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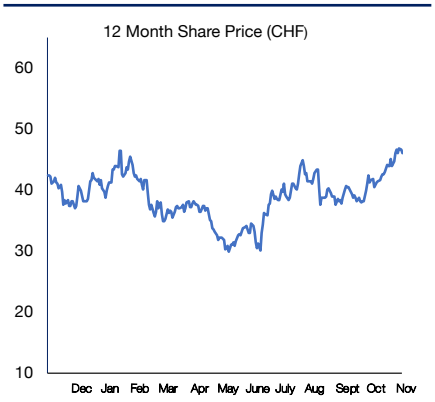
Basilea Pharmaceutica

9 November 2022

Share Price (CHF)	**46**
CP Fair Value (CHF)	**91**

Market Cap (CHFm)	600
Cash (CHFm)	142
EV (CHFm)	695

Country	Switzerland
Code	BSLN
Index	SIX



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Sustainable profitability

2022 has represented a transition period for Basilea as it de-emphasised its nascent oncology efforts and re-focussed on its long-established anti-infectives franchise. This strategic re-focusing has resulted in the prospect of near-term and sustainable profitability. This is a laudable objective, particularly in the current market environment. Importantly, Basilea has been actively re-populating its early-stage anti-infectives pipeline.

Cresemba driving profitability

Basilea was initially spun out from Roche as an anti-infectives focussed enterprise, with the antifungal Cresemba (isavuconazole) and the 5th generation cephalosporin ceftobiprole, the two key anti-infective pipeline products. Cresemba has been a real success story thanks to its differentiated attributes, extended spectrum, good safety profile and the commercial prowess of its partners – particularly Astellas in the key US market and, increasingly, Pfizer in other key territories. While Cresemba may be maturing in some markets, we anticipate near-term growth to remain, with key markets of China and Japan being prominent additions. We are heartened to see renewed efforts in identifying and developing novel antifungals with several exciting new candidates; our research suggests that these are highly valued assets by the pharma industry. Basilea is a significant participant, with a novel preclinical candidate set to strengthen the franchise.

Ceftobiprole set to become another growth driver

According to our forecasts, continued growth from anti-infectives, combined with the exit from oncology R&D, should drive Basilea to a sustainable cashflow positive position in 2023. We highlight the potential for ceftobiprole, Basilea's 5th-generation cephalosporin antibiotic. Ceftobiprole is on the cusp of a US regulatory filing and is a meaningful addition to the anti-infectives franchise. The positive results of both TARGET and ERADICATE suggest a favourable regulatory outcome, with ERADICATE highlighting the potential of ceftobiprole as an important new alternative to daptomycin in bacteraemia. *Staphylococcus aureus* bacteraemia (SAB), particularly caused by MRSA, continues to be a source of high levels of morbidity and mortality. We forecast that peak revenues could approach $400m in the US alone. Key to commercial success, much like Cresemba, will be the attraction of a suitable and relevant commercial partner.

A new strategy

2022 has been a pivotal year for Basilea

2022 has borne witness to several strategically important events for Basilea. Firstly, the decision to exit its oncology franchise has been realised with programmes offloaded and the sizeable associated oncology R&D spending winding down. Lead oncology candidate derazantinib will be returned to Merck & Co. (formerly Arqule) by the end of 2022, while three preclinical programmes targeting PARG, TTK/PLK1 and CLK kinases have been out-licensed to Nodus Oncology, SillaJen and Twentyeight-Seven Therapeutics, respectively.

Antifungal franchise powers ahead

Cresemba provides a strong platform

The antifungal Cresemba (isavuconazole) has long dominated Basilea's anti-infectives franchise and now represents the largest antifungal by sales value in the important US market. As we have previously intimated, Cresemba sales have consistently outpaced our expectations, and we suspect that the investment community has generally overlooked the commercial importance of antifungals. It is well-documented that fungal infections can be highly dangerous, leaving patients with a variety of life-threatening disorders that can be invasive, acute and chronic.

Invasive moulds are a real threat…

Of the invasive fungal diseases, meningitis, fungaemia, and pneumonia are particularly problematic. In the chronic setting, infections such as chronic pulmonary Aspergillosis and allergic bronchopulmonary Aspergillosis feature heavily. While Mucorales and Fusarium may be rare infections, they can be challenging to treat given resistance issues. Another morbid and concerning statistic is that only circa 50% of fatal invasive fungal infections are diagnosed (before death).

..to the immunocompromised

With most life-threatening invasive fungal infections affecting individuals suffering from a compromised immune function, the need for more effective antifungals has increased proportionately with a rise in HIV infections, increasingly aggressive cancer chemotherapy, and the use of immunosuppressant therapy in organ transplantation. These infections are associated with significant mortality risk.

Unfortunately, the development of new antifungals has not kept pace with the emergence of resistance. Available antifungals are still limited to only three classes: polyenes, azoles and echinocandins. Given the paucity of available antifungal classes, the emergence of antifungal resistance is arguably of even greater concern than in antibiotics, despite receiving significantly less publicity. Increasing resistance is a

genuine concern with the azoles and Aspergillus, and Candida with the increased use of echinocandins.

