EDISON

Basilea Pharmaceutica

Focus on oncology assets

Oncology product portfolio to drive future growth

Pharma & biotech

Basilea has successfully brought two anti-infective drugs to the market: Cresemba (severe mould infections) and Zevtera (bacterial infections). With the commercialisation of both assets largely in the hands of partners and Zevtera's Phase III US clinical programme underway, we turn our focus to the next pillar of growth, the oncology portfolio. The recent deal with ArQule (in-licensing of Phase II product, derazantinib) means Basilea now has three diversified, early/mid-stage clinical assets targeting cancer resistance in its portfolio offering. We value Basilea at CHF119/share.

Year end	Revenue (CHFm)	PBT* (CHFm)	EPS* (CHF)	DPS (CHF)	P/E (x)	Yield (%)
12/16	66.0	(50.9)	(5.06)	0.0	N/A	N/A
12/17	101.5	(18.9)	(1.78)	0.0	N/A	N/A
12/18e	113.6	(35.0)	(3.24)	0.0	N/A	N/A
12/19e	137.3	(29.4)	(2.72)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles, exceptional items and share-based payments.

Derazantinib shoring up the oncology pipeline

In April 2018, Basilea announced the in-licensing of the worldwide (ex-Greater China) rights to ArQule's derazantinib, a tyrosine kinase inhibitor (pan FGFR) with potential utility across a range of cancers that molecular test positive for FGFR genetic aberrations. Derazantinib's most advanced indication is intrahepatic cholangiocarcinoma (iCCA, bile duct cancer). Interim data from the Phase II registration trial in iCCA are anticipated in H119 and Basilea plans to start Phase II development in FGFR-driven solid cancer types in H219.

Targeting cancer resistance

Derazantinib is a complementary addition to Basilea's oncology portfolio, which consists of innovative, targeted therapies for resistant cancer subtypes. Its existing oncology pipeline is moving towards proof-of-concept clinical trials: BAL101553, a novel tumour checkpoint controller (Phase I/II for solid tumours); and BAL3833, a dual targeting kinase inhibitor which is being developed to address BRAF inhibitor resistance in solid tumours (including melanoma) as well as RAS-driven tumours.

Glioblastoma data expected end 2018

One of three ongoing Phase I/IIa BAL101553 studies has been expanded into a Phase IIa to evaluate efficacy (48-hr infusion, weekly) in recurrent glioblastoma and platinum-resistant/refractory ovarian cancer. Completion of patient recruitment in the ongoing separate arm of the oral (daily) Phase I/Ia in recurrent glioblastoma are expected by end 2018.

Valuation: rNPV of CHF1,285m or CHF119/share

Our revised valuation of CHF1,285m or CHF119/share (vs CHF1,231m previously) reflects the inclusion of derazantinib for iCCA in our model (peak sales of $59.4m), and is largely based on Cresemba (worldwide) and antibiotic Zevtera (ex-US), plus net cash of CHF114.5m at 31 December 2017. We also include risk-adjusted contributions for Zevtera US, BAL101553 and BAL3833. Further progression of the oncology assets would drive upgrades to our valuation.

16 July 2018

Price	**CHF67.40**
Market cap	**CHF795m**
	US$1.00/CHF
Net cash (CHFm) at 31 December 2017	114.5
Shares in issue	11.8m
Free float	91.46%
Code	BSLN
Primary exchange	SIX
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	(4.1)	(0.9)	(17.4)
Rel (local)	(6.6)	(1.8)	(16.1)
52-week high/low	CHF86.3		CHF65.0

Business description

Basilea Pharmaceutica is focused on anti-infectives and oncology. Its marketed products are Cresemba (an antifungal), and Zevtera (an anti-MRSA broad-spectrum antibiotic). The R&D pipeline includes three clinical-stage assets for cancer resistance.

Next events

Zevtera initiate Phase III SAB US study	Mid-2018
Data from the oncology pipeline	2018/19

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Edison profile page

Basilea Pharmaceutica is a research client of Edison Investment Research Limited

Investment summary

Company description: Focus on resistance

Basilea Pharmaceutica is a Switzerland-based biopharmaceutical company with a focus on developing innovative anti-infective agents and oncology treatments that target drug resistance (Exhibit 1). Basilea has two approved hospital products, Cresemba and Zevtera. Numerous commercial partnerships are in place for both assets (Exhibit 6). The in-licensing of late-stage oncology asset derazantinib from ArQule has bolstered Basilea's oncology R&D portfolio to three clinical-stage drug candidates. We anticipate steady newsflow on oncology assets from late 2018 through to 2020 to validate the R&D strategy, which in turn could lead to a significant licensing deal. This note focuses on the scientific rationale for Basilea's R&D efforts for novel mechanism-of-action oncology drugs. Basilea was spun out of Roche in 2000 and to date has raised around CHF925m net (including initial funding from Roche, a private placement, an IPO, a rights offer and a convertible bond issue). Basilea's headquarters are in Basel and it employs c 230 people.

Valuation: Risk-adjusted NPV of CHF1,285m or CHF119/share

We value Basilea at CHF1,285m or CHF119/share (from CHF1,231m previously) using a risk-adjusted NPV analysis based on Cresemba (worldwide) and antibiotic Zevtera (ex-US), plus net cash of CHF114.5m at 31 December 2017. Additionally, we have rolled forward our DCF and updated USD/CHF exchange rate. We also include risk-adjusted contributions for Zevtera US and Phase II asset BAL101553 for solid tumours including glioblastoma and Phase I/IIa asset BAL3833 for BRAF-resistant solid tumours including malignant melanoma. Our revised valuation reflects the inclusion of derazantinib for iCCA in our model (CHF2/share). All our other assumptions remain unchanged. Our valuation is weighted to commercially available assets Cresemba and Zevtera. Further progression of the oncology assets would drive upgrades to our valuation. This includes positive proof-of-concept data and progression into Phase III development across a range of cancer subsets.

Sensitivities: Commercialisation is key

The key sensitivities for Basilea relate to successful commercialisation (largely through respective partners) of both Cresemba and Zevtera (where approved), progress with the Phase III US Zevtera trials and crystallising value from the oncology pipeline. Success for Zevtera and Cresemba is largely in the hands of existing, or prospective, partners where we have limited visibility. For the oncology assets, key risks relate to drug development, and failure of one of more trials could lead to termination of the programme.

