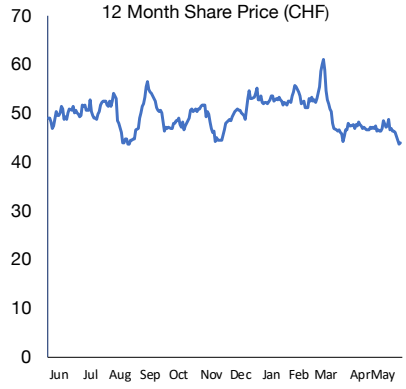
Basilea Pharmaceutica

6 May 2021

Share Price (CHF)	**43.9**
CP Fair Value (CHF)	**120**
Market Cap (CHFm)	569
Cash (CHFm)	207
EV (CHFm)	612
Country	Switzerland
Code	BSLN
Index	SIX



Source: Calvine Partners Research

Ceftobiprole – Bacteraemia is the key

Ceftobiprole is a relatively novel 5th generation cephalosporin which was initially designed and developed with multi-drug resistant infections (MRSA) in mind. While there has been a plethora of new anti-MRSA antibiotics successfully commercialised in recent years, there remains a role for 5th generation cephalosporins given the continued need for broad spectrum antibiotics which possess MRSA susceptible, Gram-negative coverage and a good tolerability profile. For ceftobiprole in particular, success in the bacteraemia (SAB) indication, would provide important differentiation in a still difficult to treat disorder where MRSA is a serious threat and the risk of life-threatening complications remains significant.

Existing datapoints portend well for bacteraemia indication

Regulatory approval for ceftobiprole in the key US market requires positive results from two Phase 3 trials in severe skin infection (ABSSSI) and SAB (TARGET & ERADICATE respectively). While TARGET has already delivered a positive result, we await the result from ERADICATE in a more challenging patient population. Despite the uncertainty, we believe that previous data portend well for a successful outcome for ceftobiprole. In particular, preclinical models, data from previous clinical studies with ceftobiprole, and also real-world data from off-label ceftaroline (another 5th generation cephalosporin) use, are supportive of ceftobiprole activity. If the data in SAB prove to be positive, this will significantly enhance the appeal of ceftobiprole to physicians and payers, and leave Basilea with a completed Phase 3 asset with which to attract a commercial partner for the key US market.

Boosting the anti-infectives franchise

The anti-infectives franchise at Basilea is currently dominated by the highly successful anti-fungal Cresemba sold through highly appropriate partners. Although ceftobiprole is already approved and sold in Europe (as Zevtera) in pneumonia (excluding VAP), the US is the key market for antibiotics and SAB is a significant issue. There is a clear unmet need for an effective antibiotic with activity against both susceptible and resistant *Staph aureus* bacteraemia. There have been few trials in SAB and only one antibiotic approval in recent times suggesting a significant market opportunity for the appropriate commercial partner. Our analysis of the market opportunity suggests that in total (both SAB & ABSSSI) ceftobiprole could deliver peak sales approaching $450m. (For Risks see Page 14).

Dr Brian White
Partner
bw@calvinepartners.com

Andrew Keith
Partner
ak@calvinepartners.com

Finally fulfilling its potential

AMR continues to be a global health concern

Antimicrobial resistance (AMR) has become a major global health concern. While there have been various initiatives and new sources of funding boosting some early-stage development, there still remains significant uncertainty regarding satisfactory financial reward. This is particularly the case for antibiotics targeting resistant infections, with the concern that reservation for last resort treatment results in unsatisfactory returns on R&D investment.

ESKAPE pathogens of particular concern

Consequently, the pharmaceutical industry (with a few exceptions) has deployed pitiful resources to develop new classes of antibiotics, particularly with respect to Gram-negative infections. The ESKAPE pathogens have been widely recognised as being of particular concern given their prevalence and the ease with which resistance can emerge, evading many widely available antibiotics. Of these, antibiotic resistant *Staphylococcus aureus* (MRSA) still represents a serious concern. *Staph. aureus* is a Gram-positive bacterium which has been associated with a multitude of infections affecting the skin, soft tissue and bone, as well as infections associated with indwelling catheters and prosthetic devices.

Bacteraemia a significant unmet need

Furthermore, *Staph aureus* has also been identified as a leading cause of bacteraemia. *Staph aureus* bacteraemia (SAB) has been implicated in metastatic infections including infective endocarditis (IE), septic arthritis, and osteomyelitis as well as sepsis and septic shock. Unsurprisingly SAB represents a particularly challenging indication and one which to date has not been satisfactorily addressed by existing antibiotics.

Efforts to improve coverage of MRSA continue

Various initiatives (such as reducing overuse, antibiotics stewardship) have successfully contained and even reduced the incidence of MRSA, however, it remains problematic. As a result, we have seen a concerted effort by the industry to deliver a range of new antibiotics with improved coverage of MRSA. It's fair to say that these are generally analogues of existing classes which while offering a rapid development, unfortunately can, unlike novel classes, be associated with the emergence of resistance.

The development of the 5th generation cephalosporin ceftobiprole at Basilea has been a protracted and tortuous affair. Early success with partner J&J in the original severe skin infection (cSSSI) indication in the US was overshadowed by concerns regarding less than acceptable scrutiny of clinical trial sites, issues over data integrity, and ultimately a complete

response letter from FDA. The fallout from lack of oversight also led to failure to gain full approval in the EU for cSSSI, while sales of Zevtera in Switzerland were discontinued in 2010. As a means of compensation, Basilea was awarded $130m in damages from J&J by an arbitral tribunal, which included lost milestones, damages and interest. Ultimately, ceftobiprole was approved in Europe (as Zevtera) for the treatment of community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) excluding ventilator-associated pneumonia (VAP) and sold through various distributors as well as out-licensed in China.