Underlying growth of immunocompromised patients

Underlying growth dynamics appear to support continued antifungal growth and the requirement for new effective options to deal with increasing resistance. 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 outlook for patients is poor…

As a result, the outlook for patients with invasive fungal infections is quite bleak. Mould infections are particularly worrisome in the immunocompromised patient population and represent a significant source of morbidity and mortality. In Aspergillosis, the mortality rate varies from 30%-60% and can be higher in high-risk patient populations such as chemotherapy-induced neutropaenia.

…and getting worse

Current antifungal classes have limitations that can restrict their use in clinical practice. The echinocandins suffer from poor bioavailability and require injection. Particularly for mould infections, echinocandins are used for salvage therapy and in combination. 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. Antifungal resistance to polyene therapy is common in Aspergillus.

Azoles are a preferred choice

The azoles, on the other hand, represent the most widely used class of antifungals. They kill fungi through the C14∞ demethylation of lanosterol, which leads to the inhibition of ergosterol production in the cell membrane, and cell death. Ergosterol regulates membrane fluidity and permeability and is required for fungal growth. Their widespread use, however, has resulted in widespread resistance, with its emergence developing by various mechanisms. These include overexpression of CYP51 or mechanisms which effectively reduce the intracellular presence of antifungal compounds such as ATP-binding cassette transporters.

Significant 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) generated peak sales of about $900m.

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. Posaconazole use is limited to prophylaxis of mould infections only. Cresemba, on the other hand, is a relatively new triazole possessing 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 treating various severe and potentially life-threatening fungal infections. Also crucial to its commercial success is the excellent volume of distribution and oral bioavailability, combined with highly predictable pharmacokinetics with little interpatient variability.

Resistance an issue

Cresemba was approved in the US for the treatment of invasive Aspergillosis (IA), having been shown to be non-inferior to voriconazole. The FDA has also approved it for the treatment of mucormycosis. Unfortunately, the role of the echinocandins as first-line treatment for invasive candidiasis was re-enforced with the negative result from the ACTIVE Phase III study where isavuconazole failed to prove non-inferiority to caspofungin.

Invasive Aspergillosis, therefore, 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.

IA is the primary market for Cresemba

The current guidelines for the treatment of invasive Aspergillosis remain those issued by the IDSA in December 2016. Voriconazole administration, therefore, still represents the centrepiece of 1st line antifungal therapy here supported by a high level of evidence, particularly in the pulmonary aspergillosis setting. Isavuconazole was provided with a relatively limited position in the guidelines as an alternative to voriconazole. The lack of an update is perhaps a frustration, but it is clear that the experience with Cresemba, particularly in the US, is growing. Several key benefits offered by isavuconazole have been highlighted, which include a lack of toxicity with no requirement for a cyclodextrin-based solubility agent (important in renally impaired patients), a once-daily dosing and a more limited drug interaction profile. Elsewhere, ASCO/IDSA guidelines (2018) for antimicrobial prophylaxis in patients with cancer-related immunosuppression also suggest a role for prophylaxis in patients at risk of *"…profound, protracted neutropaenia*".

Current guidelines helpful to an extent

Over time and certainly since the production of the IDSA guidelines, we hope that the clinical experience with

Physician experience has grown

Cresemba in the US should have grown to the extent that clinicians are better aware of its differentiated profile. Updated guidelines that better reflect the Cresemba proposition for invasive Aspergillosis would be beneficial, particularly if they were to suggest usage in earlier lines of treatment. However, as far as we know, there are no timelines for updated IDSA guidelines on IA.

Astellas has proven an excellent and effective partner

We also suspect that central to Cresemba's commercial success to date has been the attraction of Astellas in the US. Cresemba represented an important addition to the Astellas antifungal franchise. The importance of Cresemba to Astellas was reflected in the commercial agreement struck when isavuconazole was still in Phase III development. Basilea received CHF 75m upfront, up to CHF 478m on development and sales milestones, and significant double-digit tiered sales royalties. The agreement was subsequently amended with Basilea regaining full ex-US rights with the total sales-based milestones amounting to CHF 290m (after having already received CHF 42m of regulatory and CHF 5m of sales milestones). Basilea also maintained double-digit tiered royalties on US sales.

Better safety profile highlighted in EU

In Europe, the European Conference on Infections in Leukaemia (ECIL) provided recommendations for the targeted treatment of candidiasis, Aspergillosis and mucormycosis. The latest ECIL-6 meeting in March 2017 reported that isavuconazole appeared to be as effective as voriconazole for treating invasive Aspergillosis and with a better safety profile. Consequently, it was afforded an impressive A1 grade, the same status as voriconazole. As a result, Aspergillus guidelines recommend either treatment as first-line therapy for invasive Aspergillosis. It is reassuring to see the better safety profile being highlighted, which we believe should put isavuconazole in a favourable position when prescribing choices are made.

Royalties growing strongly

Outside of the US, Basilea has attracted Pfizer, firstly for Europe (in June 2017) and then for Asia Pacific (in December 2017) as a commercial partner for Cresemba. The European license delivered CHF 70m in upfront payments while the addition of Asia-Pacific a more modest $3m. Total potential milestones for the two agreements amount to an impressive $650m on unspecified regulatory and sales-related milestones. Of greater importance is the mid-teens royalties on sales which Basilea secured. For Pfizer, the originator of voriconazole (branded as VFEND), adding Cresemba provided an antifungal which can be positioned as an alternative to voriconazole as per the current guidelines and which also offers a more benign tolerability profile resulting in fewer adverse events (42% vs 60%) with an improvement in

measures such as hepatobiliary disorders, skin and eye disorders.