Financials: Cash runway beyond 2019

We believe that Basilea's gross cash (including financial investments) of CHF311m at 31 December 2017 should be sufficient to fund operations beyond 2019, even excluding future potential deals for either Zevtera in the US or the oncology pipeline. Profitability will be driven by royalties and milestones on sales of Cresemba worldwide and Zevtera in Europe/ROW. We assume an uptick in R&D spend in 2018/19 owing to Basilea's potential contribution towards the Zevtera US Phase III clinical development, funding the derazantinib iCCA and FGFR fusion solid cancers in addition to the cost of the ongoing BAL101553 and BAL3833 trials.

Cancer resistance products primed to generate value

In addition to its commercially launched anti-infectives, Basilea also has an early- to mid-stage clinical pipeline focused on oncology products that target resistance to current therapies. These include BAL101553 (solid tumours including glioblastoma and ovarian cancer) and BAL3833 (solid tumours), with both assets expected to read out initial data by year-end (BAL101553 Phase I in recurrent GBM, and Phase I dose escalation study for BAL3833in solid tumours). The recent in-licensing of derazantinib adds a complementary oncology asset that targets subtypes of cancers, which arise from FGFR genetic aberrations. Interim analysis data from the Phase II registrational trial in iCCA are expected in early 2019; full data are expected in 2021.

Cancer is a complex disease, both in how it arises and how it evades treatment options in time through multiple mutations. Basilea's R&D efforts are targeting a different part of cancer development and prolongation cycle for a range of cancers (Exhibit 1). Accelerated development (breakthrough therapy designation) could be possible for some indications where current treatments are limited (eg derazantinib for iCCA BAL101553 for refractory glioblastoma or platinum resistant/refractory ovarian cancer).

Exhibit 1: Overview of Basilea's R&D pipeline

Product	Indication	Status	Comments
Derazantinib	Intrahepatic Cholangiocarcinoma (iCCA)	Phase II	Registrational trial (orphan drug designation by FDA and EMA). Interim results expected H119.
	Solid tumours	Phase II	Start 2019.
BAL101553	Treatment-refractory solid tumours	Phase IIa (IV)	Ongoing 48-hour IV infusion.
	Glioblastoma	Phase I/II (oral)	Separate arm of the solid tumour Phase I/IIa trial enrolling, results expected end 2018.
	Glioblastoma and ovarian cancer	Phase IIa (IV)	Expansion part of the ongoing Phase I/IIa study (48-hour infusion) in platinum-resistant or refractory ovarian cancer and resistant GBM.
	Newly diagnosed GBM	Phase I	Oral in combination with radiotherapy. This trial has been initiated by The Adult Brain Tumor Consortium (ABTC).
BAL3833	Treatment-refractory solid tumours including metastatic melanoma and RAS-driven cancers	Phase I	Data at end 2018 are a possibility.

Source: Edison Investment Research, corporate presentations

Overview of oncology strategy

Basilea's approach to the development and commercialisation of its oncology portfolio will depend on the clinical profile of its assets and whether data are supportive of use in a wider range of cancer indications. In the near term we model that Basilea will develop BAL101553 (solid tumours including glioblastoma and ovarian cancer) and BAL3833 (malignant melanoma) to Phase IIb proof-of-concept data. Given the potential across a wide range of tumour types and thus the possible requirement for multiple late-stage clinical trials, Basilea could elect to partner these assets to enhance economic value. For derazantinib, while the overall strategy will again depend on its potential across different cancer indications, we model that Basilea elects to market and distribute the drug for iCCA in the US through its Zevtera US infrastructure (which will likely be built up following the Phase III ABSSSI and SAB data). We anticipate further in-licensing of assets to further bolster the oncology pipeline.

Derazantinib (ARQ 087) beefs up oncology pipeline

Basilea announced in April 2018 that it had in-licensed the worldwide ex-China, Hong Kong, Macau and Taiwan (Greater China) rights to research and develop, manufacture and commercialise ArQule's derazantinib worldwide (Basilea paid $10m upfront with up to $326m in milestones payable, in addition to tiered royalties starting in the single digits going into double-digit royalties). ArQule had already licensed derazantinib's Greater China rights to Sinovant Sciences. This small-molecule, oral drug therapy is in registrational Phase II trials for iCCA, a form of bile duct cancer.

We expect Basilea to start Phase II trials in other FGFR-driven cancers in 2019. Both the FDA and EMA have granted ArQule orphan drug designation for iCCA, which translates into longer exclusivity periods. We currently assume a US/EU5 launch in 2023 following a traditional development path including a Phase III trial. However, we note that, depending on the strength on the Phase II data, an accelerated approval before this date could be a possibility. Interim analysis of data on 40 patients from the Phase II registrational trial is expected in mid-2019.

Highly selective FGFR inhibitor

Derazantinib is a selective and potent pan-FGFR (fibroblast growth factor receptor) inhibitor (FGFR1, FGFR2, FGFR3 and, to a lesser degree, FGFR4) anticipated to have efficacy in tumours that test positive for FGFR fusion mutation biomarker. FGFR is a tyrosine kinase signalling pathway that is normally involved in biologic processes including embryonic development, tissue repair and angiogenesis. FGFR may be upregulated in various tumour cell types leading to tumour cell differentiation and proliferation, tumour angiogenesis, and consequently tumour cell survival. Inhibition of the FGFR receptors aims to prevent uncontrolled proliferation of the tumour cells. There are multiple oncogenic driver alterations in the FGFR pathway including gene amplification, mutation, translocation and fusion. The complicated genetic changes in FGFR affect multiple tumour types (at low incidence rates and ongoing tumour analysis at both research and commercial levels is increasing working knowledge in the FGFR aberration space).

Several FDA approved tyrosine kinase inhibitors have now been identified as FGFR inhibitors – regorafenib (advanced CRC and drug-resistant GIST), ponatinib (drug resistant CML and Philadelphia chromosome-positive ALL) and pazopanib (renal carcinoma and sarcoma). However, as these non-selective, multi-kinase inhibitors have demonstrated limited response in FGFR-mutated cancers, it is hypothesised that multi-kinase activity limits the therapeutic doses required for FGFR inhibition due to dose-limiting toxicities mediated through blocking other kinase pathways.