Ceftobiprole an extended spectrum 5th generation cephalosporin

The positive nature of the data in cSSSI data however effectively de-risked further clinical risk in the ABSSSI indication, while the bacteraemia (SAB) indication was identified as a significant unmet need. As a result, Basilea embarked on the Phase 3 development of ceftobiprole for both ABSSSI and SAB with the TARGET and ERADICATE clinical studies.

US Phase 3 development in ABSSSI & SAB

Despite the undoubted frustration at the failure of the original clinical development programme in the US, ceftobiprole has benefited this time from the financial help from BARDA which provides up to circa 70% of the cost of the Phase 3 development programme. Additionally, the commercial longevity of ceftobiprole should benefit from its QIDP status (ABSSSI, SAB & CAP) which will bring an additional five years of data exclusivity in addition to the five years Hatch Waxman exclusivity that comes with a new NCE approval in the US.

Funding from BARDA and QIDP designation has provided longevity

Ceftobiprole as a 5th generation cephalosporin has an extended spectrum of activity against clinically important gram-positive bacteria, including MRSA, PRSP, and *Enterococcus faecalis*. Importantly, it also has activity against susceptible Gram-negative pathogens, including *Citrobacter, Escherichia coli, Enterobacter, Klebsiella, Serratia marcescens,* and *Pseudomonas aeruginosa*. Despite its availability commercially outside the US, ceftobiprole has demonstrated a low propensity to develop resistance.

Extended spectrum and low propensity to cause resistance

Despite the desire for increased use of narrow spectrum antibiotics as we try to improve antibiotic stewardship and reduce the risk of resistance developing, there remains a need for antibiotics which possess broad-spectrum activity as part of empiric therapy against many of the important Gram-positive and Gram-negative pathogens. While many of the ABSSSI infections that result in hospitalisations are caused by Gram-positive bacteria, there remains a not insignificant proportion which involve, at least in part, a Gram-negative

Need for broad spectrum antibiotics in empiric therapy

organism. In addition to Gram-positive coverage, ceftobiprole offers Gram-negative coverage.

Ceftobiprole active on MSSA & MRSA

Much of the recent activity in antibiotic development in the ABSSSI indication has been to improve coverage of resistant Gram-positive MRSA. This has been highly relevant given the emerging resistance to last resort antibiotic vancomycin at least as far as Gram-positive infections are concerned. In this regard, one of the key benefits associated with ceftobiprole is that it is bactericidal and more effective in treating MSSA than vancomycin which is bacteriostatic. The activity against MRSA and MSSA is important given membership of the ESKAPE pathogen group. The ESKAPE pathogens have been highlighted as particularly insidious given their ability to develop rapid resistance to commonly used antibiotics.

Extended coverage particularly relevant to ABSSSI

Historically the treatment of severe skin infections has been the chosen route to initial commercialisation for many antibiotics. This is unsurprising given the increasing incidence and the high number of hospitalisations (750,000 in 2011). The causative bacteria are often Gram-positive (usually MSSA, but also MRSA), and Gram-negative infections can be the culprit. As a result, empiric therapy (often first choice in a busy hospital), optimally requires broader coverage than Gram-positive alone. As a result, the 5th generation cephalosporins potentially offer the requisite profile as a first-choice empiric therapy for severe skin infections.

Multiple new entrants with anti-MRSA activity

The antibiotic field has benefited from the introduction of new antibiotics available complementing the existing classes. These including relatively newer classes such as the oxazolidinones with Sivextro (tedizolid) joining Zyvox (linezolid) offering coverage of resistant strains. However, the oxazolidinones are bacteriostatic with minimal Gram-negative coverage. While daptomycin may offer additional benefits (bactericidal and activity on biofilms), it has a minimal impact on Gram-negative infections, and also poor pulmonary penetration.

Largely analogues from existing classes so future resistance remains an issue

With AMR an important focus for the industry, new antibiotics (largely from existing classes) have emerged. For example, Baxdela (delafloxacin), Nuzyra (omadacycline) and Xenleta (lefamulin), amongst others, in the treatment of severe skin infections, complicated urinary tract infections (cUTIs) and ultimately HAP/VAP. With the exception perhaps of lefamulin (retapamulin available topically for impetigo since 2006), these are all analogues of existing classes that expand the physicians' armamentarium with new agents which have activity against bacteria resistant to similar antibiotics from the

same class. With respect to new antibiotics, Baxdela, Nuzyra and Xerava provide MRSA coverage.

Recent and late-stage development antibiotics

Antibiotic	Class	Route of admin	Spectrum	Indication	New class
Zerbaxa	cephalosporin/beta-lactam	IV	Broad	cUTI, cIAI, HAP/ VAP	No
Avycaz	cephalosporin/beta-lactam	IV	Medium	cUTI, cIAI, HAP/ VAP	No
Vabomere	cephalosporin/beta-lactam	IV	Broad	cUTI, HAP/ VAP	No
Baxdela	fluoroquinolone	IV/oral	Broad	ABSSSI	No
Nuzyra	tetracycline	IV/oral	Broad	ABSSSI, cUTI	No
Xenleta	pluromutilin	IV/oral	Broad	ABSSSI/ CAP	1st systemic
Xerava	tetracycline	IV/oral	Broad	cIAI	No
Fetroja	siderophore cephalosporin	IV	Broad	HAP/ VAP, cUTI, CRE, AP	No
Zemdri	aminoglycoside	IV/oral	Broad	CRE, cUTI, AP	No
Solithera	macrolide	IV/oral	Broad	CAP	No

cUTI, complicated urinary tract infections; cIAI, complicated intra abdominal infections; CAP/HAP/VAP, community, hospital & ventilator acquired pneumonia; ABSSSI, acute bacterial skin & skin structure infections; CRE, carbopenem resistant enterobacteriaceae

Source: Calvine Partners Research

Availability of oral options increases convenience

For omadacycline, unlike the 5th generation cephalosporins, there is the additional prospect of an oral version to complement the intravenous formulation. This should offer patients the potential to continue therapy outside the hospital setting (hospital to home switch), as well as providing a treatment for community acquired bacterial infections, where resistance is a concern.