Suitable for empiric therapy

Fortunately, invasive Aspergillosis is relatively uncommon, and mucormycosis even less so. Both are challenging to diagnose, which is reflected in the underreporting of these conditions. In its favour, isavuconazole's broad spectrum (including Mucorales) should position it well in the empiric setting, compared to alternative agents (such as voriconazole), where infection is suspected but not confirmed.

IA is the most common invasive mould

Invasive Aspergillosis is the most common invasive mould, although surveillance for IA and mucormycosis has been limited, and neither are reportable diseases. However, it would appear that both are growing in prevalence along with an increasing population of immunocompromised patients. Data may be hard to find, and we note various sources which suggest that the scale of the issue is potentially significant, with 10m patients at risk of contracting invasive Aspergillosis. However, data from US hospital discharge rates suggest a rate per 1m of circa 46 for invasive Aspergillosis and 3.4 per 1m for mucormycosis in 2013.

The majority of the antifungal market is outside the US

We note that 80% of the antifungal market resides outside the US, with 70K patients in Europe dying from invasive Aspergillosis. By extrapolation, assuming that the mortality rate for patients with IA was 41% in solid organ transplant patients and 75% among stem cell transplant patients, this suggests a potential market opportunity in Europe alone approaching 200,000, assuming a conservative blended mortality rate.

Although mucormycosis is considerably rarer, the population at risk is growing, suggesting a similar population in the US, although the actual number of cases is small (circa 1000). The figure in Europe for deaths from mucormycosis is higher at approximately 3,000. Therefore, in our forecasts, we have assumed that there are circa 200,000 patients in the combined IA and mucormycosis markets in the US and Europe. Ultimately, Cresemba is available on a much broader basis, and we have endeavoured to capture this opportunity as well (although at a lower effective price).

Looking at the commercial potential, we have assumed Cresemba is used for 47 days, representing the mean treatment duration in the Phase III pivotal IA study (as per the prescribing label). We have also assumed that the IV formulation (one vial) was used for 8 days, with the oral capsule for the remainder. We have also used a price of $180/day for the oral capsules and $319 for IV administration. Using these figures suggests a price per course of therapy of circa

$10000. We have assumed a similar price in Europe in line with typical antifungal pricing.

Cresemba is maturing but plans are afoot

New geographies continue the growth story

Cresemba has been a highly rewarding success story for Basilea, its licensees, and distributors. We forecast continued growth in major markets despite its maturity, mainly due to an increasing number of at-risk immunosuppressed patients. Cresemba has also enjoyed a protracted rollout as Basilea has identified new distributors and licensing partners. Currently, the expectation is that Cresemba will be available in over 70 countries by the end of 2022. In the near term, we look forward to growth receiving a boost from availability in China (in particular) and Japan.

Healthy pipeline developing

Given the unmet need, efforts are underway to identify and develop new antifungal classes. However, this is not easy compared to other anti-infective development, given the similarity between fungal and human processes. Nevertheless, there has been significant progress, and we note the ongoing development of fosmanogepix. 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 a novel antifungal. Manogepix targets glycosylphosphatidylinositol-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 resistant to the echinocandins. However, it appears to have a lack of activity against some Mucorales.

Keep an eye on fosmanogepix

Fosmanogepix has been studied in a Phase II trial in patients with invasive candidiasis. This open-label single-arm study demonstrated that fosmanogepix was well tolerated and efficacious, with 80% of patients benefiting from Candida clearance. Efficacy was also seen in patients with isolates resistant to anidulafungin and amphotericin B. The importance and relevance of the activity of fosmanogepix have been reflected in the awarding of fast-track status by the FDA for various invasive fungal infections, including invasive Aspergillosis, candidiasis and mucormycosis.

Pfizer is a good partner

Given the Pfizer ownership, we expect fosmanogepix to represent an important treatment option when it has successfully navigated Phase III trials. Early indicators are

promising, with activity against difficult to treat fungi and a good side effect profile.

Ibrexafunberg promising

Elsewhere, we are heartened to see ongoing clinical evaluation of other novel antifungal candidates, including the triterpenoid ibrexafungerp, which shares the same target as the echinocandins, although it 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 ibrexafungerp's availability in oral form, there is the potential for it to be used as an oral step-down therapy to injectable echinocandins in the short term. Three Phase III trials are ongoing (MARIO) in invasive candidiasis, and refractory invasive fungal infections (FURI and CARES), as well as a Phase II study in IA. In addition, an intravenous formulation of ibrexafungerp is in development and, according to Scynexis, should be available by 2025.

Olorofim awarded Breakthrough Therapy

Another novel approach is represented by olorofim (F2G), a member of the ortomide antifungal class. Olorofim targets 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. Although clinical trial data may be limited, we note encouraging efficacy in patients with previously intractable fungal infections.

Shionogi is a highly relevant partner

Available orally, olorofim is distinguished from all its peers for achieving 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 and double-digit sales royalties. Olorofim has entered a global Phase 3 trial (OASIS) which will compare the treatment of olorofim versus AmBisome followed by standard of care (SOC) in patients with lower respiratory tract invasive fungal disease that is likely caused by IA.