Therefore, such second-generation selective FGFR inhibitors (BridgeBio's BGJ398 and Janssen's erdafitinib) are being developed together with biomarker strategies. Selectivity to FGFR should enable higher doses, and thus better target and therapeutic coverage. Molecular profiling data of cancer patients for FGFR aberrations by Helsten et al's The FGFR landscape in cancer revealed that FGFR aberrations were found in 7.1% of cancers, with 66% of the aberrations being gene amplification, 26% mutations and 8% rearrangements. In this patient population (4,853 tumours were analysed by next-generation sequencing) the most common cancers affected were bladder/ureter (32% FGFR aberrant), breast (185), endometrial (1,350) and ovarian cancer (9%).

Cholangiocarcinoma's rare cancer type with poor prognosis

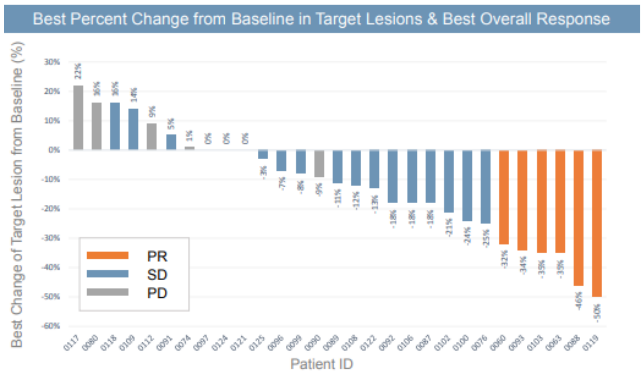
Derazantinib's most advanced indication is for intrahepatic cholangiocarcinoma (second line for FGFR2 fusion iCCA), a rare cancer that affects the biliary tract located in the liver. Cholangiocarcinoma is an uncommon and aggressive malignancy that arises from the epithelial cells of the biliary tract (a system of vessels that link up the gallbladder and liver to aid in the secretion of bile). These tumours may arise anywhere along the intrahepatic or extrahepatic biliary tree (located in or just outside the liver). iCCA, a form of biliary tract cancer, is the second most common primary malignancy of the liver representing 10-20% of all primary liver tumours. During the past 40 years, the US incidence of iCCA has risen to 2.1 per 100,000 in western countries (~6,500 cases per year in the US). However, the true incidence could be higher. The use of molecular diagnostic tests for the identification of targeted mutations (DH1/2 mutations10 and FGFR2 fusions) has in part improved the ability to diagnose some of these tumours. Although a substantial number of patients do not have identifiable risk factors, those for developing iCCA include infectious diseases (viral hepatitis, liver flukes), uncommon biliary tract diseases such as PSC (primary sclerosing cholangitis) metabolic syndrome, lifestyle factors (alcohol and smoking) and cirrhosis.

Around 10% of patients that present with early stage disease may be cured by full liver resection. However, cholangiocarcinoma presents a major diagnostic and treatment challenge, with the majority of patients representing late-stage with surgically unresectable disease and survival prognosis of less than a year (based on palliative chemotherapy with gemcitabine and a platinum agent). While there are currently no approved targeted therapies for iCCA, the discovery of FGFR2 fusions in ~10-20% of patients could change the treatment paradigm for these patients. While small patient populations in iCCA are expected, there is an unmet need and thus the FDA and EMA have granted orphan drug designation. Orphan drug status can provide financial incentives such as market exclusivity (7.5 years from approval in the US, 12 years in the EU), reduced R&D costs (eg through tax credits, R&D grants) and substantial pricing incentives.

Encouraging Phase I/II trial iCCA data so far

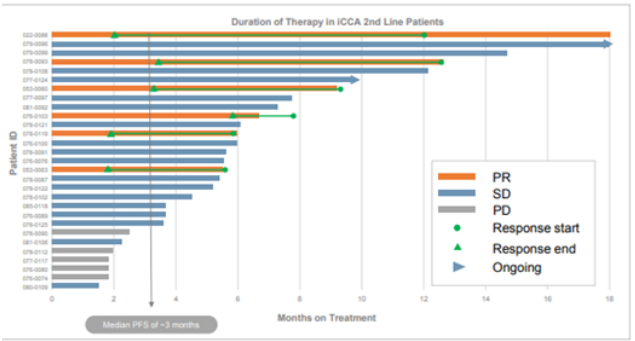
In its Phase I/II study in second-line FGFR2 fusion-positive iCCA patients, 21% achieved a response as defined by stable disease (SD), partial response (PR) or overall survival (OR), which translates to three times the rate observed with chemotherapy (7.7%), and 83% achieved disease control rate. In terms of safety, ArQule notes that the data show a best-in-class safety profile with continuous oral QD dosing schedule* and low discontinuation rate due to adverse events (AEs).

Exhibit 2: Derazantinib Phase I/II POC in iCCA



Source: ArQule corporate presentations

Exhibit 3: Derazantinib Phase I/II POC in iCCA – durable responses



Source: ArQule corporate presentations

Following this encouraging Phase I/II proof-of-concept data in iCCA ,ArQule initiated the derazantinib registrational Phase II trial in second-line iCCA (ClinicalTrials.gov Identifier: (NCT03230318) in November 2017. The open-label, single-arm study is anticipated to recruit ~100 patients with tumours harbouring FGFR2 gene fusions (as identified by fluorescence in situ hybridization testing) across 16 clinical sites (the US, Canada and Italy). The primary endpoint being evaluated is overall response rate (ORR) timeframe up to 32 weeks by central radiology review, as per RECIST v1.1 criteria. The estimated study completion date is September 2020 and interim analysis data based on 40 patients are expected in H119.

Phase I/II solid tumours study data to drive Phase II programme

The ongoing Phase I/II study in patients with advanced solid tumours with FGFR genetic alterations (n=109) is due to complete in December 2018, with data likely in early 2019. The trial does include iCCA patients, but more of interest is derazantinib's safety and preliminary efficacy data in patients with other solid tumour types. Depending on the results, we anticipate Basilea to explore additional derazantinib clinical trial programmes focusing on tumour subtypes that are positive for FGFR fusion mutation biomarkers. Examples of such cancers include bladder, breast, gastric and lung cancer. The width and depth of the Phase IIb/III clinical programme will become clearer as the Phase IIa trial in solid tumours reads out, and as Basilea and its peers deepen the understanding of

FGFR aberrations and how this relates to patient stratification in this increasingly relevant scientific area.

