Business report

Performance / Multi-year comparison

Indexed performance since launch

BB Biotech AG (SIX)-CHF

Annual performance

31.12.2022

	SHARE	NAV	NBI TR
2022	(24.3%)	(11.0%)	(9.1%)
2021	8.3%	(11.5%)	3.0%
2020	19.3%	24.3%	15.8%
2019	18.5%	23.4%	23.0%
2018	(5.2%)	(14.5%)	(8.0%)

Cumulated performance

31.12.2022

	SHARE	NAV	NBI TR
1 year	(24.3%)	(11.0%)	(9.1%)
3 years	(2.1%)	(2.1%)	8.4%
5 years	10.0%	3.3%	22.7%
10 years	404%	274%	212%
since inception [1)]	2 319%	2 016%	1 261%

[1] 09.11.1993

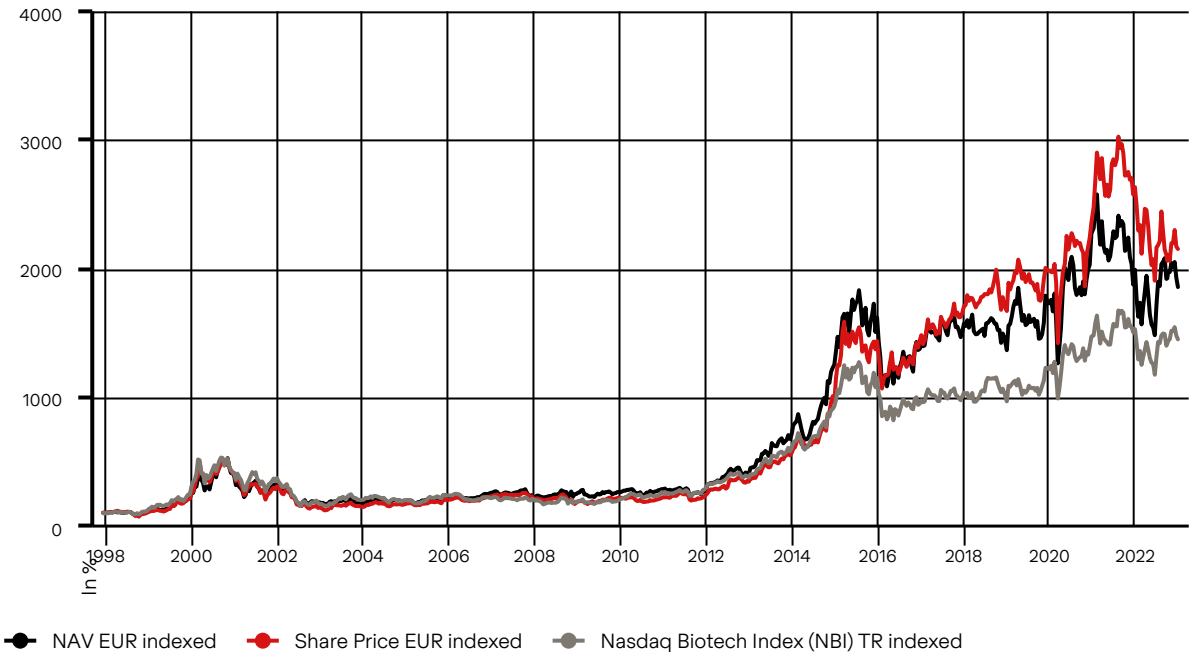
Annualized performance

31.12.2022

	SHARE	NAV	NBI TR
1 year	(24.3%)	(11.0%)	(9.1%)
3 years	(0.7%)	(0.7%)	2.7%
5 years	1.9%	0.7%	4.2%
10 years	17.5%	14.1%	12.0%
since inception [1)]	11.6%	11.0%	9.4%

[1] 09.11.1993

BB BIOTECH AG (XETRA)-EUR



Annual performance

31.12.2022

	SHARE	NAV	NBI TR
2022	(19.0%)	(6.7%)	(4.5%)
2021	13.3%	(7.8%)	7.4%
2020	18.1%	24.8%	16.1%
2019	23.4%	28.1%	27.6%
2018	(2.2%)	(11.1%)	(4.3%)

Cumulated performance

31.12.2022

	SHARE	NAV	NBI TR
1 year	(19.0%)	(6.7%)	(4.5%)
3 years	8.4%	7.3%	19.1%
5 years	30.9%	22.2%	45.4%
10 years	530%	356%	281%
since inception [1)]	2 051%	1 755%	1 404%