As a truly novel antifungal with activity against isolates, which are resistant to current treatment options, olorofim represents an exciting prospect, we believe. Furthermore, the attraction of Shionogi for Europe and Asia represents a valuable endorsement from a company with a long and well-established anti-infectives heritage. According to Shionogi, the company commits a higher proportion of its R&D spend to anti-infectives than any other pharma company.

Basilea is active, although at an early stage

For its part, Basilea has in-licensed a novel antifungal from the Fox Chase Chemical Diversity Centre in April 2022. No details on this new preclinical candidate have been provided apart from its description as a first-in-class broad-spectrum antifungal with activity against intractable mould infections.

Given the maturity of Cresemba in major markets and the limited life cycle in the US in particular, visibility on the future of this programme is key to the overall longevity of the antifungal franchise.

All eyes are on ceftobiprole to broaden the franchise

The US is the key for ceftobiprole

The financial contribution from ceftobiprole (branded as Zevtera) has been modest to date. Sales are limited to ex-US (mostly Europe), and the European label has been limited to CAP/HAP (excluding VAP). As Basilea has recognised, the US remains the key market for novel antibiotics, thanks mainly to the high level of antimicrobial resistance and MRSA in particular.

MRSA activity highly relevant for target indications

As a 5th-generation cephalosporin, ceftobiprole was designed with the increasing prevalence of MRSA in mind. It has an extended spectrum of activity against clinically important Gram-positive bacteria, including MRSA, PRSP, and *Enterococcus faecalis*. Importantly, from an empiric therapy perspective, ceftobiprole also has activity against susceptible Gram-negative pathogens. Despite its extended spectrum and availability outside the US for many years, ceftobiprole has shown a low propensity to develop resistance. We are pleased to note that this has been confirmed following the positive reporting of both the TARGET and ERADICATE Phase III trials.

The role of the 5th generation cephalosporins is well established, with ceftaroline treating severe skin infections and nosocomial pneumonia. However, we believe the more significant need lies in treating bacteraemia and sepsis caused by *Staph. aureus* (particularly where MRSA is suspected), and this is where ceftobiprole will differentiate from its peers.

Staph. aureus is the causative agent of several infections, including skin, soft tissue infections and pneumonia. These infections can lead to the development of bacteraemia and infect distal sites and organs such as the heart, lungs and brain. Bacteraemia represents a particularly dangerous development, often leading to metastatic infections, such as infective endocarditis, and life-threatening complications, such as sepsis. It often develops secondary to another site of

Bacteraemia indication is the ultimate objective

infection (e.g. vascular catheter), but for a substantial proportion (c25%), the initial site of infection can't be identified.

There are various risk factors for bacteraemia development, including a compromised immune system and respiratory disorders such as cystic fibrosis and emphysema, which increase the risk of complications. Moreover, risk factors for nosocomial infections include catheters (intravascular, urinary and feeding) and tubing used for dialysis and nutrition.

Emerging resistance is a growing concern

Over time, *Staph. aureus* has successfully developed various strategies to evade the human immune system. This includes forming biofilms which adhere to implantable devices. *Staph. aureus* biofilms are notoriously difficult to treat with current antibiotic-based strategies. In patients with SAB, complications such as endocarditis, abscesses, vertebral osteomyelitis and implanted device infections can develop several weeks or months after the initial infection.

The US is the primary target

The prevalence of SAB varies geographically, with developing countries significantly more affected than their first-world counterparts. For example, Southern European countries fare worse than those in the North, with 7 out of the 29 EU countries reporting that MRSA is found in 25% of *S. aureus* infections. In the key US market for ceftobiprole, the annual incidence of SAB is 38.2 – 42.7 per 100,000 person-years compared to 10-30 per 100,000 person-years in the developed world. This suggests a total SAB population of between 125,000 and 140,000.

High risk of death

Overall, bacteraemia is associated with a mortality rate of 20%. This rate has improved modestly in the recent past despite efforts to better manage patients suffering from bacteraemia. Over 40% of *Staph. aureus* bloodstream infections in the US are caused by MRSA, justifying the development of antibiotics such as ceftobiprole in this important territory. The US is the target market for Basilea, and we believe that ceftobiprole, with its extended spectrum and potent activity against MRSA, should have significant commercial appeal.

Efforts to reduce MRSA bearing fruit

According to the CDC, 80% of MRSA bacteraemia events originate in the community, and while there has been significant progress in reducing hospital-acquired MRSA bacteraemia, the rate of decline has slowed since 2012. On a more positive note, US Veterans Affairs centres have reduced levels of MRSA by 55% and MSSA by 12%, thanks to implementing screening of new patients.

Less so in the community

Also, we note that while hospital-acquired MRSA bloodstream infections have declined, thanks to the implementation of infection control procedures (such as decolonisation before high-risk surgery), the same cannot be said for community-acquired infections. The CDC noted that the apparent increase in SAB in the community was likely linked to the opioid crisis. Data from CDC suggest that SAB remains a significant concern, with 119,000 infections recorded in 2017 with almost 20,000 dying.