Deal economics and sales potential

Under the terms of the deal, Basilea has made an upfront payment of $10m to ArQule for the exclusive licence for all indications ex-Greater China. Furthermore, a $3m milestone could be payable if the Phase II derazantinib second-line iCCA meets predetermined milestones before its conclusion. We note that under certain conditions ArQule could have the opportunity to commercialise derazantinib directly in the US. However, we note that this is at Basilea's discretion. ArQule will be eligible to receive single to double, sliding scale-digit, tiered royalties on net sales, plus up to $326m in regulatory and sales milestones. We anticipate these milestones to be more heavily weighted to sales-related milestones for other indications (including solid tumours). We anticipate that small milestones will be payable (regulatory and sales) relating to the iCCA indication. Given its current stage of development, we model derazantinib for the second-line iCCA indication only. We model peak sales of $59.4m in the US and top EU5. In the US we assume derazantinib is commercialised and marketed by Basilea through the establishment of the US marketing infrastructure that it intends to build for Zevtera (contingent on positive US Phase III trial results and US approval). We note that Basilea may need to hire a small but targeted oncology salesforce to target the specialist oncologists.

Competitive landscape

The most advanced competitor assets (selective FGFR inhibitors) in development are:

- BridgeBio's BGJ398 (oral, selective, ATP competitive pan-FGFR inhibitor) is currently in Phase II clinical trials for advanced cholangiocarcinoma with FGFR genetic alterations (40 patients with FGFR2 gene fusion/translocation and 15 patients with other FGFR alterations), bladder cancer and recurrent glioblastoma multiforme. BridgeBio in-licensed the drug from Novartis in January 2018.
- Janssen's erdafitinib (oral pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor). BTD granted for metastatic urothelial cancer (Phase II interim data estimated in October 2019). This drug is also being studied across multiple tumour types.

The relevance of the competitive landscape is important, as competitor trial data will widen all participant knowledge in this novel field of targeted therapy.

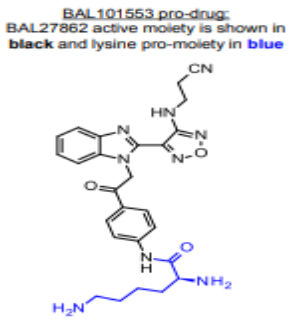
BAL101553 novel tumour checkpoint controller

BAL101553, a novel, small-molecule tumour checkpoint controller, is being evaluated in Phase I/IIa clinical trials in advanced solid tumours. The trial design includes evaluation of the drug once a day orally or as an intravenous infusion (over two hours and over 48 hours weekly). The rationale is to explore the drug's pharmacokinetic and pharmacodynamic profile in different dosing settings to maximise its potential utility. For example, the oral daily (lower doses) could enable it to be used as backbone therapy in combination with other therapies (such as immunotherapy, targeted therapy), whereas resistant cancers may benefit from longer exposure through intravenous administration.

BAL101553 has shown anti-cancer activity in diverse preclinical models that are refractory to standard therapies. It is a highly water-soluble, lysine prodrug of BAL27862. Once administered into the body, BAL101553 is converted to the active form (Exhibit 4). BAL27862 has been observed to affect tumour blood supply in preclinical models and shown to activate a checkpoint involved in preventing cell proliferation; therefore, it could have utility across multiple tumour types. BAL27862 has also been shown to have penetration into the brain.

BAL27862 is a novel microtubule-destabilizing drug, which induces tumour cell death through activation of a checkpoint important for tumour cell division. It targets microtubules, but with a binding site and mechanism of action distinct from that of currently approved microtubule-targeting agents (MTA) such as Taxol, Taxotere, Abraxane, Jevtana and the Vinca alkaloids. Specifically, BAL27862 binds the colchicine site of tubulin with distinct effects on microtubule organisation, resulting in the activation of the "spindle assembly checkpoint", which promotes tumour cell apoptosis (Exhibit 5). At present, there are no approved drugs that target the BAL27862 binding site. Other drug effects include tumour hypoxic adaptation and vascularisation (BAL27862 interferes with hypoxia-inducible factor-1 alpha stabilisation and downstream VEGF secretion). In preclinical models BAL101553 (IV and oral formulations) in combination with anti-VEGFR drug Avastin (Roche) had an additive impact on tumour necrosis and functional tumour vasculature compared to monotherapy.

Exhibit 4: BAL101553, a prodrug of the active moiety BAL27862



Source: Basilea Pharmaceutica

Exhibit 5: BAL27862 activates "spindle assembly checkpoint", which promotes tumour cell death

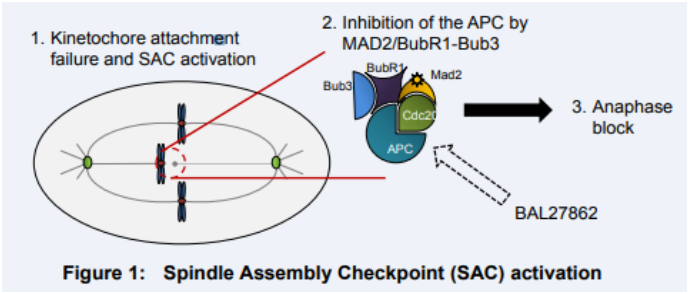


Figure 1: Spindle Assembly Checkpoint (SAC) activation

Source: Basilea Pharmaceutica

Preclinical models reveal that BAL27862's anti-proliferative effects are total exposure driven (ie area under the concentration-time curve [AUC], which reflects the actual body exposure to a drug after administration of a dose of the drug), whereas its tumour anti-vascular effects (transient blood pressure increases, myocardial injury and potentially neuropathy) are driven by Cmax (maximum or peak serum concentration achieved after a single dose of a drug has been administered) and this could be attenuated by daily oral dosing. The clinical Phase I trials have therefore been investigating the drug in daily oral and IV infusions (two-hour and prolonged 48-hour) to enable understanding of its clinical dosing strategies to minimise the Cmax and maximise the AUC of BAL27862 and enable higher dosing of BAL101553. Basilea's approach includes the early evaluation of potential biomarkers (BubR1 and EB1) to optimise patient and tumour selection; these are already being tested in Phase I/IIa clinical studies.

BAL101553 has shown anticancer activity in a number of treatment-resistant tumour models, including tumours resistant to standard MTAs, as well as other therapeutic approaches including radiotherapy. BAL27862 has also been shown to have penetration into the brain, thereby supporting the rational to extend the ongoing Phase I/IIa study to include patients with recurrent glioblastoma.

