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Basilea Pharmaceutica

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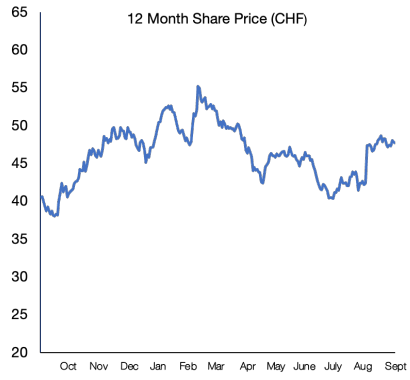
Share Price (CHF)	**46.5**
CP Fair Value (CHF)	**91**
Market Cap (CHFm)	609
Cash (CHFm)	113
EV (CHFm)	647
Country	Switzerland
Code	BSLN
Index	SIX



Source: Calvine Partners Research

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A bright future beckons

The ongoing success of Cresemba has provided Basilea with a strong platform to establish a world-leading anti-infectives franchise. Cresemba has grown to become the largest antifungal for the treatment of invasive fungal infections by value in the US and, through a protracted roll out, is now available in 67 countries globally. Despite Cresemba's increasing maturity, with exclusivity expected to expire in key US and European (after paediatric extension) markets from approximately Q4 2027, we forecast a slow decline in revenues attributable to Cresemba. We believe that Basilea will be able to deliver novel antifungal compounds, providing longevity to the antifungal franchise. This will likely be through in-licensing in the near term, as internal efforts are at an earlier stage.

Cresemba still dominant

Revenues at Basilea are dominated by Cresemba, which looks set to continue until 2027. This is a golden period for Cresemba with continued growth from key markets in the US and Europe and an increasing contribution from new substantial markets such as China and Japan. The out-licensing and distributor model has worked well for Basilea, with much of the success of Cresemba due to the existing antifungal franchises of Astellas and Pfizer in major markets. It is worth highlighting that other distributors in smaller markets (e.g. the Nordics) have also performed well, which we believe is a combination of successful execution and the differentiated profile of Cresemba, capitalising on its extended-spectrum and good safety profile.

Increasing importance of ceftobiprole

Ceftobiprole's forthcoming US approval should provide a significant boost to Basilea's anti-infectives franchise. Ceftobiprole promises to be a meaningful new addition to empiric treatment for patients with bacteraemia caused by *Staphylococcus aureus* (including MRSA), given its coverage of Gram-positive and Gram-negative infections and the limited treatment options (particularly where resistance is suspected). Our forecasts suggest that peak sales in the US alone could approach $400m. Basilea is in a very strong financial position, and we expect a commercial agreement to maximise the long-term value of the ceftobiprole franchise with a partner that possesses a strong anti-infectives or hospital-based franchise.

Substantial de-risking ahead

Our forecasts suggest that a combination of the anti-infectives franchise's continued near-term growth and a more manageable R&D burden should provide continued profitability. Management appears confident in the availability of novel antifungal candidates as well as its ability to deliver a commercial partner for ceftobiprole in the US. We believe that achieving these near-term objectives would represent important de-risking events for the company.

New strategy executing

All about the antifungal franchise for now

Arguably, 2023 is turning out to be very important for the company as it seeks to deliver on its ambitions to become a global leader in anti-infectives. The focus for Basilea has been on the antifungal and antibiotic fields, eschewing the highly competitive antivirals challenge. Of the two, we remain more enthusiastic about the prospects for a growing anti-fungals franchise given the threat of increased resistance, the paucity of truly novel additions, and the increasing prevalence of immunocompromised patients – often due to the increased use of aggressive chemotherapy.

Given the ongoing success of Cresemba, with little direct competition looming, it may seem churlish to focus on the expected expiration of exclusivity in the US and Europe, likely in 2027. Nevertheless, given the high-value potential of the antifungal market, management is keen to ensure that Basilea has a continued presence in this key high-growth market.

Efforts ongoing to boost the antifungal pipeline

The focus for Basilea is to in-license or acquire multiple candidates from later preclinical through to Phase 2 development. At the recent H1 results meeting, the company remained confident in the availability of novel antifungal compounds, which could fulfil the company's mid- and long-term ambitions in the anti-fungals field. As we have intimated, we suspect that the growing awareness of the need for new anti-fungals has generated significantly more investment in the underlying science. We have previously noted the advanced clinical development of novel anti-fungals such as olorofim, ibrexafungerp and fosmanogepix as examples of the advances in novel antifungal development.

Renewed ceftobiprole importance

It is important to remember that the continuation of the anti-infectives franchise is not entirely dependent on finding a successor to Cresemba. Basilea's participation in the AMR field is set to receive a significant boost should the 5th generation cephalosporin, ceftobiprole, achieve approval for bacteraemia caused by *Staphylococcus aureus* (*S.aureus*).

Ceftobiprole bridging the gap

Fortunately for ceftobiprole, despite its availability outside of the US, it has not previously been approved in the US. Significantly, the granting of Qualified Infectious Disease Product (QIDP) has refreshed the period of exclusivity it will enjoy.

QIDP status important

The availability QIDP status has provided 10 (5+5) years of exclusivity for ceftobiprole in the US as well as Priority Review with the exclusivity period beginning on approval. For Basilea, until recently a loss-making entity, the funding from BARDA provided approximately 75% of the development costs with non-dilutive funding of $112m. The agreement was signed in April 2016 with the intention of developing ceftobiprole in the US for *S. aureus* bacteraemia (SAB), acute bacterial skin & skin structure infections

(ABSSSI) and community-acquired bacterial pneumonia (CABP) – although the latter indication was not a subject of the agreed Special Protocol Assessment (SPA).