Treatment choices for SAB are limited

Effective treatment for MSSA

For patients with susceptible infections (MSSA), treatment with a beta-lactam antibiotic remains the first choice. If treatment guidelines are adhered to, it can reduce mortality risk by as much as 50%. Treatment for SAB can be for up to six weeks if the infection has become metastatic compared to two weeks if the bacteraemia remains uncomplicated. Antibiotics typically used for MSSA include anti-Staphylococcal penicillins such as flucloxacillin and first-generation cephalosporins such as cefazolin.

MRSA associated with poor outcomes

Although MSSA can be treated effectively, infection with MRSA leads to poorer outcomes, with 15%-50% mortality in patients with MRSA bacteraemia. The glycopeptides vancomycin and daptomycin are used as 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.

Resistance increasing

However, 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, suggesting a much-reduced dosing schedule. Therefore, dalbavancin provides the potential for a shorter and less invasive treatment regimen, lowering risks associated with prolonged central venous access. These include secondary bacteraemia of the central line, thrombosis, and general malfunction.

DOTS is an encouraging approach

The DOTS (dalbavancin as an option for treatment of SAB) trial has been designed as a prospective Phase 2b study evaluating the potential for dalbavancin in the treatment of complicated SAB. DOTS enrolled 200 SAB patients who had already experienced bacteraemia clearance before randomisation treated with two doses of dalbavancin or with a total of 4-8 weeks of standard intravenous antibiotic therapy.

According to clinicaltrials.gov the primary completion date is June 2023.

Resistance is still a concern though

However, even if DOTS is successful, we note that there are (largely theoretical) concerns that dalbavancin's long half-life could promote the emergence of resistance, not only to itself but also to related antibiotics such as vancomycin. Nevertheless, various analyses of completed trials which have also included several patients with SAB, have provided a significant degree of confidence in the merits of evaluating dalbavancin formally in patients with SAB.

ERADICATE first prospective Phase 3 in SAB for 5th gen cephalosporins

Despite the availability of anti-MRSA cephalosporins such as ceftaroline, ERADICATE was the first prospectively defined randomised Phase III study evaluating a 5th-generation cephalosporin in SAB. Consequently, the positive result from ERADICATE places ceftobiprole in a solid position to be the first 5th generation cephalosporin approved for the SAB indication. Indeed we believe that ceftobiprole should be able to differentiate itself from ceftaroline with an approval and label that highlights not only ABSSSI but also SAB. In the longer term, we hope that ceftobiprole's ultimate approval in SAB should provide a very strong position for inclusion in relevant guidelines as they evolve. However, we note that the guidelines have not been updated since 2011, although we hope that the long-awaited update could well benefit ceftobiprole given the result of ERADICATE.

We have previously highlighted the limitations of daptomycin and vancomycin, which include emerging resistance (and the potential for cross-resistance) and vancomycin's poor tissue distribution and risk of renal toxicity. Additionally, daptomycin is inactivated in the lung, rendering it useless for treating respiratory infections. Ultimately, there is a clear need for additional antibiotics in SAB with a notable shortage of high-quality controlled studies. Salvage therapy using a non-approved (off-label) antibiotic (such as dalbavancin and ceftaroline) has proven to be a last resort in those with a persistent infection.

Ceftaroline has a limited bacteraemia claim

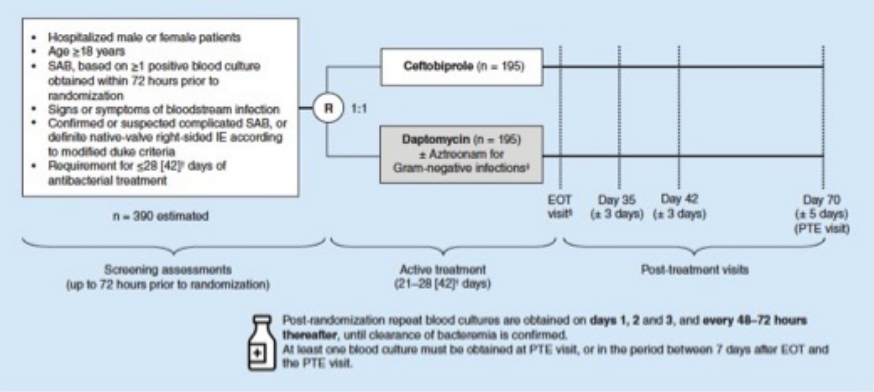
The 5th generation antibiotic ceftaroline (branded as Teflaro) was granted a label expansion to include ABSSSI patients suffering from concurrent bacteraemia. Ceftaroline was approved to treat patients with CAP and ABSSSI in 2010. The approval in 2015 was based on patients in the two identical pivotal CANVAS 1 & 2 trials. CANVAS 1 & 2 compared ABSSSI patients treated with ceftaroline to patients treated with vancomycin plus aztreonam. The activity of ceftaroline in SAB in ABSSSI patients was included in the clinical trials part of its

prescribing label. However, the numbers were small, and this is a narrower claim than a general SAB indication.

ERADICATE puts ceftobiprole in pole position

ERADICATE is an endorsement of ceftobiprole's role in SAB treatment

In the ERADICATE study, ceftobiprole was compared to daptomycin, with aztreonam available for Gram-negative coverage. ERADICATE employed a non-inferiority (NI) design, with a generous non-inferiority margin of 15%. Daptomycin was specified as a relevant comparator, given its activity in both MSSA and MRSA. At the same time, its approval in (right-sided) infective endocarditis (IE) facilitated the double-blind design of ERADICATE.