Ceftaroline offers direct competition but not in SAB

More direct competition in ABSSSI to ceftobiprole comes from another 5th generation cephalosporin, ceftaroline (Teflaro), currently indicated for ABSSSI and community-acquired bacterial pneumonia (but not SAB). Like ceftobiprole, ceftaroline was developed with anti-MRSA activity in mind. However, with first approvals as far back as 2010, ceftaroline enjoys significant lead time advantage in the treatment of severe skin infections. As with previous generations, the spectra of activity versus resistant bacteria has improved to include MRSA and extensively resistant strains such as vancomycin resistance bacteria (VRSA) and vancomycin intermediate *Staphylococcus aureus*.

Increased Gram negative coverage a clear unmet need

With the 5th generation cephalosporins possessing limited activity against Gram-negative bacteria, it is worth highlighting the approval of a novel cephalosporin cefiderocol (Fetroja) indicated for the treatment of cUTI as well as HAP/VAP patients harbouring susceptible Gram-negative infections. Unlike ceftobiprole and ceftaroline, Fetroja does not provide MRSA coverage.

Positive outcome of TARGET unsurprising

SPA designation for Phase 3 programme should de-risk the regulatory pathway

As mentioned previously the registrational clinical programme for ceftobiprole in the US involves two interdependent Phase 3 programmes targeting ABSSSI (TARGET) and SAB (ERADICATE). Both have received a Special Protocol Assessment (SPA) from FDA and a positive result from both is required for approval. The receipt of SPA status should ensure that there are no regulatory issues this time round assuming a positive result from both clinical studies.

TARGET already successfully completed

Of the two, TARGET has been successfully completed as a double-blind, active-controlled, parallel group, noninferiority study comparing ceftobiprole with vancomycin plus aztreonam (for Gram-negative coverage) in the treatment of ABSSSIs. The study incorporated two primary endpoints to satisfy the requirements of both FDA and EMA. The FDA defined primary endpoint was early clinical response in the ITT population 48–72 hours after the start of treatment while the EMA primary endpoint was investigator-assessed clinical success at the test of cure visit, both in the ITT and CE populations.

Positive data with signs of superiority

Looking at the results of TARGET, it was pleasing to see the overtly positive outcome for ceftobiprole, confirming its activity with a >90% response at both the primary and secondary endpoints while meeting the non-inferiority requirements (10% NI margin). In addition, early clinical success was significantly better for ceftobiprole than vanco/aztreonam albeit in the CE population (a secondary FDA endpoint).

Better activity on MSSA as expected

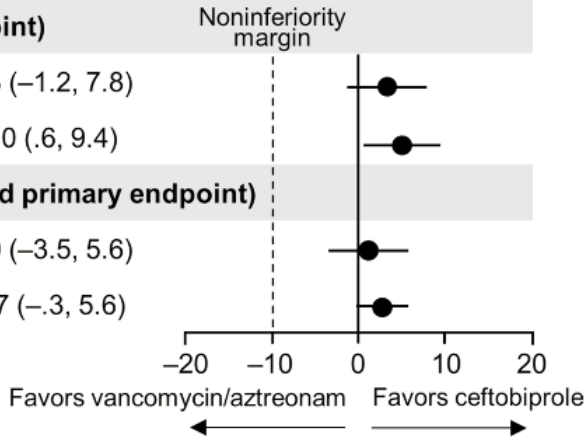
With respect to microbiological eradication in TARGET, it was encouraging to see a statistically significant shorter time to achieve this endpoint with ceftobiprole compared to vanco/aztreonam. Furthermore, although microbiological response rates were generally similar, perhaps unsurprisingly given its bactericidal activity, MSSA patients experienced a higher response rate compared to vanco/aztreonam.

Tolerability acceptable

From a safety perspective side effects appear typical for the well characterised cephalosporin class. Encouragingly, the rates of treatment related AEs were similar between the two groups while patients receiving ceftobiprole experienced a lower rate of severe AEs. Overall tolerability with ceftobiprole has proven to be acceptable with discontinuation rates low (1.8%) for ceftobiprole-related adverse events.

Ceftobiprole compared with vancomycin plus aztreonam in ABSSSI

	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)



Source: Overcash et al, CID

Although anti-MRSA market in ABSSSI more competitive, it's a large market

The positive result of ceftobiprole in TARGET has effectively completed the regulatory journey started with its initial development with J&J. However, over the intervening years, the competitive environment has changed markedly with several new antibiotics available, albeit from existing classes. This suggests a more limited market opportunity in this indication, certainly when compared to the initial timelines of a 2009 expected market introduction. Nevertheless, the 5th generation cephalosporins (ceftobiprole and ceftaroline) offer broader coverage including many important Gram-negative pathogens.

Even a modest market share could be significant

Additionally, the ABSSSI indication remains an important element of the regulatory filing process in the US. Ultimately, this is a large market, and our analysis suggests that even a small market share should generate meaningful revenues for ceftobiprole.

Anticipating a 2023 approval – requires positive SAB study too

For the ABSSSI indication, we believe that pricing will be similar to that achieved by other 5th generation cephalosporins. ABSSSI has a shorter course of treatment than SAB (5-14d), and we have therefore assumed a price of $1200 per treatment. We expect ceftobiprole to reach the market in 2023, taking into account any further COVID-19 related delays in recruitment, as well as the extended duration protocol amendment.

We have probability adjusted sales based on need for two positive studies

Although the ABSSSI indication has been de-risked with a positive TARGET study, we have employed the same probability of success as ERADICATE (65%) in our sales projections given that a positive result from both studies is required for approval. We assume 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.

