,819**
Interest, net	627	7,614	180	160	-6	-6
Tax provision	0	0	0	0	0	0
EBIT	**-1,225**	**-4,248**	**-15,380**	**-9,500**	**-32,800**	**-37,825**
Depreciation and amortisation	0	13	1,000	750	780	800
EBITDA	**-1,225**	**-4,235**	**-14,380**	**-8,750**	**-32,020**	**-37,025**
Changes in working capital	418	605	837	-210	-210	-465
Other adjustments	32	2,489	2,200	0	0	0
Operating cash flow	**-774**	**-1,141**	**-11,343**	**-8,960**	**-32,230**	**-37,490**
CapEx	0	0	53	41	-85	-217
Free cash flow	**-774**	**-1,141**	**-11,289**	**-8,919**	**-32,315**	**-37,707**
Other investments	0	3,439	53	41	35	33
Cash flow from investing	**0**	**3,439**	**53**	**41**	**-85**	**-217**
Debt Financing, net	0	-163	-1,333	-370	-377	-526
Equity Financing, net	0	10,126	200	20,000	30,000	30,000
Cash flow from financing	**691**	**11,833**	**-1,333**	**19,460**	**29,623**	**29,474**
Net cash flows	**-84**	**14,132**	**-12,623**	**10,541**	**-2,692**	**-8,233**
Cash, start of the year	411	294	14,368	1,746	12,287	9,595
Change of effect of exchange rates	-33	-58	0	0	0	0
Cash, end of the year	**294**	**14,368**	**1,746**	**12,287**	**9,595**	**1,362**
Y-Y Growth						
Operating Cashflow	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Free cashflow	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
EBITDA/share	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

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Category		1	2
Current market capitalisation (in €)		0 - 2 billion	> 2 billion
Strong Buy[1]	An expected favourable price trend of:	> 50%	> 30%
Buy	An expected favourable price trend of:	> 25%	> 15%
Add	An expected favourable price trend of:	0% to 25%	0% to 15%
Reduce	An expected negative price trend of:	0% to -15%	0% to -10%
Sell	An expected negative price trend of:	< -15%	< -10%

[1] The expected price trend is in combination with sizable confidence in the quality and forecast security of management.

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Report No.:	Date of publication	Previous day closing price	Recommendation	Price target
Initial Report	25. January 2023	CHF0.42	Buy	CHF1.80

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