Source: Hamed, Engelhardt, Jones et al., Future Microbiology

Ceftobiprole showed clear non-inferiority to daptomycin

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.

IDWeek presentation, a high-profile event

The recent presentation of additional data at IDWeek 2022 in Washington DC has provided further comfort into ceftobiprole's activity in SAB. Notably, the primary endpoint was achieved irrespective of whether patients were infected with MSSA or MRSA bloodstream infections at baseline. This result was also reflected when contributing underlying conditions were evaluated and included skin and skin structure infections, abdominal abscesses, chronic dialysis, septic arthritis, osteomyelitis, definite right-sided IE, and patients with persistent SAB.

Secondary endpoints included all-cause mortality and microbiological eradication. Data on these endpoints were also presented at IDWeek. The overall success rate in the clinically evaluable patient population was 77.9% (vs 77.8%

Secondary endpoints are highly supportive

with daptomycin. Microbiological eradication was 82% (vs 77.3% with daptomycin), while all-cause mortality was 9% (vs 9.1% with daptomycin). Finally, the emergence of new SAB complications was 5.8% (vs 5.6% with daptomycin).

Reassuring lack of resistance seen

We have already highlighted the increasing risk of daptomycin resistance and note that three patients experienced daptomycin resistance in ERADICATE. However, encouragingly and despite the widespread use of the cephalosporin class (including alternative 5th gen cephalosporins), we note that there were no cases of ceftobiprole resistance observed in ERADICATE. All told, we believe that these data align with our previous expectations and provide Basilea with a highly competitive package to secure a relevant commercial partner.

$250m peak sales forecast in SAB

As a result, our forecasts for ceftobiprole are unchanged compared to our previous expectations. We believe that ceftobiprole could achieve a 20% 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 2-6 weeks. In our financial model, we have assumed that patients receive treatment for 5 weeks at $6000 per treatment.

Total approaching $400m

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 suggests that even a small market share should generate meaningful revenues for ceftobiprole. Therefore, we have assumed that ceftobiprole can secure a 3-4% share of the sizeable 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. Accordingly, we forecast that ceftobiprole could deliver peak in-market sales of $380m.

Risks

Basilea's currently marketed products are out-licensed to third parties, suggesting little influence over sales performance. Nevertheless, the commercialisation of key product Cresemba has been successful by engaging highly appropriate partners (particularly Astellas and Pfizer).

While the antibiotic Zevtera (ceftobiprole) is already marketed outside of the USA for treating CAP and HAP (excluding VAP), we see the more significant market opportunity in the *Staph. aureus* bacteraemia (SAB) indication, particularly where MRSA is suspected. The positive results of ERADICATE and TARGET have reduced clinical and regulatory risk. Basilea has intimated that it will seek a commercial partner for ceftobiprole in the US. There is, therefore, commercial risk until a partner is secured and the franchise of the new partner is assessed. However, Basilea has historically proven to be adept at securing relevant commercial partners.

In February 2022, Basilea announced its decision to exit oncology R&D by the end of the year, seeking transactions for its current clinical and preclinical oncology assets. The forecast of reduced R&D spending is dependent on achieving this objective. Encouragingly the company has been able to partner or return rights to existing oncology programmes.

Our financial forecasts suggest that the business re-focus will result in Basilea moving towards a cash flow positive position in 2023 and sustainable profitability. With our expectation of a 2023 launch for ceftobiprole, our forecasts do not incorporate the expected upfront payment that the company would receive from a commercial partnership, suggesting some near-term financial upside.

Summary and Financial Model

Cresemba maturing in the US

The antifungal Cresemba has dominated the anti-infectives franchise at Basilea. It is now well established as a treatment option, particularly in Invasive Aspergillosis (IA), although it has lacked optimal positioning in relevant (but outdated) guidelines. Astellas has proven to be a powerful partner in the US, and although we believe that there is still underlying growth, we note that the US is maturing, and Cresemba faces the loss of exclusivity in 2027.

Longer-term growth elsewhere

Elsewhere, the Pfizer partnership has gained traction in Europe and other important markets. Although the loss of exclusivity in Europe could be as early as 2025, success in the paediatric population could extend the period into 2027. In the near-term future growth looks assured with little in the industry's late-stage pipeline, which could usurp Cresemba's current strong position. Fosmanogepix may be progressing and looks to have a strong profile, but it will likely have little impact in the short term.

China represents an important new geography

New territories will be critical to the longer-term growth of Cresemba, with Basilea suggesting that by the end of 2022, Cresemba should be available in around 70 countries. Of the new territories, launches in China and Japan possibly represent the most substantial opportunities for Cresemba. Both oral and IV preparations of Cresemba are now available in China, which, according to the company, represents 20% of global sales for newer antifungals. Cresemba has been approved for IA and invasive mucormycosis. Numbers for China are difficult to find, but we note data presented at ECCMID in 2013 suggested that there were 162,000 cases of IA and 2,726 cases of mucormycosis. These numbers are clearly conservative with other growth drivers, including a marked increase in organ transplantation (particularly lung) in China over the past few years. In addition, 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.