Phase I/IIa development in solid tumours and glioblastoma

BAL101553 is currently undergoing evaluation in three Phase I/IIa clinical trials: the dose escalation in a separate recurrent glioblastoma arm of the Phase I/IIa once-a-day oral administration (NCT02490800), the Phase IIa study weekly 48-hour IV infusion (NCT02895360) in patients with solid tumours and the ABTC (US National Cancer Institute [NCI] funded) initiated Phase I trial (NCT03250299) of oral BAL101553 in combination with radiotherapy in patients with newly diagnosed glioblastoma (GBM).

- NCT02490800 includes patients with solid tumours or glioblastoma or high-grade glioma. The Phase I dose-escalation part of this trial was expanded in December 2016 to include a

separate trial arm for recurrent glioblastoma; this arm of was expected to complete in H118 with data likely in 2018/19. The oral once-a-day in advanced solid tumours dose-escalation part of the study has completed; MTD for daily oral BAL101553 was 16mg/day in patents with solid tumours. Daily doses above 20mg/day were associated with hyponatremia and hallucinations; however, no vascular side effects were seen, as observed with the two-hour weekly infusion.

- NCT02895360 includes glioblastoma patients and patients with platinum-resistant/refractory ovarian cancer. This is the Phase IIa expansion part of the ongoing Phase I/IIa study, which has established the MTD/RP2D of BAL101553 48-hour infusion as 70mg/m^2. The Phase IIa expansion completion date is anticipated in September 2019. As there were indications of potential clinical benefits in patients with ovarian and endometrial cancers the trail has been expanded into a separate arm to include platinum resistant/refractory ovarian cancer.
- The Adult Brain Tumor Consortium (ABTC) initiated a Phase I trial (NCT03250299) to study the safety and tolerability of the drug in combination with radiotherapy in patients with newly diagnosed glioblastoma (GBM). This study is expected to complete in July 2022.

Additionally, the weekly two-hourly BAL101553 infusion, Phase I/IIa study has completed (safety and early indications of efficacy) in a small patient population that included patients with colorectal, gastric, NSCLC, ovarian, pancreatic and triple negative breast cancers that are refractory to current treatments. The recommended Phase II dose (RP2D) of two-hourly IV BAL101553 infusion was 30mg/m^2 weekly (NCT01397929). Higher doses (60mg/m^2) of two-hourly IV infusion were associated with a transient increase in blood pressure; no effects on blood pressure (BP) were apparent with oral or 48-hour IV BAL101553 and vascular toxicities appear related to Cmax.

Glioblastoma: Limited treatment options

There are currently limited treatment options for patients with glioblastoma, an aggressive cancer of the brain with a poor prognosis. Chemotherapy and radiotherapy are not curative and the average survival for these patients is ~15 months. The presence of cancer stem-like cells (CSLC) contribute to therapeutic resistance and invasiveness; overexpression of microtubule plus end-binding 1-protein (EB1) correlates with glioblastoma progression and poor survival (EB1 is overexpressed in the CSLC line GBM6). BAL27862 inhibits the growth of two glioblastoma CSLCs.

The ABTC is designed to develop more effective treatments for malignant brain tumours. The consortium introduces new drugs and treatment approaches using early-phase clinical trials and collaborations with other researchers. Basilea and ABTC have entered into an agreement where the consortium will conduct a Phase I trial to determine the safety and tolerability of the oral formulation of BAL101553 in combination with standard radiation in patients with newly diagnosed glioblastoma who have a reduced sensitivity to standard chemotherapy due to an unmethylated MGMT promoter. Patients will be selected if they are unlikely to respond to chemotherapy, as determined by the detection of an unmethylated MGMT promoter, a key biomarker for glioblastoma patients. Oral (daily) BAL101553 has shown to improve survival in preclinical models of both MGMT-methylated and un-methylated GBM (promoter methylation status is an important molecular genetic biomarker in glioblastoma). The majority of the study costs will be borne by the NCI funded ABTC and the study started patient enrolment in January 2018.

BAL3833 for BRAF-resistant refractory solid tumours

BAL3833 is a multi-kinase inhibitor in Phase I development for treatment-refractory solid tumours, including metastatic melanoma (skin cancer) and RAS-driven tumours. The product was in-licensed by Basilea in April 2015 under an agreement with a consortium of organisations including The Institute of Cancer Research, London, Cancer Research Technology, the Wellcome Trust and The University of Manchester. BAL3833 equipotently inhibits three different kinases; BRAF and CRAF

(part of the RAF family of kinases), and inhibits the SRC family kinase (SFK), which is involved in cell growth.

- BRAF mutations are found in certain cancers, most notably melanoma (around 50% of melanomas express too much BRAF). Mutation in the BRAF protein activates the RAS-RAF-MEK-ERK pathway, which in turn drives tumour cell proliferation, survival and progression. Approved BRAF inhibitors such as Zelboraf (approved to treat BRAF mutation-positive but not BRAF wild-type melanoma) and combinations of BRAF and MEK inhibitors have led to improvement in both PFS and OS in melanoma patients with BRAF mutation melanoma. However, patients develop resistance to these drugs after a relatively short period of time (a few months as monotherapy, nine months in combination) and, furthermore, 20% of patients with BRAF mutation positive are resistant to Zelboraf from the onset. Preclinical data suggest that BAL3833 has activity in models resistant to current BRAF inhibitors.
- Preclinical data also suggest that BAL3833 has activity in KRAS-driven cancer models, suggesting it could have clinical utility in major tumour types beyond BRAF-driven melanoma. KRAS is mutated in several cancer types (eg ~80% of pancreatic ductal adenocarcinoma, ~35% of colorectal cancer and ~20% of non-small-cell- lung cancer). KRAS has proved to be an elusive target in terms of durability and frequency of resistance mechanisms.

BAL3833 is currently being tested in a Phase I dose-escalation study; patient enrolment is ongoing, and the study aims to determine the maximum tolerated dose. This trial (NCT02437227) is being conducted by the Institute of Cancer Research at the Royal Marsden under the initial funding it received from the Wellcome Trust. Basilea will move forward with the programme after completion of the Phase I; given its 3+3 plus design, the exact date for data is unpredictable, but end 2018 is a possibility. The Phase I trial includes melanoma and other solid tumour patients and, given its MOA and hypothesis in treating resistant melanoma patients, we would anticipate it to move forward in that indication. BAL3833 could have activity in other tumours, but it is too early to say which tumours and what the programme will be; future trials will be biomarker and patient stratification led.