SPAs should reduce regulatory risk

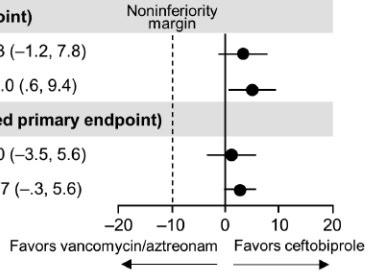
Basilea has reduced the regulatory risk associated with Phase 3 development by agreeing a Special Protocol Assessment with FDA. SPAs are a useful approach for coordinating the trial endpoints and hopefully smoothing the approval process should those endpoints be achieved. A positive result from both studies was required for regulatory approval.

Impressive data in Phase 3

Reassuringly, both TARGET (severe skin infections) and ERADICATE (bacteraemia) were positive, with ceftobiprole meeting all primary and secondary endpoints. Although severe skin infections are generally well served, current empiric treatments often target Gram-positive bacteria, Gram-negative infections can be more problematic, and ceftobiprole does offer coverage of important Gram-negative bacteria. TARGET met regulatory criteria for both FDA (early clinical response) and EMA (clinical response at the test of cure visit), with ceftobiprole demonstrated to be non-inferior to vancomycin plus aztreonam in the intention to treat (ITT) population. It is also worth noting that in TARGET, ceftobiprole was superior to vanco + aztreonam in the clinically evaluable (CE) patient population (secondary endpoint).

Target Study

	Ceftobiprole n/N (%)	Vancomycin/ aztreonam n/N (%)	Adjusted difference (ceftobiprole minus vancomycin/aztreonam) (95% CI)[a]
Early clinical response (FDA-defined primary endpoint)			
ITT	306/335 (91.3)	303/344 (88.1)	3.3 (–1.2, 7.8)
CE[b]	267/283 (94.3)	262/293 (89.4)	5.0 (.6, 9.4)
Investigator-assessed clinical success (EMA-defined primary endpoint)			
ITT	302/335 (90.1)	306/344 (89.0)	1.0 (–3.5, 5.6)
CE	277/283 (97.9)	279/293 (95.2)	2.7 (–.3, 5.6)



Overcash et al., Clinical Infectious Diseases

Additionally, time to microbiological eradication was significantly shorter with ceftobiprole, and the results were similar irrespective of MSSA or MRSA.

SAB is the real value-added

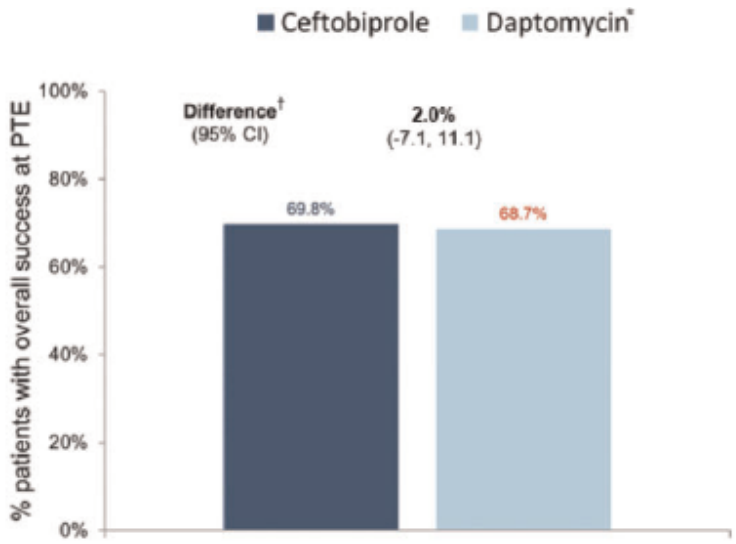
The SAB indication presents a significantly more lucrative opportunity than ABSSSI, we believe, given the unmet need and the limited treatment options for patients suffering from resistant infections.

SAB data is equally impressive

The primary endpoint of ERADICATE evaluated overall success at post-treatment evaluation (day 70 post-randomisation +/-5 days). Ceftobiprole was associated with an overall success rate of 69.8% in the mITT population at 70 days, which compared favourably to

daptomycin (68.7%). With a NI delta of +2% (-7.1%-11.1%), the result of ERADICATE was well within the predefined 15% NI margin for the primary endpoint.

ERADICATE Study



Holland et al., Open Forum Infectious Diseases

Data in resistant infections reassuring

Importantly, the primary endpoint results were similar between the treatment groups irrespective of whether patients were infected with MSSA or MRSA bloodstream infections at baseline. This result was confirmed when contributing underlying conditions were evaluated and included skin and skin structure infections, abdominal abscesses, chronic dialysis, septic arthritis, osteomyelitis, definite right-sided IE, as well as in patients with persistent SAB.

We believe ceftobiprole is suitable for empiric therapy

As we have noted previously, inclusion in treatment guidelines is important for adoption. Unfortunately, perhaps for ceftobiprole, the available US guidelines for both SAB and ABSSSI are significantly outdated. The IDSA guidelines for ABSSSI were last issued in 2013. As a result, they do not incorporate important long-standing clinical practices such as including dalbavancin (a second-generation lipopeptide). Ceftobiprole offers important Gram-negative coverage, and data from TARGET effectively show that it is relevant to a broad selection of patients with ABSSSI. Each of the three different types of ABSSSI was well represented (cellulitis/erysipelas, infected wounds and cutaneous abscess), while 93% involved patients with Gram-positive infections and 13% with Gram-negative infections supporting the use of ceftobiprole as a monotherapy for empiric treatment of patients with ABSSSI.

Still waiting for SAB guidelines

The IDSA SAB guidelines date from 2011, and while there has been a paucity of new antibiotics approved for complicated SAB, they are overdue. We note that new guidelines are currently in development, and perhaps ceftobiprole may feature, given the strength of the data, if and when they are published.