Overreliance on Cresemba is a nice problem to have

Basilea's current overreliance on Cresemba is a nice problem to have given its current growth trajectory. However, initially approved in the US in 2015, Cresemba is maturing in initial launch markets while IP protection will wane from 2027 in the US and Europe. As a result, the prospect of adding ceftobiprole in the US represents an important source of new revenues and additional growth. 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 funding sources are available with the Novo REPAIR fund, CARB-X, and financing through the PASTEUR Act (when approved) in the US and the AMR Action Fund.

BARDA is an important source of non-dilutive funding

From Basilea's perspective, the availability of circa 70% of R&D funding for ceftobiprole from BARDA has represented an important source of non-dilutive financing. Additionally, ceftobiprole's award of QIDP status (as part of the GAIN Act) has provided 5 years of additional exclusivity. This results in 10 years of exclusivity in the US.

Looking at the potential market opportunity for ceftobiprole, our forecasts suggest that it will be the SAB indication that will drive uptake. The severe skin indication may be large but is congested with little differentiation over well-established alternative 5th-generation antibiotics such as ceftaroline. However, we are hopeful that the perception of ceftobiprole generally will benefit from the recent data presentation, particularly at a high-profile event like IDWeek.

Potential peak sales approaching $400m in total

Our financial model suggests peak sales approaching $400m in the USA alone. Despite recognising that Basilea will seek a commercial partner for ceftobiprole in the US, our financial model continues to include end-market sales and associated costs as we await details of any potential transaction. On the other hand, we have not included the impact of any upfront payment to Basilea. Longer-term, there is potential to bring the US label to Europe, which could significantly boost Zevtera sales. However, this is beyond our current financial model.

All eyes are now on a partner for ceftobiprole

We have updated our financial model to reflect recent events which include the sale of rights to BAL0891 as well as the CHF75m senior secured loan agreement. With its operational spending significantly reduced in 2023, our forecasts suggest that Basilea should move towards an enviable position of positive cash flow and sustainable profitability. Given the uncertainty associated with the value of antibiotic assets recently, all eyes are now on the company’s ability to secure a relevant partner for ceftobiprole in the US. Successful completion should materially de-risk the commercialisation of ceftobiprole and remove a key overhang from the Basilea investment case.

Basilea Income Statement (CHF' 000)

Year to December	2019A	2020A	2021A	2022E	2023E	2024E	2025E
Total revenue	**134381**	**127629**	**148122**	**120278**	**130556**	**125312**	**150822**
COGS	(18,868)	(24,054)	(24,072)	(22,251)	(26,111)	(25,062)	(22,623)
Gross profit	**115,513**	**103,575**	**124,050**	**98,027**	**104,445**	**100,250**	**128,198**
Gross margin	86.0%	81.2%	83.7%	81.5%	80.0%	80.0%	85.0%
R&D	(102,662)	(97,410)	(93,157)	(81,789)	(52,223)	(48,872)	(50,073)
SG&A	(30,051)	(29,422)	(29,721)	(30,070)	(35,250)	(37,594)	(37,705)
Total cost and operating expenses	(151,581)	(150,886)	(146,950)	(134,110)	(113,584)	(111,528)	(110,401)
Non-underlying items	0.00	15,035	0.00	0.00	0.00	0.00	0.00
Operating profit US GAAP	**(17,200)**	**(8,222)**	**1,187**	**(13,832)**	**16,972**	**13,784**	**40,420**
Finance income	28	104	66	161	167	152	22
Finance expense	(6,424)	(7,589)	(8,151)	(6,784)	(8,353)	(8,353)	(3,353)
Other financial income	1,583	2,057	1,676	0	0	0	0
Other financial expense	(369)	(1,017)	(1,573)	0	0	0	0
Underlying PBT	(22,382)	(29,702)	(6,810)	(20,455)	8,787	5,584	37,090
PBT IFRS	(22,382)	(14,667)	(6,795)	(20,455)	8,787	5,584	37,090
Loss before tax	(22,382)	(29,702)	(6,810)	(20,455)	8,787	5,584	37,090
Tax	(40)	(55)	(37)	(60)	(1,248)	(793)	(5,267)
Underlying net income	**(22,422)**	**(29,757)**	**(6,847)**	**(20,515)**	**7,539**	**4,791**	**31,823**
Net income US GAAP	**(22,422)**	**(14,722)**	**(6,832)**	**(20,515)**	**7,539**	**4,791**	**31,823**
EPS Basic (CHF)	(2.09)	(1.43)	(0.67)	(1.82)	0.67	0.42	2.82
EPS Diluted (CHF)	**(2.08)**	**(1.36)**	**(0.61)**	**(1.82)**	**0.67**	**0.42**	**2.82**

Source: Calvine Partners Research

Basilea Cash Flow Statement (CHF' 000)