[1] 10.12.1997

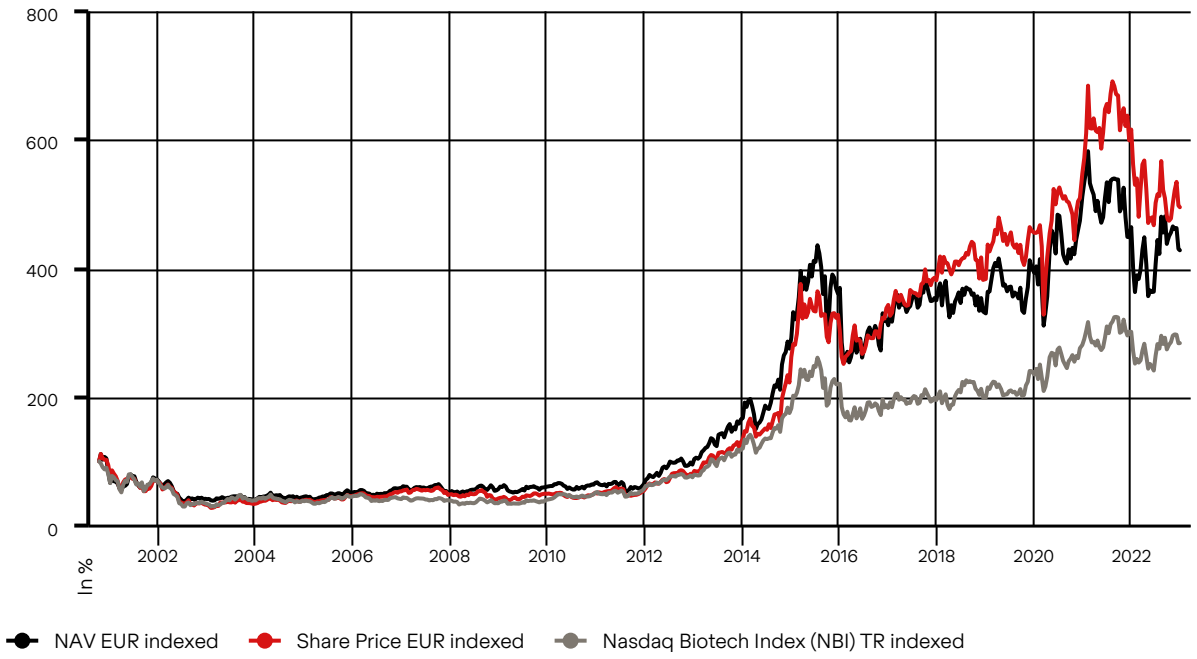
Annualized performance

31.12.2022

	SHARE	NAV	NBI TR
1 year	(19.0%)	(6.7%)	(4.5%)
3 years	2.7%	2.4%	6.0%
5 years	5.5%	4.1%	7.8%
10 years	20.2%	16.4%	14.3%
since inception [1)]	13.0%	12.4%	11.4%

[1] 10.12.1997

BB BIOTECH AG (MILAN)-EUR



Annual performance

31.12.2022

	SHARE	NAV	NBI TR
2022	(19.6%)	(6.7%)	(4.5%)
2021	13.0%	(7.8%)	7.4%
2020	19.7%	24.8%	16.1%
2019	22.6%	28.1%	27.6%
2018	(1.3%)	(11.1%)	(4.3%)

Cumulated performance

31.12.2022

	SHARE	NAV	NBI TR
1 year	(19.6%)	(6.7%)	(4.5%)
3 years	8.8%	7.3%	19.1%
5 years	31.6%	22.2%	45.4%
10 years	525%	356%	281%
since inception [1)]	395%	328%	184%

[1] 19.10.2000

Annualized performance

31.12.2022

	SHARE	NAV	NBI TR
1 year	(19.6%)	(6.7%)	(4.5%)
3 years	2.8%	2.4%	6.0%
5 years	5.6%	4.1%	7.8%
10 years	20.1%	16.4%	14.3%
since inception [1)]	7.5%	6.8%	4.8%