Treatment with a beta-lactam antibiotic remains first line for patients with susceptible infections (MSSA). Treatment for SAB can be for up to six weeks if the condition has become metastatic compared to two weeks if the bacteraemia remains uncomplicated. Antibiotics typically used for MSSA include anti-Staphylococcal penicillins such as flucloxacillin as well as first-generation cephalosporins such as cefazolin.

MRSA is the real challenge

MRSA, on the other hand, leads to poorer outcomes, with 15%-50% mortality rates in patients with MRSA bacteraemia. The glycopeptides vancomycin and daptomycin are first-line treatments in MRSA bacteraemia, requiring 4-6 weeks of intravenous therapy. Metastatic infections often require surgical intervention and can result in extended hospitalisation.

Dalbavancin used off-label

Worryingly, although still relatively rare, there is a growing risk of resistance to both agents. The lipoglycopeptide dalbavancin may be used (currently off-label) as an alternative to vancomycin-resistant infections and has the added benefit of offering a lower level of renal injury in comparison and a long half-life resulting in a much-reduced dosing schedule. Dalbavancin offers the potential for a shorter and less invasive treatment regimen, lowering risks associated with prolonged central venous access.

With a view to confirming the potential of dalbavancin in complicated SAB, the DOTS (dalbavancin as an option for treatment of SAB) trial has been designed as a prospective Phase 2b study. DOTS enrolled 200 SAB patients who had already experienced bacteraemia clearance before randomisation to two doses of dalbavancin or 4-8 weeks of standard intravenous antibiotic therapy. According to clinicaltrials.gov, the primary completion date is August 2023.

Significant risk of treatment failure with standard of care…

The standard of care (vancomycin and daptomycin) has been associated with a significant risk of treatment failure. Despite not being approved for first-line SAB, efforts to improve SAB patients' outcomes have led to several exploratory trials using the 5th-generation cephalosporin antibiotic ceftaroline. The benefits of such a combination appear compelling, given ceftaroline's inherent activity against MRSA and the observation that reduced susceptibility against glycopeptides and lipopeptides leads to increased susceptibility to beta-lactams like ceftaroline. The data generated have been very supportive of this approach, resulting in complete clearance of persistent bacteraemia when the combination is used as salvage therapy. These data point to the need for additional treatment options for patients with intractable SAB and the attractive proposition offered by the 5th-generation cephalosporin class, such as ceftaroline and ceftobiprole.

Furthermore, both daptomycin and vancomycin have concerns over emerging resistance (and the potential for cross-resistance), as well as vancomycin's poor tissue distribution and risk of renal toxicity. Additionally, daptomycin is inactivated in the lung, rendering it useless for the treatment of respiratory infections. Ultimately, we

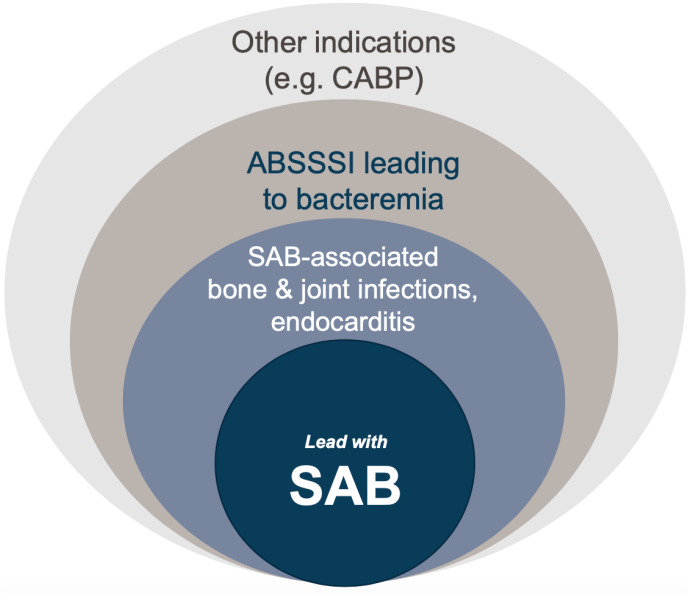
…as well as emerging resistance issues

believe there is a clear need for additional antibiotics in SAB with a notable shortage of high-quality controlled studies. As noted above, salvage therapy using a non-approved (off-label) antibiotic (such as the combination with ceftaroline) has proven to be a last resort approach in those with a persistent infection

Commercial partner should de-risk the commercial opportunity

We look forward to Basilea securing a relevant commercial partner to ensure an effective US launch. Basilea has highlighted the broad relevance of ceftobiprole following approval in SAB, ABSSSI and CABP. The CABP addition should also be helpful, and we note that there are sufficient Phase 3 data available to aid with this approval despite not being formally part of the SPA agreed with FDA. The company described a likely commercial scenario starting with SAB and subsequently involving other complications such as SAB-associated bone and joint infections, bacteraemia caused by ABSSSI and other related indications.

Ceftobiprole's commercial opportunity



Source: Company reports

Clearly, much will depend on the partner with respect to the final commercial strategy, although targeting the most acute unmet need would appear to be a sensible approach. Basilea has guided to securing a commercial partner before US approval, currently expected in H2 2024.

$250m peak sales in SAB alone

We forecast ceftobiprole to achieve a 15% peak penetration of the US bacteraemia market, resulting in an un-risked peak sales opportunity of $250m. Patients with SAB usually receive antibiotics for between 2 to 6 weeks. In our financial model, we have assumed that patients receive treatment for 5 weeks at circa $7500 per treatment.