Malignant melanoma the opportunity

Malignant melanoma refers to cancer of the melanocyte cells found in the skin. According to the World Health Organization, 132,000 new cases of melanoma are diagnosed worldwide each year; the incidence is higher in Caucasian populations. The Aim Foundation estimates that there will be 91,270 new cases of melanoma in the US alone. Around 50% of melanomas are associated with mutation in the BRAF oncogene (over 90% V600E) and 20% carry mutations in NRAS. According to EvaluatePharma estimates, the 2017 market for melanoma drug sales was $4.9bn and the PDL-1 inhibitors accounted for bulk of sales.

Treatment of malignant melanoma depends on the stage. Early stages (0, 1 and 2) can be treated by surgical excision of the melanoma and surrounding tissue plus/minus regional lymph nodes. Radiotherapy may also be used, while chemotherapy is being used less with the advent of other drug options. Advanced (unresectable) melanoma surgery can be combined with immunotherapy or targeted therapy. The critical question for advanced tumours is whether the tumour is BRAF mutation-positive or wild type:

- Immunotherapy: for patients with no BRAF mutation (so-called wild type), either single-agent immunotherapy with a PD-1 Inhibitor (pembrolizumab or nivolumab) or combination therapy with nivolumab plus ipilimumab is recommended by the US National Comprehensive Cancer Network (NCCN) guidelines.
- Targeted therapy: for BRAF mutation-positive melanoma patients, combination targeted therapy with dabrafenib/trametinib or vemurafenib/cobimetinib is recommended by NCCN.

Selective BRAF inhibitor use is followed by acquired resistance through reactivation of the mitogen-activated protein kinase pathway. It is thought that if multiple nodes in the pathway are blocked, this

could not only enhance efficacy but also reduce the potential for acquired resistance; the scientific theory is that the inhibition of Pan-Raf and RTKs might be a tractable strategy to overcome the resistance of melanoma induced with the current selective BRAF V600E inhibitors.

The major hypothesis for BAL3833 is that its mechanism of action (equipotently inhibits three different kinases) could enable it to be a first-line treatment for BRAF and NRAS mutation-positive melanomas, and second-line for BRAF mutation-positive patients who develop resistance to BRAF inhibitors. Resistance to BRAF and MEK inhibitors in BRAF mutation-positive melanoma is often mediated by pathway reactivation through receptor tyrosine kinase (RT)/SRC family kinase (SFK) signalling or mutant NRAS. Paradoxical reactivation of the MEK/ERK pathway by BRAF inhibitors in the presence of oncogenic RAS is driven by CRAF activation; thus, by also inhibiting CRAF, BAL3833 should be able to prevent the reactivation. Additionally, BAL3833 inhibits signal transduction through SRC family kinases, which is a potential resistance mechanism/salvage pathway of tumours to circumvent the inhibition of downstream BRAF.

BAL3833 could have activity in other tumours, but it is too early to say which tumours and what the programme will be; future trials will be biomarker and patient stratification-led as Basilea increases its understanding of this novel mechanism of action drugs relevance in BRAF and RAS positive.

Competitive landscape

Roche's Zelboraf (vemurafenib) is a kinase inhibitor approved to treat unresectable or metastatic melanoma in patients with BRAF V600E mutation, as detected by an approved FDA test. The drug is not approved for treatment of patients with wild-type BRAF melanoma. Available in the US market since 2011, the drug reported CHF213m sales in 2016. In April 2018, Novartis received FDA approval for its BRAF inhibitor Tafinlar (dabrafenib) plus MEK inhibitor (Mekinist) as the first oral targeted adjuvant combination therapy with BRAF mutation-positive melanoma. This combination is the standard of care in BRAF-positive malignant melanoma. Novartis reported Tafinlar/Mekinist sales of $837m in 2017.

Marketed drug portfolio Cresemba and Zevtera

Basilea has multiple licensing deals in place for its commercially available anti-infective products, Cresemba and Zevtera. Exhibit 6 highlights the existing partnerships for both Cresemba and Zevtera. We note that in many instances partners have chosen to in-license both products given the significant overlap in the physician prescribing base.

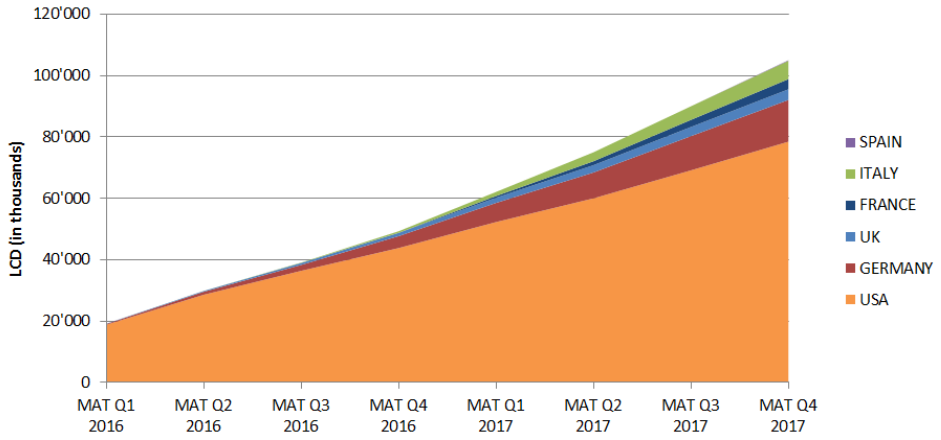
Exhibit 6: Cresemba and Zevtera partners/distribution agreements