[1] 19.10.2000

Multi-year comparison

	2022	2021	2020	2019	2018
Market capitalization at the end of the period (in CHF mn)	3 058.1	4 274.1	4 107.9	3 670.3	3 235.4
Net Asset Value at the end of the period (in CHF mn)	2 686.1	3 283.5	3 887.5	3 393.0	2 884.5
Number of shares (in mn)	55.4	55.4	55.4	55.4	55.4
Trading volume (in CHF mn)	1 482.0	2 101.0	2 315.6	2 004.2	2 610.7
Profit/(loss) (in CHF mn)	(357.8)	(404.8)	691.2	677.4	(471.3)
Closing price at the end of the period in CHF	55.20	77.15	74.15	66.25	58.40
Closing price (G) at the end of the period in EUR	56.70	74.05	68.00	61.40	52.00
Closing price (I) at the end of the period in EUR	56.50	74.40	68.50	61.00	52.00
Stock performance (incl. distributions) [1)]	(24.3%)	8.3%	19.3%	18.5%	(5.2%)
High/low share price in CHF	78.15/51.00	92.20/73.40	74.70/45.44	73.20/59.35	74.10/56.10
High/low share price in EUR	75.40/49.60	86.20/67.80	69.00/43.04	64.70/52.10	64.80/48.60
Premium/(discount) (annual average)	20.5%	19.5%	9.2%	11.8%	9.7%
Dividend in CHF (*proposal)	2.85*	3.85	3.60	3.40	3.05
Degree of investment (quarterly figures)	112.8%	108.6%	106.8%	109.1%	108.4%
Total Expense Ratio (TER) p.a. [2)]	1.27%	1.22%	1.25%	1.26%	1.25%

[1] All figures in CHF %, total return-methodology
[2] Based on market capitalization

Shareholder letter

The year 2022 saw volatile market conditions for global equity and bond markets, with substantial stepwise increases in central bank rates, led by the US Federal Reserve Bank. Flight from growth into value sectors and into diversified, large, profitable companies was a major theme for 2022. In the heterogenous biotechnology sector, large cap companies gained value throughout 2022 whereas pipeline-dependent small and mid cap companies experienced significant corrections. While the COVID-19 pandemic has been declared less threatening in the US, booster vaccination initiatives have continued, while the world watches China's about-face from restrictive isolation policies towards re-opening. The focus for the biotech sector is already shifting back to chronic diseases and seasonal vaccines.

Dear Shareholders

The Dow Jones (–6.9% in USD), the Dax (–12.4% in EUR), and the SPI (–16.5% in CHF) indices each declined in 2022, while the technology-heavy Nasdaq Composite (–32.5% in USD) declined even more. The Nasdaq Biotech Index (NBI) traded in line with the broader markets for the year (–10.1% in USD).

BB Biotech's total share return of –24.3% in CHF and –19.0% in EUR in 2022 tracked European equity indices, performed worse than biotech indices and deviated from the underlying portfolio performance. Exchange rates fluctuated throughout the year but closed with a small gain for the USD relative to the CHF and the EUR which created some support for EUR-denominated performance. This meant that the BB Biotech portfolio Net Asset Value (NAV) declined 11.0% in CHF, 6.7% in EUR and 12.1% in USD for 2022. Consolidated full year 2022 data showed a net loss of CHF 358 mn compared to a net loss of CHF 405 mn for 2021.

During the last quarter of the year major global equity indices rebounded and recovered some of 2022's earlier losses. Most equity and bond markets closed the year in negative territory associated with persistently high inflation and strong labor market data which surprised investors and central banks. Interest rate expectations for the US at the beginning of 2022 stayed below 1%, with the December 2022 rate hike pushing the Federal fund interest rate to 4.25% with more rate hikes to be expected in 2023.

For the fourth quarter of 2022, BB Biotech's share price increased 4.7% in CHF and 4.4% in EUR. BB Biotech's Net Asset Value (NAV) decreased 1.2% in CHF, 3.5% in EUR and gained 5.4% in USD, impacted by currency fluctuations and by the underperformance of small and mid cap companies in the portfolio, while the NBI index gained 12.0% in USD for the same period – driving a net loss of CHF 35 mn compared to the net loss of CHF 546 mn for the fourth quarter 2021.

Stability in the Board of Directors of BB Biotech

During 2022, BB Biotech expanded the Board of Directors. Dr. Pearl Huang, CEO of Dunad Therapeutics, and Laura Hamill, former Executive Vice President Worldwide Commercial Operations for Gilead joined the Board. All six current board members will stand for re-election by the shareholders at the Annual General Meeting (AGM) scheduled for March 23, 2023.