US Ceftobiprole ABSSSI forecasts

Ceftobiprole sales US ($'000)	2023E	2024E	2025E	2026E	2027E	2028E
Patients available ABSSSI label	3859.69	3898.28	3937.27	3976.64	4016.41	4056.57
growth	1.0%	1.0%	1.0%	1.0%	1.0%	1.0%
% infected with S. aureus	76.0%	76.0%	76.0%	76.0%	76.0%	76.0%
Available patients	2933.4	2962.7	2992.3	3022.2	3052.5	3083.0
Penetration	0.1%	0.6%	0.8%	1.2%	1.6%	2.0%
Patients treated	2.9	17.8	23.9	36.3	48.8	61.7
Price	1,126	1,149	1,172	1,195	1,219	1,243
…growth	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%
Probability	65.0%	65.0%	65.0%	65.0%	65.0%	65.0%
Revenue	**2147.24**	**13272.50**	**18231.11**	**28172.54**	**38697.80**	**49833.09**

Source: Calvine Partners Research

Bacteraemia represents a significant unmet need

Bacteraemia remains problematic – more so when MRSA involved

Bacteraemia is a particularly insidious infection often leading to metastatic infections (such as IE) and complications such as sepsis. It often develops secondary to another site of infection (e.g. vascular catheter) but for many (c25%), the initial site of infection can't be unidentified. For patients with susceptible infections (MSSA), treatment with a beta-lactam antibiotic remains first choice. Undoubtedly, infection with MRSA leads to poorer outcomes with up to 50% mortality in patients with MRSA bacteraemia.

Hygiene initiatives have helped the situation in hospitals

According to the CDC, 80% of MRSA bacteraemia events originate in the community, and while there has been significant progress in reducing hospital onset MRSA bacteraemia, the rate of decline has slowed since 2012. Also, we note that while hospital acquired MRSA bloodstream infections have declined, the same cannot be said for community associated infections.

The prevalence of SAB varies geographically, with developing countries faring significantly worse than their first-world counterparts. In Europe, Southern countries fare worse than

The US SAB market represents a large opportunity for ceftobiprole

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 between 10-30 per 100,000 years in the developed world. This suggests a total SAB population of between 125,000 and 140,000.

Staph aureus a leading cause of bacteraemia

The predominant bacteria associated with bacteraemia include *E. Coli, S. aureus*, *S. pneumoniae* and coagulase negative *staphylococci*. The bacteraemia indication is important given its high and increasing frequency, with *Staph. aureus* a leading cause of bloodstream infections. Bacteraemia associated with *Staph. aureus* generally results in poor outcomes, with complications arising such as infective endocarditis, septic (infectious) arthritis and osteomyelitis. Infective endocarditis, for example, involves infection of the heart surface (which can involve the heart valves), leading to heart failure and abscesses. Death is the usual outcome if patients do not receive adequate antibiotic therapy.

MRSA involvement associated with significantly worse outcomes in SAB

Overall, bacteraemia is associated with mortality rates of 20-30%. This rate has improved only 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. Infection with MRSA is associated with significantly worse patient outcomes, justifying the development of antibiotics such as ceftobiprole. The US is the target market for Basilea, and ceftobiprole with its extended spectrum and potent activity against MRSA, has high commercial appeal we believe.

Need for updated guidelines

IDSA guidelines may look old (2011 although an update is in preparation), but little appears to have changed in the interim with vancomycin the first-choice antibiotic for many. Daptomycin is also approved for SAB and the prescribing label in the US also includes approval for right sided IE.

Shortcomings associated with first line antibiotic therapy

We have previously highlighted the limitations of both of the above agents which includes emerging resistance (and the potential for cross resistance) as well as vancomycin's poor tissue distribution and risk of renal toxicity. Also, there is a clear need for additional antibiotics in SAB with a notable dearth of high-quality controlled studies in this particularly needy patient population. Salvage therapy using a non-approved (off-label) antibiotic has proven to be a last resort approach in those with a persistent infection.

As a result ceftaroline used off label in salvage therapy

Perhaps unsurprisingly, the 5th generation cephalosporin ceftaroline has found off-label use in the treatment of SAB given its approved status (for ABSSSI & community-acquired bacterial pneumonia) in the US. Often this has been as a salvage therapy and in patients with complex bacteraemia. Reassuringly, cure rates have proven to be similar to those in clinical studies with vancomycin and daptomycin.