Product	Partner/Distributor *	Territory	Comments
Cresemba	Astellas	US	CHF122m upfront and regulatory milestones received with up to CHF285m of sales milestones outstanding. Tiered royalty starting in the mid-teens and ramping up to mid-20s on sales
Cresemba	Pfizer	Over 40 countries in Europe (excluding Nordics), Russia, Turkey and Israel. Extended to include China (incl Hong Kong & Macau) and 16 countries in Asia Pacific.	CHF73m upfront and up to US$650m sales and regulatory milestones plus mid-teen on sales royalties
Zevtera	Correvio	Europe (excluding Nordics) and Israel	Upfront CHF5m and regulatory and commercial milestone payments. Participate in sales through a transfer price.
Zevtera	CR Gosun	China, Hong Kong and Macau	CHF3m execution payment and up to CHF145m additional payments on achievement of pre-specified regulatory and commercial milestones.
Cresemba & Zevtera	Unimedic Pharma*	Nordic countries including Sweden, Denmark, Norway and Finland	Upfront and sales milestone payments. Participate in sales through a transfer price.
Cresemba & Zevtera	Grupo Biotoscana (GBT)*	19 countries in Latin America including Brazil, Mexico, Argentina and Colombia	CHF11m upfront plus milestone payments. Participate in sales through a transfer price.
Cresemba	Asahi Kasei Pharma (AKP)	Japan	CHF7m upfront and up to CHF60m regulatory and commercial milestone payments plus double-digit tiered royalties
Cresemba & Zevtera	Avir Pharma*	Canada	Upfront and sales milestone payments. Participate in sales through a transfer price.
Cresemba & Zevtera	Hikma*	MENA region	Financial terms not disclosed. Participate in sales through a transfer price.

Source: Edison Investment Research, Basilea Pharmaceutica. Note: *Distribution agreements where Basilea supplies product at a transfer price. Cresemba steadily growing in launched markets.

Cresemba (isavuconazole), a broad-spectrum antifungal for the treatment of severe, life-threatening fungal infections, is available in the US and major European countries through regional partners. In the US, partner Astellas has reported sales of $87m (+64%) for FY17 (year ending 31 March 2018). Basilea is entitled to a tiered royalty on Cresemba sales, starting in the mid-teens and ramping up to the mid-20s, with up to CHF285m of remaining sales milestones. Exhibit 7 highlights the steady growth in sales in the US and the increasing contribution from new markets, amounting to in-market sales of over $100m. Basilea anticipates growth in existing markets and further launches worldwide to drive top-line growth. Pfizer is expected to roll out the drug across Europe continually (timing is dependent on individual country pricing and reimbursement discussions as Cresemba received approval through a centralised process in Europe). Outside Europe and the US, partners are filing or have filed for marketing authorisation, so further approvals should come through in additional territories within the next couple of years.

Exhibit 7: Cresemba sales growth in key launched markets



Source: IQVIA, Basilea presentations

In April 2018 Japanese partner, Asahi Kasei Pharma, started enrolment of the Phase III registration study (n=100) for potential approval in Japan for the treatment of invasive fungal infections (deep-seated mycosis, comprising invasive aspergillosis, chronic pulmonary aspergillosis, mucormycosis and cryptococcosis).

Zevtera fortunes depended on US Phase III outcome

Zevtera/Mabelio (ceftobiprole) is a broad spectrum antibiotic for the treatment of Gram-positive, including MRSA (methicillin-resistant *Staphylococcus aureus*) infections, which are resistant to a number of existing antibiotics, and Gram-negative bacterial infections, including *Pseudomonas*. The product is available in major European counties (through Correvio), Canada (through Avir Pharma) and Argentina (through GBT). Additionally, partner Hikma has launched Zevtera in Saudi Arabia, the first launch in the MENA region; further roll-out into the Middle East, North Africa and Latin America is expected later through 2018 to 2020. Uptake remains slow as sales of antibiotics take time to build post-launch due to the requirement for regional reimbursement across Europe as well as the need to be added to individual hospital formularies, microbial stewardship programmes and a tendency to keep new antibiotics in reserve use.

Zevtera is not currently approved in the US (further clinical studies are needed to secure approval), where we believe the bulk of its sales opportunity resides; in terms of value, the US in 2017 accounted for 50% of anti-MRSA antibiotics and 70% of the branded hospital antibiotic market. Basilea has initiated the first of two cross-supportive Phase III clinical trials required for regulatory approval of ceftobiprole: the acute bacterial skin and skin structure infections (ABSSSI) trial started enrolment in February 2018 and the *Staphylococcus aureus* bacteraemia (SAB, bloodstream infections) is expected to initiate shortly. For further details on Zevtera, see our March update note, Strength in numbers.

Sensitivities

Basilea is subject to the usual biotech and drug development risks, including clinical development delays or failures, regulatory risks, competitor successes, partnering setbacks, and financing and commercial risks. The key sensitivities for Basilea relate to successful commercialisation of both Cresemba and Zevtera in the respective approved territories, progress of the Zevtera Phase III programme in the US and crystallising value from the oncology pipeline. For the earlier-stage pipeline, both clinical development and partnering risks remain.

Valuation

We have updated our valuation of Basilea to CHF1,285m or CHF119/share (versus CHF1,231m previously), as a result of including the risk-adjusted contribution from derazantinib and second-line iCCA. Additionally, we roll forward our DCF, update for spot FX rates and reflect a net cash position CHF114.5m at 31 December 2017. Our valuation is based on an NPV analysis, which includes the main portfolio of products and net cash. Cresemba, based on $0.873bn peak sales, is worth CHF948.5m. We also include Zevtera in Europe, in addition to risk-adjusted contributions for the US opportunity and the earlier-stage pipeline. We include indicative valuations for BAL101553 and BAL3833, and for simplicity assume that both will be partnered post-completion of Phase II trials, in exchange for a royalty on sales (starting at 15% for both, given we have assumed partnering once proof-of-concept data become available). Assessing the potential for each product is challenging in the absence of proof-of-concept data and without knowing the indications that will be pursued in the future. The breakdown of our valuation is shown in Exhibit 8.

Exhibit 8: Basilea rNPV valuation

Product	Indication	Launch	Peak sales (US$m)	NPV (CHFm)	Probability	rNPV (CHFm)	NPV/share (CHF/share)
Cresemba (isavuconazole)	Severe mould infections	2015 (US); 2016 (EU); 2018 (ROW); 2022 Japan	873	997.4	75-100%*	948.5	87.8
Zevtera/Mabelio (ceftobiprole)	Severe bacterial infections	2015 (EU); 2018 (ROW); 2023 (US); 2023 (China)	550	222.9	75-100%**	180.8	16.7
BAL101553	Tumour resistance	2023	500	141.5	20%	20.6	1.9
BAL3833	Tumour resistance	2024	500	104.2	15%	6.5	0.6
Derazantinib	iCCA	2023	59	47.5	30%	14.3	1.3
Net cash/(debt)				114.5	100%	114.5	10.6
Valuation				1,628.1		1,285.1	119.0

Source: Edison Investment Research. Note: *100% probability for the US and EU, 75% for ROW and Japan. **100% probability for the EU, 75% probability for China, ROW and the US.