Additionally, the ABSSSI indication remains an important element of the regulatory filing process in the US, with both studies required for FDA approval. Ultimately, this is a large market, and our analysis

Peak sales approaching $400m

suggests that even a small market share should generate meaningful revenues for ceftobiprole. We have assumed that ceftobiprole is able to secure a 3-4% share of the large ABSSSI market at peak, recognising that much will depend on the capabilities of the partner selected. Nevertheless, such is the size of the ABSSSI indication in the US, even this modest market penetration suggests an un-risked peak sales market potential of $130m. Overall, we forecast that ceftobiprole could deliver peak in-market sales of $380m in the US.

The requirement for new antifungals is apparent

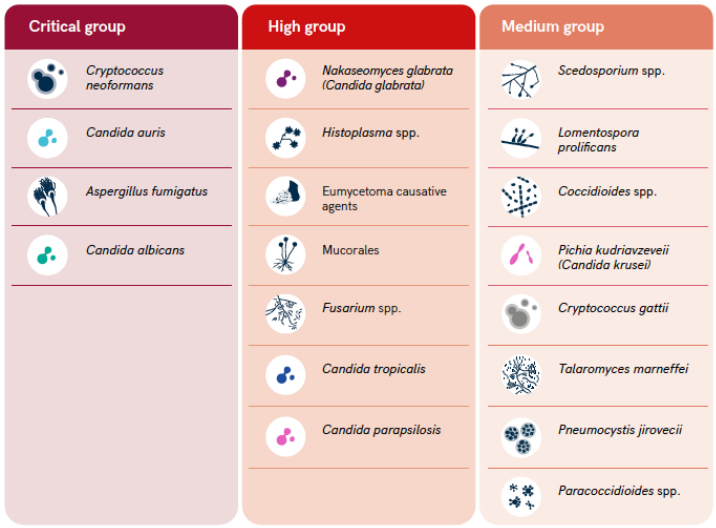
A dearth of antifungal approvals…

The antifungal Cresemba (isavuconazole) has long dominated Basilea's anti-infectives franchise and now represents the largest antifungal for treating invasive fungal infections by sales value in the important US market. Perhaps surprisingly, before the recent approval of the next-generation echinocandin Rezzayo (rezafungin), Cresemba held the unexpected accolade of being the only antifungal approval in the previous 10 years.

…but light at the end of the tunnel

After many years of apparent inactivity in the field of anti-fungals, there have been notable advances, with fosmanogepix now under the stewardship of Pfizer, while olorofim is under regulatory review in the US (for the treatment of invasive fungal infections in patients who have limited or no treatment options), and partnered with Shionogi elsewhere. In tandem with these advances, it is important to note that the threat from fungal disease has been reflected in the WHO releasing (October 2022) its first-ever list of health-threatening fungi, raising awareness in a field which has been overlooked for too long. This effort by the WHO is important and should stimulate increased interest in developing new antifungals and has generated significant interest, we believe.

WHO fungal priority pathogens list



Source: World Health Organization

CDC warning adding to awareness

The report categorises fungal infections into those which are critical threats and comprise *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Candida auris* and *Candida albicans*. The high-priority group includes Mucorales, *Fusarium* spp, *Histoplasma* spp, *Candida tropicalis*, *Candida parapsilosis* and *Candida glabrata*. The medium priority group comprises a further eight fungal infections. Aspergillus, Cryptococcus, Candida, Histoplasma and Pneumocystis cause over 90% of deaths from invasive fungal infections, although emerging pathogens, including *Mucorales*, *Fusarium spp* and *Scedosporium spp*, have become increasingly problematic. Recently (March 2023), the CDC issued a warning regarding the increasing risk of infection from drug-resistant *Candida auris* following a spike of cases in California.

Growth for the foreseeable future

Several factors have driven the underlying growth in demand for antifungal treatment. In particular, the use of aggressive chemotherapy regimens, particularly as they relate to haematological cancers, has been a significant driver of invasive fungal infections. Furthermore, it is important to note that stem cell transplantations have effectively more than doubled in the past 20 years.

The pandemic has added complications

The COVID-19 pandemic also highlighted the risk in patients with this respiratory pathogen and an increase in the incidence of co-morbid fungal infections with aspergillosis, mucormycosis, and candidaemia reported. Notably, COVID-19-associated pulmonary aspergillosis (CAPA) has become a significant concern, particularly given that it has been associated with a 48.5% mortality rate in the ICU. Specifically, hospitalised patients co-infected with COVID-19 and aspergillosis experienced a 57.6% mortality rate, while mortality in those co-infected with mucormycosis was 44.7% and invasive candidiasis 55.4%. Despite these data, it is important to remember that there is still likely a significant underreporting, given that many fungal infections are not reportable in the US.

Risk of increased resistance

Although the threat associated with infection by strains of SARS-CoV-2 may have receded, there have been lingering concerns surrounding the risk of increased resistance following the potential overuse of anti-fungals, often used as empiric therapy in very ill patients during the pandemic.

Additional patient groups

Furthermore, new patient groups at risk from fungal infections have been suggested, including those with COPD and other respiratory tract infections. Overall, there appears to be no shortage of growth drivers fuelling the need for increased antifungal use.

Unfortunately, neither the development of diagnostic tests nor new antifungals have kept pace with the emergence of resistance. Available antifungals have traditionally been limited to only three classes (polyenes, the azoles and the echinocandins). Increasing resistance is a real concern seen with the azoles and Aspergillus, as well as Candida and the increased use of echinocandins.

Mortality risk in IA still high

As a result, the outlook for patients with invasive fungal infections remains challenging. Mould infections are particularly concerning in the immunocompromised patient population and represent a significant source of morbidity and mortality. For aspergillosis, the mortality rate varies from 34%-58% and can be higher in high-risk patient populations such as chemotherapy-induced neutropaenia.