	2019E	2020A	2021A	2022E	2023E	2024E
Net profit/(loss)	(22,422)	(14,722)	(6,831)	(20,515)	7,539	4,791
Depreciation and amortization	1,639	1,190	754	957	1,020	1,088
Gain on disposal of assets, net	0	(15,035)	(71)	0	0	0
Stock-based compensation	3,048	3,525	4,322	0	0	0
Interest and accretion of debt issuance cost	758	1,670	1,593	534	0	0
Accounts receivable	(2,457)	(1,657)	(16,251)	1,268	(565)	288
Other receivables	8,909	(1,657)	(15,813)	0	0	0
Inventories	(4,142)	(2,618)	(1,591)	6,238	(1,712)	874
Accounts payable	378	6,394	(2,538)	(593)	(1,157)	(198)
Deferred revenue	(45,626)	(33,630)	(2,556)	0	0	0
Accruals and other current liabilities	693	(1,425)	5,440	0	0	0
Other operating cash flow items	(4,614)	4,639	1,522	0	0	0
Net cash provided by/used in operating activities	**(63,836)**	**(53,326)**	**(32,020)**	**(12,112)**	**5,124**	**6,844**
Cash flow from investing activities						
Payments for short-term investments	(20,000)	(81,023)	(35,000)	0	0	0
Maturities of short-term investments	50,000	30,000	41,023	96,253	0	0
Payments for long-term investments	(30,000)	0	0	0	0	0
Proceeds from sale of assets	0	18,325	(1,588)	0	0	0
Investments in tangible assets	(294)	(1,823)	(581)	(1,249)	(1,374)	(1,512)
Investment in intangible assets	(110)	(442)	(279)	(332)	(332)	(332)
Net cash used in/provided by investing activities	**(404)**	**(34,963)**	**3,575**	**94,671**	**(1,707)**	**(1,844)**
Cash flow financing activities						
Net proceeds from exercise of stock options	37	1,322	1,866	0	0	0
Repayment of Convertible loan	0	(53,634)	(23,212)	(123,505)	0	0
Issuance of Convertible bonds	0	93,892	0			
Senior secured loan				75,000	(37,500)	(37,500)
Purchase of treasury shares	1,272	3,487	(4,254)			
Issuance of new shares			42,240			
Net cash provided by financing activities	**1,309**	**45,067**	**16,640**	**(48,505)**	**(37,500)**	**(37,500)**
Effect of exchange rate changes on cash and cash equivalents	67	(758)	501	0	0	0
Net change in cash and cash equivalents	(62,864)	(43,980)	(11,304)	34,055	(34,082)	(32,500)
Cash and cash equivalents at beginning of period	173,908	111,044	66,256	54,952	89,007	54,925
Cash and cash equivalents at end of period	**111,044**	**67,064**	**54,952**	**89,007**	**54,925**	**22,424**

Source: Calvine Partners Research

Basilea Balance Sheet (CHF' 000)

Year to December	2019A	2020A	2021A	2022E	2023E	2024E
Non-current assets						
Tangible assets, net	5,162	2,627	2,018	6,871	7,558	8,313
Intangible assets, net	372	672	632	632	632	632
Long-term investments	30,000	0	2,390	0	0	0
Other non-current assets	1,073	2,967	1,161	1,161	1,161	1,161
Total non-current assets	36,607	6,266	6,201	8,664	9,351	10,106
Current Assets						
Cash and cash equivalents	109,024	60,749	53,700	89,007	54,925	22,424
Short-term investments	22,020	106,530	96,253	0	0	0
Accounts receivable	6,242	8,710	24,947	6,615	7,181	6,892
Other receivables	22,053	23,684	39,500	39,500	39,500	39,500
Inventories	18,569	21,192	22,783	20,038	21,751	20,877
Other current assets	6,952	2,663	3,883	3,883	3,883	3,883
Total current assets	184,860	223,528	241,066	159,043	127,239	93,576
Total assets	**221,467**	**229,794**	**247,267**	**167,707**	**136,589**	**103,683**
Current liabilities						
Convertible senior unsecured bonds			123,505	75,000	37,500	
Accounts payable	6,765	13,151	10,617	4,682	3,525	3,327
Deferred revenue	32,873	2,556	1,233	0	0	0
Accruals and other current liabilities	35,856	34,454	39,053	39,053	39,053	39,053
Total current liabilities	75,494	50,161	174,408	118,735	80,078	42,380
Non-current liabilities						
Convertible senior unsecured bonds	197,740	239,668	94,544	103,157	103,157	103,157
Deferred revenue, less of current portion	16,471	13,158	11,926	0	0	0
Other non-current liabilities	24,722	28,853	24,996	24,996	24,996	24,996
Total non-current liabilities	238,933	281,679	131,466	128,153	128,153	128,153
Total liabilities	**314,427**	**331,840**	**305,874**	**246,888**	**208,231**	**170,533**
Shareholders equity (deficit)						
Share capital	11,882	11,922	12,992	12,992	12,992	12,992
Additional paid-in capital	927,342	982,438	1,029,796	1,029,796	1,029,796	1,029,796
Accumulated other comprehensive loss	(24,555)	(27,252)	(21,617)	(21,617)	(21,617)	(21,617)
Treasury shares held by a subsidiary	(5,963)	(52,766)	(56,559)	(56,559)	(56,559)	(56,559)
Loss carried forward	(979,244)	(1,001,666)	(1,016,388)	(1,023,220)	(1,043,735)	(1,036,196)
Net loss for the year	(22,422)	(14,722)	(6,832)	(20,515)	7,539	4,791
Total shareholders' equity (deficit)	(92,960)	(102,046)	(58,608)	(79,123)	(71,584)	(66,792)
Total liabilities and equity (deficit)	**221,467**	**229,794**	**247,266**	**167,765**	**136,647**	**103,741**

Source: Calvine Partners Research

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