Financials: Cash runway beyond 2019

We believe that Basilea's gross cash (including financial investments) of CHF311m at 31 December 2017 should be sufficient to fund operations beyond 2019, even excluding future potential deals for either Zevtera in the US or the oncology pipeline. Profitability will be driven by royalties and milestones on sales of Cresemba worldwide and Zevtera in Europe/ROW. We forecast total revenues of CHF113.6m in 2018 and CHF137.3m in 2019. Our 2019 top-line forecasts include significant sales milestone income for US Cresemba, and EU Cresemba sales from partners Astellas and Pfizer, respectively. Our forecasted 2018 gross R&D costs have been increased to reflect the $10m payment to Arqule and, additionally, we increase 2019 R&D costs to CHF113m (from CHF95.0m) to reflect the investment in the derazantinib clinical trial programme (iCCA and solid tumours).

Exhibit 9: Financial summary

CHF000s	2016	2017	2018e	2019e
December	US GAAP	US GAAP	US GAAP	US GAAP
PROFIT & LOSS				
Revenue	65,984	101,521	113,583	137,255
Cost of Sales	(5,347)	(9,025)	(11,994)	(12,429)
Gross Profit	60,637	92,496	101,589	124,826
Research and development (gross)	(48,449)	(53,493)	(96,000)	(113,000)
SG&A	(56,077)	(53,139)	(35,337)	(36,114)
EBITDA	(41,570)	(12,236)	(27,287)	(21,533)
Operating Profit (before amort. and except.)	(43,789)	(14,036)	(29,625)	(24,060)
Intangible Amortisation	(100)	(100)	(123)	(228)
Exceptionals	0	0	0	0
Other	0	0	0	0
Operating Profit	(43,889)	(14,136)	(29,748)	(24,288)
Net Interest	(7,065)	(4,890)	(5,375)	(5,375)
Profit Before Tax (norm)	(50,854)	(18,926)	(35,000)	(29,435)
Profit Before Tax (reported)	(50,954)	(19,026)	(35,123)	(29,663)
Tax	(333)	(334)	(26)	(26)
Profit After Tax (norm)	(51,187)	(19,260)	(35,027)	(29,461)
Profit After Tax (reported)	(51,287)	(19,360)	(35,150)	(29,689)
Average Number of Shares Outstanding (m)	10.1	10.8	10.8	10.8
EPS - normalised fully diluted (CHFc)	(505.74)	(178.36)	(324.36)	(272.82)
EPS - (reported) (CHFc)	(506.73)	(179.28)	(325.50)	(274.93)
Dividend per share (c)	0.0	0.0	0.0	0.0
Gross Margin (%)	91.9	91.1	89.4	90.9
EBITDA Margin (%)	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A
BALANCE SHEET				
Fixed Assets	59,264	58,189	59,335	60,899
Intangible Assets	232	326	526	726
Tangible Assets	8,878	7,768	8,714	10,078
Investments	50,154	50,095	50,095	50,095
Current Assets	268,494	292,976	215,891	165,438
Stocks	14,931	15,320	16,431	13,621
Debtors	2,492	4,955	5,290	6,393
Cash	239,030	260,724	182,193	133,447
Other	12,041	11,977	11,977	11,977
Current Liabilities	(72,914)	(79,491)	(54,144)	(66,713)
Creditors	(72,914)	(79,491)	(54,144)	(66,713)
Short term borrowings	0	0	0	0
Long Term Liabilities	(289,844)	(313,114)	(284,293)	(247,903)
Long term borrowings	(195,466)	(196,224)	(195,466)	(195,466)
Other long term liabilities	(94,378)	(116,890)	(88,827)	(52,437)
Net Assets	(35,000)	(41,440)	(63,211)	(88,279)
CASH FLOW				
Operating Cash Flow	(75,003)	19,014	(69,522)	(39,026)
Net Interest	0	0	(5,375)	(5,375)
Tax	0	0	(26)	(26)
Capex	(394)	(711)	(3,408)	(4,118)
Acquisitions/disposals	0	0	0	0
Financing	0	0	0	0
Other	(51,021)	2,633	558	(200)
Dividends	0	0	0	0
Net Cash Flow	(126,418)	20,936	(77,773)	(48,746)
Opening net debt/(cash)	(169,982)	(43,564)	(64,500)	13,273
HP finance leases initiated	0	0	0	0
Other	0	(0)	0	0
Closing net debt/(cash)	(43,564)	(64,500)	13,273	62,019

Source: Edison Investment Research, company reports

Contact details	Revenue by geography
Grenzacherstrasse 487 PO Box 4005 Basel Switzerland +41 61 606 11 11 www.basilea.com	N/A

Management team

CEO: Mr David Veitch	CFO: Mr Donato Spota
Mr Veitch has been CEO since April 2018; he joined Basilea in 2014 as chief commercial officer, having spent over 25 years in the pharmaceutical industry. Before Basilea, he was president of European operations at Savient Pharmaceuticals and spent 15 years at Bristol-Myers Squibb, including leading the commercial operations in Europe, the Middle East and Asia. Mr Veitch holds a BSc degree in biology.	Mr Spota joined Basilea in 2002 and became CFO in 2013. Before Basilea he worked for Roche. Mr Spota has more than 16 years' experience in the pharmaceutical industry, including finance, strategic financial planning and analysis, as well as audit and risk management. He holds an MBA from the University of Applied Sciences Nürtingen, Germany.
CMO: Dr Marc Engelhardt	
Dr Engelhardt has been the chief medical officer since January 2018; he joined Basilea in 2010 as head of clinical research. In 2012, he was promoted to head of development. In this role, Dr Engelhardt led Basilea's clinical research and development group. Prior to joining Basilea, Dr Engelhardt served as global program medical director at Novartis Pharma AG in Basel, before which he held various positions with increasing responsibility at Bracco-Altana, Konstanz, Germany and Bracco Diagnostics in Princeton, NJ, US. Dr Engelhardt holds a medical degree and a PhD from the University Frankfurt/Main, Germany and is board certified in internal medicine.	

Principal shareholders*	(%)
CI Investments	5.07
Credit Suisse	3.28

*SIX Stock Exchange Regulation

Companies named in this report

Astellas (4503 JP), Pfizer (PFE US), Roche (ROG VX), Novartis (NVN VX), Hikma