Many suffer from limitations

Moreover, antifungal classes have limitations that can restrict their use in clinical practice. The echinocandins suffer from poor bioavailability and require injection. The echinocandins are used for salvage therapy and in combination, particularly for mould infections. The polyenes (such as amphotericin B) suffer from limited efficacy and substantial toxicities (acute renal failure) in high-risk patients, leading to the successful introduction of lipid formulations.

Azoles, the most widely used

The azoles, on the other hand, represent the most widely used class of antifungals. Their widespread use, however, has resulted in increased resistance in several geographies. Major advantages of the second-generation triazoles, posaconazole and voriconazole, include their extended antifungal spectrum and availability in both oral and intravenous formulations (voriconazole). As the leading branded antifungal VFEND (voriconazole), it generated peak sales of about $900m.

Cresemba is leading the charge

However, the use of these agents is often limited by their variable bioavailability, severe adverse events, significant drug-drug interactions, and the emergence of resistance. Cresemba, on the other hand, has an extended spectrum with activity against yeasts, moulds, and dimorphic fungi. It also possesses an excellent safety profile, which, combined with good pharmacokinetic properties, has led to its success in the treatment of various severe and potentially life-threatening fungal infections. Also important to its commercial success is the good volume of distribution and oral bioavailability combined with highly predictable pharmacokinetics with little interpatient variability.

Broad label

Cresemba is approved in the US for the treatment of invasive aspergillosis (IA) as well as for the treatment of mucormycosis. Undoubtedly, IA represents the major commercial opportunity for Cresemba. Mucormycosis is much rarer, although its prevalence is increasing. Mucormycosis results in high morbidity and mortality (40-80% in neutropenic patients and disseminated infections) and results in a burden to the US healthcare system of circa $100,000 per patient.

Partner and distribution model has worked well

Central to Cresemba's commercial success in the US has been the capabilities of partner Astellas. Outside of the US, Cresemba is sold by Pfizer, firstly as it related to Europe (in June 2017) and then to Asia Pacific (in December 2017) as a commercial partner for Cresemba. For Pfizer, the originator of voriconazole (branded as Vfend), adding Cresemba provided an antifungal that can be positioned as an alternative to voriconazole as per the current guidelines and offers a more benign tolerability profile.

Fortunately, invasive aspergillosis is relatively uncommon and mucormycosis even less so. However, we note a Mucorales outbreak in India (where it is more common) in 2020 in patients (with diabetes) infected with COVID-19. However, IA and Mucorales are challenging to diagnose, which is reflected in the underreporting of these conditions. Also, while Mucorales infections may be increasing, they remain rare, making it difficult to conduct meaningful clinical evaluation of novel agents.

Cresemba has performed well in the empiric setting

Thankfully for Cresemba, its broad spectrum has positioned it well in the empiric setting compared to alternative agents (such as voriconazole), where infection is suspected but not confirmed. Global Mucorales guidelines issued in 2019 placed lysosomal amphotericin B as first-line therapy with intravenous isavuconazole and posaconazole also recommended with moderate strength and strongly recommended for salvage therapy. This is an important distinction, given that Mucorales are inherently resistant to the echinocandins as well as voriconazole and fluconazole.

New antifungals suggest a more promising future

Significant pipeline progress

Given the unmet need and efforts to raise awareness of the threat of the spread of invasive fungal infections, there has been a significant increase in effort and resources to develop new and improved antifungals. However, this is not an easy task compared to other anti-infectives, given the similarity between fungal and human processes. Nevertheless, there has been significant progress, and we have previously highlighted new molecules in development, such as olorofim (F2G/ Shionogi), fosmanogepix (Amplyx/ Pfizer) and ibrexafungerp (Scynexis).

Rezzayo approval is encouraging

We also note the recent approval of Rezzayo (rezafungin), a next-generation echinocandin. Rezafungin has a significantly longer half-life that permits extended interval (once weekly) dosing. The extended half-life could potentially help reduce the risk of resistance occurring. Rezzayo has been approved in the US for patients who have limited or no alternative options for the treatment of candidemia and invasive candidiasis. Rezafungin has been licensed to Melinta in the US and Mundipharma elsewhere (ex-Japan).

Olorofim, the first genuinely novel antifungal – CRL issues

Olorofim commercial partnership is impressive

Olorofim is a member of the ortomide antifungal class targeting fungal dihydroorotate dehydrogenase (DHODH), which is involved in pyrimidine synthesis. Although not a broad-spectrum antifungal, it has broad microbiologic activity against several important invasive moulds. Available orally, olorofim possessed the apparent distinction of all of its peers of having achieved FDA Breakthrough Therapy Designation. In a strong endorsement of its commercial potential, F2G was able to attract the attention of Shionogi in a licensing agreement, which provided both funding for development as well as commercial rights in Europe and Asia. Signed in May 2022, F2G received $100m in upfront payments and could receive up to a further $380m in regulatory and commercial milestones as well as double-digit sales royalties.

Olorofim was developed using the Limited Population Pathway for Antibacterial and Antifungal drugs, and US submission was based on the first 100 patients from a Phase 2b open-label study (Study 32). Unfortunately for F2G and partner Shionogi, olorofim received a complete response letter from FDA in June 2023 following its application for approval with a proposed label for the treatment of invasive fungal infections in patients who have limited or no treatment options. At the time, F2G suggested that the resubmission would include data from the entirety of the Phase 2b study (which has completed enrolment).

CRL unexpected

Olorofim's clinical development is ongoing and features a Phase 3 study (OASIS) comparing olorofim to liposomal amphotericin B (AmBisome) in patients with IA whose infection is either refractory to or unsuitable for azole therapy.