ERADICATE first double blind study in SAB

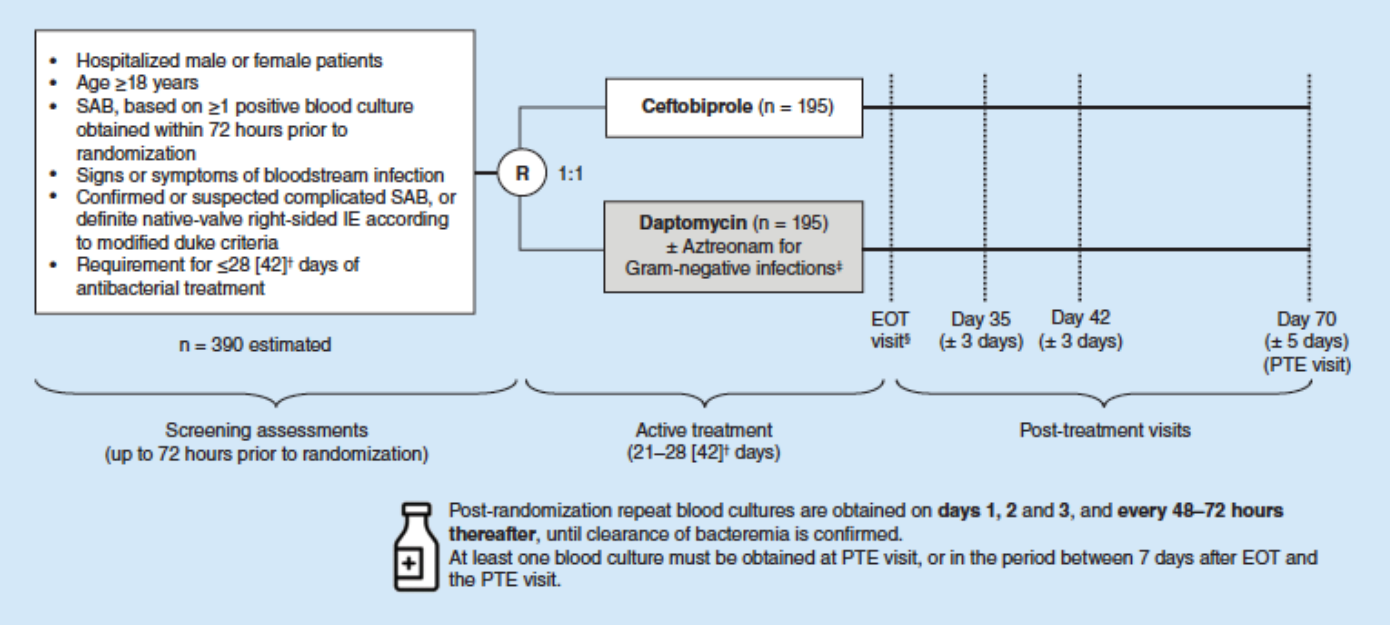
Despite these encouraging results, there is no substitute for well controlled clinical studies, particularly with respect to optimal dosing and long-term treatment. Clearly, this represents a significant opportunity for another 5th generation cephalosporin such as ceftobiprole in the treatment of SAB should it successfully navigate the ERADICATE study and differentiate itself from ceftaroline with an approval and label that contains not only ABSSI but also SAB. Indeed, we suspect that success will provide ceftobiprole with a very strong position for inclusion in relevant guidelines as they evolve.

ERADICATE will compare ceftobiprole to daptomycin

ERADICATE is one of two Phase 3 trials required for FDA approval of ceftobiprole in the US. Target enrolment for ERADICATE is 390 patients, where ceftobiprole is being compared to daptomycin with the option to add aztreonam to daptomycin in order to provide coverage for Gram-negative pathogens if needed in a non-inferiority design, with a non-inferiority margin of 15%. Daptomycin has been chosen as a relevant comparator given its activity in both MSSA and MRSA while its approval in (right sided) IE facilitates the double-blind design of ERADICATE.

The primary endpoint of ERADICATE is evaluating overall success at post-treatment evaluation (day 70 post randomisation +/-5 days). Secondary endpoints include all-cause mortality and microbiological eradication. As we move through enrolment, Basilea has sought to improve the positioning of ceftobiprole by extending the maximum treatment duration from four to six weeks. This extension allows ERADICATE to capture patients with more severe infections such as osteomyelitis and epidural/cerebral abscesses. ERADICATE is anticipated to read out in H1 2022.

ERADICATE study design



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

Difficult patient population but reasons to be encouraged

Preclinical data supports ceftobiprole activity in SAB

As we await the outcome of ERADICATE, it is important to note that the potential of ceftobiprole in the treatment of SAB is supported by preclinical data and emerging clinical data. The preclinical data show rapid clearance of heart valve bacterial infections in models of aortic valve endocarditis and superior efficacy over vancomycin, linezolid and daptomycin.

Case studies also helpful

There have also been case study data reported which have demonstrated the activity of ceftobiprole in infective endocarditis patients (Tascini *et al*., JGAR 2020), albeit in combination with daptomycin (the comparator in ERADICATE). As resistance emerges to approved SAB antimicrobial therapy such as daptomycin, it is unsurprising we believe, that physicians look to alternative approaches where ceftobiprole's activity against both MSSA and MRSA is desirable.

Previous clinical data supportive

Of significant relevance, Basilea previously generated positive data from patients with bacteraemia in the four completed Phase 3 trials in cSSSI, HAP/VAP and CAP. Here, although admittedly in a *post-hoc* analysis 51 patients of the 3031 patients enrolled were found to have *Staph. aureus* bacteraemia. The conclusion was that ceftobiprole is associated with a similar clinical response to the comparators used (vancomycin, vancomycin/ceftazidime, and

linezolid/ceftazidime) with ceftobiprole treated patients benefiting from a trend towards lower 30-day all-cause mortality.

Positive experience with ceftaroline provides positive readthrough

Finally, we have also noted the off-label use of ceftaroline in bacteraemia with apparently promising results. We believe these data provide an important additional source of real-world positive data regarding the 5th generation cephalosporin class. However, despite this highly encouraging observation there is clearly more work to be done with respect to optimising dosing (both dose and frequency). As a result, should ERADICATE be successful, ceftobiprole would be the only beta-lactam antibiotic approved for SAB (including MRSA) with a fully characterised dosing schedule.

SAB key to ceftobiprole commercial success

A positive ERADICATE study and a prescribing label including SAB suggests commercial success. In our analysis, the prescribing label for daptomycin in bacteraemia, recommends therapy to last for between two and six weeks - hence the importance of the recent trial extension for ceftobiprole.

65% probability of success reflects previous data offset by challenging population

Along with the positive real-world experience with ceftaroline we believe that the clinical risk associated with ERADICATE has been reduced. Consequently, we have employed a probability adjustment of 65%, with our expectation that ceftobiprole could achieve a 20% peak penetration of the US bacteraemia market. Ultimately, if successful, we believe that this could be an un-risked peak sales opportunity of $250m. Additionally, we expect the addition of a SAB indication should raise the profile of ceftobiprole with clinicians generally, as a differentiated 5th generation cephalosporin antibiotic. A better profile could have an impact on its use in other infections where MRSA is suspected.