Dividend 2023

CHF 2.85

(Proposed)

A proposed dividend of CHF 2.85 per share

The Board of Directors will propose a regular dividend of CHF 2.85 per share at the AGM. A 5% dividend yield will be applied to the average share price of December 2022, consistent with the dividend policy introduced in 2013.

Portfolio adjustments in the fourth quarter 2022

During the fourth quarter, the investment team made no new investments, but added to existing portfolio positions. The additions focused on oncology companies such as Revolution Medicines, Fate Therapeutics, Black Diamond Therapeutics and Essa Pharma – each of which suffered valuation dislocations. Additions in Macrogenics and Mersana followed important pipeline deals strengthening the companies' balance sheet. Additions in Relay Therapeutics followed positive clinical data reports for the firm's FGFR2 asset.
BB Biotech also added shares of commercial stage Incyte and genetic medicines company Ionis. The investment management team took profits in Neurocrine following a rebound of Ingrezza growth, and from Alnylam and Vertex – each trading close to their all-time high share prices. Taken together, these additional investments increased the BB Biotech investment level by 2.4% compared to the third quarter, closing 2022 at 113.6%.

The additions focused on oncology companies such as Revolution Medicines, Fate Therapeutics, Black Diamond Therapeutics and Essa Pharma – each of which suffered valuation dislocations.

Fourth-quarter portfolio update

The fourth quarter 2022 provided multiple major milestones for our portfolio holdings such as clinical results, regulatory decisions, licensing deals and some takeovers. The clinical results for the biotechnology industry and our portfolio saw a more positive picture in the last quarter. The difficult capital market environment influenced industry behavior, resulting in more licensing deals as an alternative source of non-dilutive access to capital. Additionally, opportunistic takeover activity focused on commercial-stage companies and lifted the acquisition targets towards their all-time highs thanks to the premiums offered.

2023: Exciting sector fundamentals and anticipated licensing deals/ M&A

During 2022, SARS-CoV-2 variant waves remained a focus for healthcare authorities. Yet the pandemic was said (more than once) to be over. Meanwhile, the US FDA tallied up 37 NDA (New Drug Application) approvals and 7 BLA (Biologics License Application) approvals (vaccines, blood and cell products) for the year.

BB Biotech believes that 2023 will include multiple catalysts for the sector and for its portfolio companies, including product launches, important clinical trial results, licensing deals and M&A activity.

Many clinical trial read-outs are eagerly anticipated from portfolio companies in 2023. The focus for mRNA vaccines shifts away from SARS-CoV-2 to seasonal respiratory viruses. Moderna is expected to report data from mRNA-1010, an influenza vaccine, and mRNA-1345, an RSV vaccine in 2023. Neurocrine will report Phase III data for Crinecerfont in congenital adrenal hyperplasia. Argenx, is expected to reveal Phase III data for chronic inflammatory demyelinating polyneuropathy (CIDP). Ionis plans to report late clinical data for Olezarsen, an ApoCIII antisense oligonucleotide for familial chylomicronemia syndrome. Esperion announced positive results for the CLEAR outcomes trial ofbempedoic acid in late 2022 and is scheduled to disclose details at a late breaker presentation during the annual American College of Cardiology meeting on March 4, 2023. We also look forward to important results from smaller platform companies including Generation Bio, Homology Medicines, Wave Life Sciences and Fate Therapeutics.

Multiple product approvals and important label expansions are expected to drive future revenue and profit opportunities:

- Two antisense oligonucleotide drug candidates from Ionis: Eplontersen for TTR-polyneuropathy and Tofersen for SOD1 amyotrophic lateral sclerosis
- The first gene editing candidates from Crispr Therapeutics and Vertex: CTX001 for sickle cell disease and beta thalassemia
- A subcutaneous formulation of efgartigimod gMG from Argenx
- A second indication for Valbenazine for chorea in Huntington's disease from Neurocrine
- A Patisiran sNDA for TTR-CM from Alnylam
- Two mRNA vaccines, mRNA1010 for seasonal influenza, and mRNA1345 for seasonal RSV from Moderna
- Zuranolone for major depressive disorder and postpartum depresseion (PPD) from Sage/ Biogen
- A bempedoic acid sNDA including cardiovascular outcomes data from Esperion

The challenging capital markets environment placed even greater investor focus on new product launch metrics including markers of sustainable profitability. Neurocrine Biosciences, Intra-Cellular Therapeutics, Incyte and Argenx will be in focus. The launch of Orgovyx and Myfembree by Myovant is less noteworthy since the firm has been acquired by Sumitomo Pharma.