Development ongoing

Fosmanogepix is taking a more considered regulatory pathway

We view the acquisition of privately owned Amplyx Pharmaceuticals in 2021 by Pfizer for an undisclosed amount as a positive endorsement of the commercial potential of fosmanogepix. Fosmanogepix is a pro-drug of manogepix exhibiting highly selective antifungal properties and possesses good oral bioavailability. It interferes with fungal cell wall synthesis by targeting GPI-anchored protein maturation by inhibiting Gwt1. Gwt1 is essential for mannoprotein-mediated fungal adhesion to mucosal and epithelial surfaces before colonisation. Manogepix appears to have a broad spectrum of activity against various Aspergillus and Candida, including those that are resistant to the echinocandins. However, it appears to lack activity against some Mucorales.

Pfizer ownership reflects potential

Fosmanogepix development has attracted fast-track status by FDA for various invasive fungal infections, including invasive aspergillosis, candidiasis and mucormycosis.

Fast-track status

Given the Pfizer ownership, we expect fosmanogepix to represent an important treatment option when it has successfully navigated Phase 3 trials. Early indicators are promising, with activity against difficult to treat fungi and a good side effect profile.

Ibrexafungerp offers an oral step-down therapy option

Ibrexafungerp (SCY-078) may also share the same target as the echinocandins but targets a different binding site. Ibrexafungerp displays fungistatic activity against Aspergillus and fungicidal activity against Candida. Given a general lack of cross-resistance with the echinocandins and its availability as an oral presentation, there is the potential for ibrexafungerp to be used as an oral step-down therapy to injectable echinocandins in the short term. A Phase 3 study (MARIO) with ibrexafungerp as a step-down therapy is ongoing in the treatment of invasive candidiasis, with top-line approval in H2 2024.

GSK relationship endorses ibrexafungerp

Brexafemme (ibrexafungerp tablets) was approved for the treatment of recurrent vulvovaginal candidiasis (VVC and RVVC) and represented the first approval of a new antifungal class for 20 years

and the first non-azole agent approved by the FDA for this indication. The approval of Brexafemme would appear to have been sufficiently compelling to result in the attraction of anti-infective heavyweight GSK, with Scynexis receiving $90m in upfront payments as well as future performance-based milestone payments and tiered royalties in return for an exclusive license (ex-China).

Approval a milestone in novel antifungal development

More relevantly for Basilea, we note that a small Phase 2 ibrexafungerp study (SCYNERGIA) is ongoing in IA. While enrolment was completed, the number of patients enrolled was lower than initially planned. It is worth highlighting that the study evaluates Ibrexafungerp in combination with a mould-active azole (voriconazole), comparing the combination to voriconazole alone.

Study ongoing in IA

We believe that the efforts of GSK and Shionogi to in-license novel late-stage antifungal assets are a testament to the heightened awareness surrounding the increasing threat of fungal infections. It also demonstrates the advances in scientific endeavour, which has produced several novel anti-fungals after an apparent dearth for many decades. Although novel anti-fungals appear to be highly sought-after assets, we believe that a combination of Basilea's existing expertise in anti-infectives and a strong cash position should position the company as a partner of choice for prospective licensors. Undoubtedly, Basilea is determined to ensure the longevity of the anti-fungals franchise as part of its anti-infective ambitions. As a result, we believe that Basilea would be a fully committed partner, providing speedy development and significant resources.

Replenishment of antifungal pipeline a near-term priority

Fortunately for the Cresemba franchise, many late-stage novel development programmes do not present a near-term competitive threat. As a result, our forecasts suggest that Cresemba revenues should continue to grow until exclusivity expiration in 2027, retreating modestly thereafter.

Risks

Basilea's business model currently involves partnerships and out-licensing to third parties, suggesting little influence over sales performance. Nevertheless, execution on key product Cresemba has been through highly appropriate partners (particularly Astellas and Pfizer), and we believe this model has worked well for Basilea and its partners.

While the antibiotic Zevtera (ceftobiprole) is already marketed outside of the USA for the treatment of CAP and HAP (excluding VAP), we see a more significant market opportunity in the SAB indication, particularly where MRSA is suspected. Ceftobiprole has been filed for approval in the key US market for SAB, ABSSSI and CABP. Basilea has sought to reduce the regulatory risk by securing SPAs requiring positive results from TARGET and ERADICATE Phase 3 studies.

The key to maximising ceftobiprole's value in the US is attracting a commercial partner. There remains a partnering risk until an appropriate partnership is secured. Basilea has historically proven to be adept at securing relevant commercial partners.

With a focus back on anti-infectives, Basilea needs to re-populate its development pipeline. Cresemba is maturing, with loss of exclusivity expected from 2027 in the US and Europe. To ensure the longevity of the franchise, we would like to see clinical stage addition(s) in the antifungal field. Basilea should be an attractive partner, although novel antifungal programmes could be expensive.

Our financial forecasts suggest sustainable profitability. The current low level of R&D spending may need to rise should Basilea be successful in progressing multiple anti-infective programmes into late-stage trials.

Financial Model and Summary

Cresemba maturing in the US and Europe

The highly creditable performance of Cresemba continues to dominate the financials at Basilea. This has continued into FY'23, with guidance raised albeit modestly, largely on the back of continued Cresemba sales performance and specifically significant milestone payments received already during the year. As Cresemba matures, it is important that Basilea and its partners maximise the remaining sales potential. Although exclusivity in the US wanes from September 2027 and as early as 2025 in Europe, success in the paediatric population should extend Europe to October 2027. We have previously highlighted that the late-stage antifungal pipeline elsewhere has improved, noting that there is little direct competitive threat in the near term. Irrespective, the delay to olorofim has further delayed the entry of truly novel treatments, at least in the near term.