Our forecasts appear conservative but will depend on partner

Patients with SAB usually receive antibiotics for between 2-6 weeks. In our financial model we have assumed conservatively that patients receive treatment for 5 weeks at $6000 per treatment.

US ceftobiprole bactaeremia forecasts

Ceftobiprole sales US ($'000)	2023E	2024E	2025E	2026E	2027E	2028E
Patient available for SA bacteremia label ('000)	140.8	142.2	143.6	145.0	146.5	148.0
…growth	1.0%	1.0%	1.0%	1.0%	1.0%	1.0%
Penetration	1.0%	5.0%	12.0%	15.0%	18.0%	20.0%
Patient treated ('000)	1.408	7.109	17.232	21.756	26.368	29.590
Price $	6,892	7,030	7,171	7,314	7,460	7,609
…growth	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%
Probability	65.0%	65.0%	65.0%	65.0%	65.0%	65.0%
Revenue	**6306.38**	**32484.16**	**80316.45**	**103427.50**	**127861.22**	**146358.47**

Source: Calvine Partners Research

Risks

Basilea's currently marketed products are out-licensed 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).

While the antibiotic Zevtera is already marketed outside of the USA for the treatment of CAP and HAP (excluding VAP), we see the more significant market opportunity in the *Staph aureus* bacteraemia indication. While data from those patients in the four completed Phase 3 trials which suffered from a bacteraemia are supportive of this approach, there is uncertainty associated with this difficult to treat patient population which is reflected in the probability adjustment we have employed. Approval of ceftobiprole in the US requires a positive outcome for both the (lower risk) ABSSSI indication (already achieved) as well as the bacteraemia indication.

Our forecasts suggest that Basilea will self-commercialise ceftobiprole in the US and have burdened the income statement with the costs associated with such an eventuality. Basilea on the other hand has communicated that it will seek to attract a commercial partner for ceftobiprole in the US, and while there is a partnering risk associated with this strategy, we believe that Basilea has a successful track record.

The oncology programmes are also unpartnered. This is a highly competitive field, but we note Basilea's endeavours to differentiate derazantinib, and we would highlight the combination with the checkpoint inhibitors as a starting point.

Our financial forecasts suggest Basilea will experience several years of losses. 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. Consequently, we are forecasting a negative cash position for several years, but recognise that there are many puts and takes to our forecasts. Additionally, we have effectively taxed the company on its first year of profits despite the observation that there are significant tax losses which will significantly reduce the tax burden in the near term.

Financial Model and Summary

R&D focus at Basilea has been on the oncology franchise

The near-term financials at Basilea are well underpinned by sales and royalties received from Cresemba and to a lesser extent Zevtera. Much of this has been deployed to fund the emerging oncology franchise. Over time, the FGFR inhibitor class has proven to be an effective approach in targeting several FGFR driven tumours in a highly targeted fashion. Basilea for its own part has de-risked the biliary cancer indication and is pursuing a combination approach in urothelial and gastric cancers, largely with the checkpoint inhibitor Tecentriq for now, to optimise the positioning of derazantinib. If confirmed in clinical trials, derazantinib offers the intriguing prospect of a targeted FGFR inhibitor which should also act to remove the negative immunosuppressive impact of tumour-associated macrophages, so that checkpoint inhibition becomes a viable option in these patients.

Ceftobiprole potential overlooked for now

These efforts are laudable and will over time lead to a greater appreciation of the oncology expertise in Basilea. At the same time, the baggage associated with early development of the 5th generation cephalosporin ceftobiprole has likely led to many discounting its continued importance. Here we would highlight the clear unmet need resulting in the off-label use of ceftaroline often as a salvage therapy in SAB. SAB remains a problematic infection, particularly so when it involves MRSA, with the risk of life-threatening complications such as IE, sepsis and septic shock.

Positive TARGET and encouraging data in SAB – looking forward to ERADICATE result

While there is perhaps greater uncertainty associated with the outcome of ERADICATE when compared to the positive TARGET result, we believe that there is increasing evidence in support of success here. We have taken into consideration a combination of positive data from preclinical models of SAB (including IE), patients in previous ceftobiprole clinical trials with SAB, as well as the positive experience with off-label ceftaroline use.

Attracting a commercial partner after Phase 3 should prove lucrative

Ultimately, we do not believe that Basilea has the wherewithal or desire to self-market ceftobiprole in the US. Basilea's business model to date has involved out-licensing to appropriate commercial partners with strong existing franchises.

Success would significantly boost the existing anti-infectives franchise

With the majority of the R&D funding associated with ceftobiprole paid for by BARDA and the commercialisation likely to be funded by a commercial partner, ceftobiprole has the opportunity to flesh out the anti-infectives franchise complementing the excellent performance of anti-fungal Cresemba.

As a completed Phase 3 pipeline asset, ceftobiprole should represent a very valuable asset. Despite the reticence of the major pharma companies to participate in new antibiotic

Market overly gloomy on prospects for differentiated antibiotics - results and partner would change this

development we suspect that it will be the owners of the current crop of anti-MRSA antibiotics which would be interested in adding ceftobiprole to their anti-infectives franchise. A cursory glance suggests that Merck & Co (owner of Cubicin) and Allergan (owner of Teflaro) could be potential partners for a relatively novel 5th generation cephalosporin.

Potential to increase geographic availability but US the key

In our sales forecasts for ceftobiprole, this review has been limited to prospects for the US alone. We note that the clinical trial design should be supportive also regarding other markets including Europe and the UK. The opportunity for Zevtera in its approved nosocomial pneumonia indication may be large, and ceftobiprole offers a broad-spectrum coverage which potentially simplifies empiric therapy, particularly where MRSA is suspected. However, financial performance to date has been muted. We suspect that the lack of a specific VAP indication is unhelpful with respect to market perception. Within the nosocomial pneumonia opportunity, VAP is generally seen as the more urgent medical need where the presence of multidrug resistant bacteria is associated with a significantly worse outcome, and where 50% of antibiotic usage in the ICU lies.