Companies with earlier clinical programs and technology platforms may be challenged to raise capital. Consequently, some have fallen back on licensing deals with larger companies to avoid dilutive equity funding. Those needing immediate funding were obliged to raise money at unattractive valuations. BB Biotech sees compelling opportunities under these circumstances and also expects more M&A activity, with large companies constantly seeking pipeline opportunities.

A focus on big data and artificial intelligence

BB Biotech is focusing more and more on large healthcare data sets which provide insights into R&D and commercial opportunities. BB Biotech has expanded the data science team recently – adding experts to the investment management team to strengthen the investment process. The investment management team continues to build and balance a portfolio of established mid capitalization companies and exciting earlier stage companies, as defined and outlined in its investment guidelines. BB Biotech's structure as an investment company enables and demands a long-term view which will continue to generate leading returns in our sector. In BB Biotech's view, the growth case for biotechnology and the value which the sector will create are compelling.

We thank you for the trust you have placed in the Company.

The Board of Directors of BB Biotech AG

Dr. Erich Hunziker
Chairman
Laura Hamill
Member
Prof. Dr. Mads Krogsgaard Thomsen
Member
Dr. Clive Meanwell
Vice Chairman
Dr. Pearl Huang
Member
Dr. Thomas von Planta
Member

Portfolio Update Q4 2022

The fourth quarter 2022 provided multiple major milestones for our portfolio holdings such as clinical results, regulatory decisions, licensing deals and some takeovers. The clinical results for the biotechnology industry and our portfolio saw a more positive picture in the last quarter. The difficult capital market environment influenced industry behavior, resulting in more licensing deals as an alternative source of non-dilutive access to capital. Additionally, opportunistic takeover activity focused on commercial-stage companies and lifted the acquisition targets towards their all-time highs thanks to the premiums offered.

Several milestones including clinical trial data

The late-stage trial read-outs in our portfolio were mixed in the last quarter of 2022. Esperion announced that the cardiovascular outcomes trial for Nexletol (bempedoic acid) met the primary endpoint. The company's landmark trial of over 14 000 patients demonstrated statistically significant risk reduction in MACE-4 in patients treated with 180 mg/day NEXLETOL compared to placebo. Detailed results will be presented as a late-breaking abstract at the Annual Scientific Session & Expo with World Congress of Cardiology in March 2023.

Exelixis announced that the Phase III CONTACT-01 study did not meet its primary endpoint at the final analysis. In patients with metastatic non-small cell lung cancer who experienced disease progression on or after treatment with an immune checkpoint inhibitor and platinum-containing chemotherapy, Cabometyx (cabozantinib) in combination with Tecentriq (atezolizumab) did not improve the overall survival versus docetaxel.

The ever evolving SARS-CoV-2 strains remain a challenge for developing booster shots.

The ever evolving SARS-CoV-2 strains remain a challenge for developing booster shots. Moderna announced that its novel mRNA vaccines achieved strong neutralizing titers against multiple Omicron variants. In a Phase II/III study, a 50 µg booster dose of mRNA-1273.222 elicited a superior neutralizing antibody response against Omicron BA.4/BA.5 variants when compared to a 50 µg booster dose of mRNA-1273 (Spikevax) in previously vaccinated and boosted participants.

Promising proof-of-concept data was reported by many portfolio companies in the fourth quarter of 2022. Moderna together with its partner Merck announced top-line results from a Phase IIb KEYNOTE-942 study for mRNA-4157/V940, an investigational personalized mRNA cancer vaccine in combination with Keytruda. mRNA4157/V940 demonstrated a statistically significant and clinically meaningful improvement (44% risk reduction) in recurrence-free survival (RFS) versus Keytruda alone as adjuvant treatment in patients with stage III/IV melanoma following complete resection. Merck had opted into a joint development and commercialization collaboration earlier on, and both companies are expected to start multiple registrational trials for mRNA-4157/V940 in combination with Keytruda in different adjuvant settings.