However, Cresemba is still early in the launch phase in other key markets

Key to the longer-term growth of Cresemba will be new territories with launches in China and Japan, which represent substantial opportunities at about 25% of the overall global market. Both oral and IV preparations of Cresemba are now available in China, which, according to the company, represents 21% of global sales for newer antifungals. Cresemba has been approved for invasive aspergillosis and invasive mucormycosis. Numbers for China are difficult to find, but data presented at ECCMID in 2013 suggested that there were 162,000 cases of IA and 2,726 cases of mucormycosis. With other growth drivers, including a marked increase in organ transplantation (particularly lung) in China over the past few years, these numbers are clearly conservative. Recent studies have shown that IA is responsible for most invasive mould infections, with many patients treated historically with amphotericin B outside of China and Singapore.

The need for new anti-fungals is evident

Basilea is in a strong cash position with CHF112.9m in cash and investments at the end of H1 2023. We believe that this should be helpful as the company seeks to strengthen its antifungal pipeline. Given Basilea's history and expertise in antifungals and antimicrobials in general, we believe that the company should be able to deliver on this strategic priority. Furthermore, we believe the successful delivery of novel pipeline candidates would suggest greater longevity to the antifungal franchise. Clearly, successful execution would represent a significant de-risking event for the company.

Ceftobiprole is helping to fill the gap

Fortunately, it is not all about Cresemba, with the forthcoming US approval of ceftobiprole set to add a significant source of revenues to the franchise. Although there is both a recognition of the need for new antibiotics and no shortage of apparent initiatives to pay for them, there appears to be a lack of willingness from the pharma majors to invest significantly in their development. On the plus side, we note that several alternative sources of funding are available with the Novo REPAIR fund, CARB-X (part funding the DXR inhibitor programme), as well as financing through the PASTEUR Act (when/if approved) in the US and the AMR Action Fund.

The clear unmet need suggests an attractive licensing opportunity

From Basilea's perspective, the availability of approximately 75% of R&D funding for ceftobiprole from BARDA has represented an important source of non-dilutive financing. Furthermore, ceftobiprole's award of QIDP status (as part of the GAIN Act) has provided 5 years of additional exclusivity, providing 10 years of total exclusivity. With our peak sales forecast approaching $400m along with the clear unmet need in the SAB indication along with potential in ABSSSI and CABP, we believe that ceftobiprole should be an attractive proposition and remain sanguine regarding the ability of Basilea to deliver a commercial partner before US approval.

We suspect that flexibility is the key to partnering

We believe that there are three main categories of potential partner for ceftobiprole in the US, each of whom could provide relevant and appropriate partnership candidates. The obvious would be a company with an existing hospital antibiotic-based franchise. The second would be a company with an existing hospital sales infrastructure, while the third would be where there may be no obvious fit, but the partner has a clear strategic desire and capability to enter the hospital-based antibiotic marketplace. It is probably worth highlighting the outcome for the previously standalone company Paratek, providing an example of the flexibility required when commercialising new antibiotics in the US. While Paratek has enjoyed success with the launch of Nuzyra, the company has attracted the attention of private equity, with Novo Holding and Gurnet Point acquiring the company in June 2023.

Further de-risking in 2023

We have also suggested that with a clear 10-year time horizon and a strong cash position, Basilea should seek to maximise the royalty rate, which we anticipate could be north of 20%. Historically, our forecasts have incorporated both the sales and associated costs of self-marketing, which we have retained until details of any collaboration are disclosed. We believe that the successful attraction of a partner would represent another important de-risking event for the company.

Our forecasts include new management guidance for 2023F reflecting a slightly higher FY'23 revenue. As a result, our forecasts continue to reflect a period of positive cash flow and sustainable profitability. Given the scale of operating loss carry forwards, we do not anticipate tax payments for the next several years. We have prudently forecast a modest increase in R&D spending at Basilea but recognise that this likely incorporates limited spending on new, as yet unidentified, projects. We will review the quantum of R&D spending should Basilea successfully deliver new late-stage candidates into its antifungal (or antibiotic) pipeline, taking into account the phase of development and the need for additional clinical evaluation.

Basilea Income Statement (CHF' 000)

Year to December	2021A	2022A	2023E	2024E	2025E	2026E
Total revenue	**148122**	**147765**	**159232**	**159231**	**163218**	**179927**
COGS	(24,072)	(24,603)	(28,662)	(31,846)	(32,644)	(32,387)
Gross profit	**124,050**	**123,162**	**130,570**	**127,385**	**130,575**	**147,541**
Gross margin	83.7%	83.3%	82.0%	80.0%	80.0%	82.0%
R&D	(93,157)	(73,804)	(46,177)	(49,362)	(52,230)	(53,978)
SG&A	(29,721)	(30,815)	(31,846)	(35,031)	(40,805)	(39,584)
Total cost and operating expenses	(146,950)	(129,222)	(106,685)	(116,239)	(125,678)	(125,949)
Non-underlying items	0.00	0.00	0.00	0.00	0.00	0.00
Operating profit US GAAP	**1,187**	**18,543**	**52,546**	**42,992**	**37,540**	**53,978**
Finance income	66	326	2,148	2,774	2,661	3,497
Finance expense	(8,151)	(9,848)	(9,750)	(9,777)	(4,803)	(4,830)
Other financial income	1,676	2,015	0	0	0	0
Other financial expense	(1,573)	1,066	0	0	0	0
Underlying PBT	(6,810)	12,102	44,945	35,989	35,398	52,645
PBT IFRS	(6,795)	12,102	44,945	35,989	35,398	52,645
Loss before tax	(6,810)	12,102	44,945	35,989	35,398	52,645
Tax	(37)	45	0	0	0	0
Underlying net income	**(6,847)**	**12,147**	**44,945**	**35,989**	**35,398**	**52,645**
Net income US GAAP	**(6,832)**	**12,147**	**44,945**	**35,989**	**35,398**	**52,645**
EPS Basic (CHF)	(0.66)	1.02	3.79	3.03	2.98	4.44
EPS Diluted (CHF)	**(0.61)**	**1.02**	**3.76**	**3.01**	**2.96**	**4.41**