Despite our earlier suggestion that Basilea will seek to out-license ceftobiprole, our financial model continues to depict a scenario where end-market sales are received by Basilea. Given the uncertainty regarding the outcome of ERADICATE, the identification of a suitable partner and the financial terms, we have chosen to wait until announcement of a commercial partner for greater clarity. This is with respect not only to the terms of any deal, but also the strength of partner capabilities (existing anti-infectives franchise for example) which will be important in influencing our view on the likely future financial reward to Basilea. To be fair we have included only probability adjusted revenues while burdening the income statement (and valuation) with the full extent of the selling costs. Indeed, we would anticipate Basilea receiving a significant up-front payment which would clearly strengthen the existing cash resources of the company.

Basilea Income Statement (CHF'000)

Year to December	2019A	2020A	2021E	2022E	2023E	2024E	2025E
Total revenue	**134381**	**127629**	**132743**	**133939**	**150134**	**193186**	**257229**
COGS	(18,868)	(24,054)	(25,221)	(25,448)	(26,273)	(30,910)	(33,440)
Gross profit	**115,513**	**103,575**	**107,522**	**108,491**	**123,861**	**162,276**	**223,789**
Gross margin	86.0%	81.2%	81.0%	81.0%	82.5%	84.0%	87.0%
R&D	(102,662)	(97,410)	(96,902)	(93,757)	(87,078)	(80,365)	(85,400)
SG&A	(30,051)	(29,422)	(31,858)	(31,074)	(33,029)	(36,705)	(41,157)
Total cost and operating expenses	(151,581)	(150,886)	(153,982)	(150,280)	(146,381)	(147,980)	(159,996)
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)**	**(21,239)**	**(16,341)**	**3,753**	**45,205**	**97,233**
Finance income	28	104	0	161	167	158	9
Finance expense	(6,424)	(7,589)	(7,456)	(7,480)	(3,225)	(3,225)	(3,225)
Other financial income	1,583	2,057	0	0	0	0	0
Other financial expense	(369)	(1,017)	0	0	0	0	0
Underlying PBT	(22,382)	(29,702)	(28,695)	(23,660)	696	42,139	94,016
PBT IFRS	(22,382)	(14,667)	(28,695)	(23,660)	696	42,139	94,016
Loss before tax	(22,382)	(29,702)	(28,695)	(23,660)	696	42,139	94,016
Tax	(40)	(55)	(60)	(60)	(99)	(5,984)	(13,350)
Underlying net income	**(22,422)**	**(29,757)**	**(28,755)**	**(23,720)**	**597**	**36,155**	**80,666**
Net income US GAAP	**(22,422)**	**(14,722)**	**(28,755)**	**(23,720)**	**597**	**36,155**	**80,666**
EPS Basic (CHF)	(2.09)	(1.43)	(2.80)	(2.10)	0.05	3.20	7.15
EPS Diluted (CHF)	**(2.08)**	**(1.36)**	**(2.55)**	**(2.10)**	**0.05**	**3.20**	**7.15**

Source: Calvine Partners Research

Basilea Cash Flow Statement (CHF'000)

Year to December	2019E	2020A	2021E	2022E	2023E	2024E
Net profit/(loss)	(22,422)	(14,722)	(28,755)	(23,720)	597	36,155
Depreciation and amortization	1,639	1,190	595	621	650	682
Gain on disposal of assets, net	0	(15,035)	0	0	0	0
Stock-based compensation	3,048	3,525	0	0	0	0
Interest and accretion of debt issuance cost	758	1,670	800	534	0	0
Accounts receivable	(2,457)	(1,657)	(1,203)	(2)	(891)	(2,368)
Other receivables	8,909	(1,657)	0	0	0	0
Inventories	(4,142)	(2,618)	(5,884)	2,234	(2,698)	(7,172)
Accounts payable	378	6,394	30	(131)	(263)	(93)
Deferred revenue	(45,626)	(33,630)	(20,000)	0	0	0
Accruals and other current liabilities	693	(1,425)	0	0	0	0
Other operating cash flow items	(4,614)	4,639	(2,300)	0	0	0
Net cash provided by/used in operating activities	**(63,836)**	**(53,326)**	**(56,717)**	**(20,463)**	**(2,605)**	**27,203**
Cash flow from investing activities						
Payments for short-term investments	(20,000)	(81,023)	0	0	0	0
Maturities of short-term investments	50,000	30,000	81,023	25,507	0	0
Payments for long-term investments	(30,000)	0	0	0	0	0
Proceeds from sale of assets	0	18,325	0	0	0	0
Investments in tangible assets	(294)	(1,823)	(525)	(578)	(636)	(699)
Investment in intangible assets	(110)	(442)	(332)	(332)	(332)	(332)
Net cash used in/provided by investing activities	**(404)**	**(34,963)**	**80,165**	**24,597**	**(968)**	**(1,032)**
Cash flow financing activities						
Net proceeds from exercise of stock options	37	1,322	0	0	0	0
Repayment of Convertible loan	0	(53,634)	0	(150,640)	0	0
Issuance of Convertible bonds	0	93,892	0			
Purchase of treasury shares	1,272	3,487				
Issuance of new shares			43,005			
Net cash provided by financing activities	**1,309**	**45,067**	**43,005**	**(150,640)**	**0**	**0**
Effect of exchange rate changes on cash and cash equivalents	67	(758)	0	0	0	0
Net change in cash and cash equivalents	(62,864)	(43,980)	66,453	(146,507)	(3,573)	26,172
Cash and cash equivalents at beginning of period	173,908	111,044	66,256	132,709	(13,798)	(17,371)
Cash and cash equivalents at end of period	**111,044**	**67,064**	**132,709**	**(13,798)**	**(17,371)**	**8,801**

Source: Calvine Partners Research

Basilea Balance Sheet (CHF'000)

Year to December	2019A	2020A	2021E	2022E	2023E	2024E
Non-current assets						
Tangible assets, net	5,162	2,627	2,890	3,179	3,497	3,846
Intangible assets, net	372	672	672	672	672	672
Long-term investments	30,000	0	0	0	0	0
Other non-current assets	1,073	2,967	2,967	2,967	2,967	2,967
Total non-current assets	36,607	6,266	6,529	6,818	7,136	7,485
Current Assets						
Cash and cash equivalents	109,024	60,749	132,709	(13,798)	(17,371)	8,801
Short-term investments	22,020	106,530	25,507	0	0	0
Accounts receivable	6,242	8,710	7,365	7,367	8,257	10,625
Other receivables	22,053	23,684	23,684	23,684	23,684	23,684
Inventories	18,569	21,192	24,549	22,314	25,012	32,185
Other current assets	6,952	2,663	2,663	2,663	2,663	2,663
Total current assets	184,860	223,528	216,476	42,230	42,246	77,957
Total assets	**221,467**	**229,794**	**223,005**	**49,048**	**49,381**	**85,443**
Current liabilities						
Accounts payable	6,765	13,151	5,496	5,364	5,101	5,007
Deferred revenue	32,873	2,556	0	0	0	0
Accruals and other current liabilities	35,856	34,454	34,454	34,454	34,454	34,454
Total current liabilities	75,494	50,161	39,950	39,818	39,555	39,461
Non-current liabilities						
Convertible senior unsecured bonds	197,740	239,668	249,340	99,234	99,234	99,234
Deferred revenue, less of current portion	16,471	13,158	0	0	0	0
Other non-current liabilities	24,722	28,853	28,853	28,853	28,853	28,853
Total non-current liabilities	238,933	281,679	278,193	128,087	128,087	128,087
Total liabilities	**314,427**	**331,840**	**318,143**	**167,905**	**167,642**	**167,548**
Shareholders equity (deficit)						
Share capital	11,882	11,922	11,922	11,922	11,922	11,922
Additional paid-in capital	927,342	982,438	1,019,438	1,019,438	1,019,438	1,019,438
Accumulated other comprehensive loss	(24,555)	(27,252)	(27,252)	(27,252)	(27,252)	(27,252)
Treasury shares held by a subsidiary	(5,963)	(52,766)	(52,766)	(52,766)	(52,766)	(52,766)
Loss carried forward	(979,244)	(1,001,666)	(1,016,388)	(1,045,143)	(1,068,863)	(1,068,266)
Net loss for the year	(22,422)	(14,722)	(28,755)	(23,720)	597	36,155
Total shareholders' equity (deficit)	(92,960)	(102,046)	(93,801)	(117,521)	(116,924)	(80,769)
Total liabilities and equity (deficit)	**221,467**	**229,794**	**224,341**	**50,384**	**50,718**	**86,779**

Source: Calvine Partners Research

Disclosures

This publication has been commissioned and paid for by Basilea Pharmaceutica and as defined by the FCA is not independent research. This report is considered to be a marketing communication under FCA Rules, and it has not been prepared under the laws and requirements established to promote the independence of investment research and it is not subject to any prohibition on dealing ahead of the dissemination of investment research. This information is widely available to the public.

This report in the United Kingdom is directed at investment professionals, certified high net worth individuals, high net worth entities, self-certified sophisticated investors, eligible counterparties as defined by Financial Services and Markets Act 2000 (Financial Promotion) Order 2000. The report may also be distributed and made available to persons to whom Calvine Partners is lawfully permitted. This publication is not intended for use by any individual or entity in any jurisdiction or country where that use would breach law or regulations, or which would subject Calvine Partners or its affiliates to any registration requirement within such jurisdiction or country.

Calvine Partners may provide, or seek to provide, services to other companies mentioned in this report. Partners, employees, or related parties thereof may hold positions in the companies mentioned in the report subject to Calvine Partners' personal account dealing rules.

Calvine Partners has only used publicly available information believed to be reliable at the time of this publication and made best efforts to ensure that the facts and opinions stated are fair, accurate, timely and complete at the publication date. However, Calvine Partners provides no guarantee concerning the accuracy or completeness of the report or the information or opinions within. This publication is not intended to be an investment recommendation, personal or otherwise, and it is not intended to be advice and should not be treated in any way as such. Any valuation estimates, such as those derived from a discounted cash flow, price multiple, or peer group comparison, do not represent estimates or forecasts of a future company share price. In no circumstances should the report be relied on or acted upon by non-qualified individuals. Personal or otherwise, it is not intended to be advice and should not be relied on in any way as such.

Forward-looking statements, information, estimates and assumptions contained in this report are not yet known, and uncertainties may cause the actual results, performance or achievements to be significantly different from expectations.

This report does not constitute an offer, invitation or inducement to engage in a purchase or sale of any securities in the companies mention. The information provided is for educational purposes only and this publication should not be relied upon when making any investment decision or entering any commercial contract. Past performance of any security mentioned is not a reliable indicator of future results and readers should seek appropriate, independent advice before acting on any of the information contained herein. This report should not be considered as investment advice, and Calvine Partners will not be liable for any losses, costs or damages arising from the use of this report. The information provided in this report should not be considered in any circumstances as personalised advice.

Calvine Partners LLP, its affiliates, officers or employees, do not accept any liability or responsibility with regard to the information in this publication. None of the information or opinions in this publication has been independently verified. Information and opinions are subject to change after the publication of this report, possibly rendering them inaccurate and/or incomplete.