Source: Calvine Partners Research

Basilea Cash Flow Statement (CHF' 000)

Year to December	2021A	2022A	2023E	2024E	2025E
Net profit/(loss)	(6,831)	12,147	44,945	35,989	35,398
Depreciation and amortization	754	1,097	760	803	850
Gain on disposal of assets, net	(71)	0	0	0	0
Stock-based compensation	4,322	3,598	0	0	0
Interest and accretion of debt issuance cost	1,593	497	534	534	534
Accounts receivable	(16,251)	(8,242)	(1,425)	(605)	(219)
Other receivables	(15,813)	10,829	0	0	0
Inventories	(1,591)	(1,461)	(451)	(1,832)	(664)
Accounts payable	(2,538)	(10,427)	3,177	287	165
Deferred revenue	(2,556)	(1,233)	(1,233)	0	0
Accruals and other current liabilities	5,440	(846)	0	0	0
Other operating cash flow items	1,522	1,098	0	0	0
Net cash provided by/used in operating activities	**(32,020)**	**7,057**	**46,306**	**35,176**	**36,063**
Cash flow from investing activities					
Payments for short-term investments	(35,000)	0	0	0	0
Maturities of short-term investments	41,023	94,951	0	0	0
Payments for long-term investments	0	0	0	0	0
Proceeds from sale of assets	(1,588)	0	0	0	0
Investments in tangible assets	(581)	(3,138)	(855)	(941)	(1,035)
Investment in intangible assets	(279)	(165)	(332)	(332)	(332)
Net cash used in/provided by investing activities	**3,575**	**91,648**	**(1,188)**	**(1,273)**	**(1,367)**
Cash flow financing activities					
Net proceeds from exercise of stock options	1,866	3,520	0	0	0
Debt extinguishment	(23,212)	(123,547)	(44,000)	(38,400)	0
Issuance of Convertible bonds	0				
Senior secured loan		73,875			
Purchase of treasury shares	(4,254)	656			
Issuance of new shares	42,240	250			
Net cash provided by financing activities	**16,640**	**(45,246)**	**(44,000)**	**(38,400)**	**0**
Effect of exchange rate changes on cash and cash equivalents	501	155	0	0	0
Net change in cash and cash equivalents	(11,304)	53,614	1,118	(4,498)	34,696
Cash and cash equivalents at beginning of period	66,256	54,952	108,566	109,684	105,186
Cash and cash equivalents at end of period	**54,952**	**108,566**	**109,684**	**105,186**	**139,882**

Source: Calvine Partners Research

Basilea Balance Sheet (CHF' 000)

Year to December	2021A	2022A	2023E	2024E	2025E
Non-current assets					
Tangible assets, net	2,018	4,277	4,705	5,175	5,693
Intangible assets, net	632	578	578	578	578
Long-term investments	2,390	1,266	1,266	1,266	1,266
Other non-current assets	1,161	39,363	39,363	39,363	39,363
Total non-current assets	6,201	45,484	45,912	46,382	46,900
Current Assets					
Cash and cash equivalents	53,700	84,659	109,684	105,186	139,882
Short-term investments	96,253	0	0	0	0
Accounts receivable	24,947	33,152	8,153	8,758	8,977
Other receivables	39,500	28,552	28,552	28,552	28,552
Inventories	22,783	24,244	24,695	26,528	27,192
Other current assets	3,883	4,756	4,756	4,756	4,756
Total current assets	241,066	175,363	175,840	173,780	209,359
Total assets	**247,267**	**220,847**	**221,752**	**220,162**	**256,259**
Current liabilities					
Convertible senior unsecured bonds	123,505				
Senior secured debt		37,467	36,360		
Accounts payable	10,617	191	3,368	3,654	3,819
Deferred revenue	1,233	1,233	1,233	1,233	1,233
Accruals and other current liabilities	39,053	35,959	35,959	35,959	35,959
Total current liabilities	174,408	74,850	76,920	40,846	41,011
Non-current liabilities					
Convertible senior unsecured bonds	94,544	95,000	95,534	96,068	96,602
Deferred revenue, less of current portion	11,926	10,693	0	0	0
Senior secured debt		36,360			
Other non-current liabilities	24,996	24,661	24,661	24,661	24,661
Total non-current liabilities	131,466	166,714	120,195	120,729	121,263
Total liabilities	**305,874**	**241,564**	**197,115**	**161,575**	**162,274**
Shareholders equity (deficit)					
Share capital	12,992	13,093	13,093	13,093	13,093
Additional paid-in capital	1,029,796	1,037,120	1,037,120	1,037,120	1,037,120
Accumulated other comprehensive loss	(21,617)	(3,784)	(3,784)	(3,784)	(3,784)
Treasury shares held by a subsidiary	(56,559)	(56,071)	(56,071)	(56,071)	(56,071)
Loss carried forward	(1,016,388)	(1,023,220)	(1,011,073)	(966,128)	(930,139)
Net loss for the year	(6,832)	12,147	44,945	35,989	35,398
Total shareholders' equity (deficit)	(58,608)	(20,715)	24,230	60,219	95,617
Total liabilities and equity (deficit)	**247,266**	**220,849**	**221,344**	**221,794**	**257,891**

Source: Calvine Partners Research

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