Promising proof-of-concept data was reported by many portfolio companies in the fourth quarter of 2022.

Ionis with its development partner GSK presented positive Phase II study results for bepirovirsen, an investigational antisense oligonucleotide treatment for patients with chronic hepatitis B virus. The results showed that treatment with bepirovirsen resulted in sustained clearance of hepatitis B surface antigen (HBsAg) and hepatitis B virus (HBV) DNA for 24 weeks after end of bepirovirsen treatment in people with chronic hepatitis B. GSK has announced to start registrational Phase III trials in 2023.

Arvinas announced results from the Phase II cohort expansion portion with ARV-471, a novel PROTAC estrogen receptor protein degrader. 38% of evaluable patients achieved a clinical benefit and a favorable tolerability profile was presented. ARV-471 is being co-developed with Pfizer for the treatment of patients with advanced or metastatic estrogen receptor positive, HER2 negative breast cancer patients. The companies expect to start the ARV-471 Palbociclib combination trial in the second half of 2023.

Neurocrine announced that its investigational NBI-827104 did not meet its primary endpoint in the II STEAMBOAT study evaluating the efficacy, safety, tolerability and pharmacokinetics of NBI-827104 compared to placebo in pediatric patients with epileptic encephalopathy with continuous spike-and-wave during sleep. Overall, NBI-827104 was generally well tolerated.

One of our most recent investments, Celldex Therapeutics, announced new data for its open-label Phase Ib clinical trial of barzolvolimab in patients with antihistamine refractory chronic inducible urticarias. Additionally, all cold urticaria patients achieved a complete response after treatment of a single dose of barzolvolimab, a humanized monoclonal antibody binding the receptor tyrosine kinase KIT, blocking mast cell activation.

Numerous regulatory decisions milestones

BB Biotech's portfolio holdings updated on multiple regulatory decisions in the fourth quarter 2022 such as:

- Agios Pharmaceuticals announced that the European Commission (EC) has granted marketing authorization for PYRUKYND® for the treatment of PK deficiency in adult patients. PYRUKYND® is a first-in-class, oral PK activator and the first approved disease-modifying therapy for patients in the EU with this rare, debilitating, lifelong hemolytic anemia.
- Moderna expanded the emergency use authorization for its omicron-targeting bivalent covid-19 booster with the inclusion of children from 6 months through 5 years of age. The authorization is based on a 10 µg booster dose following a completed primary series of Moderna's original vaccine. The booster dose of mRNA-1273.222 contains mRNA encoding for the spike protein of BA.4/BA.5 as well as mRNA encoding for the original strain of the SARS-CoV-2 virus.
- Macrogenics reported that the US Food and Drug Administration (FDA) announced the approval of the Biologics License Application (BLA) for teplizumab, an anti-CD3 monoclonal antibody that was previously developed by Macrogenics. Teplizumab was acquired by Provention Bio, Inc. in May 2018 pursuant to an asset purchase agreement, triggering a USD 60mn milestone payment for Macrogenics.
- Alnylam Pharmaceuticals announced that the FDA approved a label expansion for OXLUMO® (lumasiran) for the treatment of primary hyperoxaluria type 1 (PH1), both in pediatric and adult patients. The approval is based on positive efficacy and safety results of the ILLUMINATE-C Phase III study and follows the initial FDA approval in 2022. This allows the treatment of PH1 patients with compromised renal function, including those with kidney failure and undergoing treatment by hemodialysis.

Beneficial collaborations in the last quarter of 2022

Non-dilutive capital contributions have become and attractive new source of funding for smaller companies that suffered steep share depreciations over the last 18 months. Platform companies are ideally positioned to weather the situation. Macrogenics and Gilead announced an exclusive option and collaboration agreement to develop MGD024, an investigational, bispecific antibody that binds CD123 and CD3 using Macrogenics' DART® platform, and two additional bispecific research programs. As part of the agreement, Gilead will pay Macrogenics an upfront payment of USD 60 mn and Macrogenics will be eligible to receive up to USD 1.7 bn in target nomination, option fees, and development, regulatory and commercial milestones. Macrogenics will also be eligible to receive tiered, double-digit royalties on worldwide net sales of MGD024 and a flat royalty on worldwide net sales of products under the two research programs.

Similarly, Mersana announced a research collaboration and commercial license agreement with Merck KGaA to discover novel Immunosynthen ADCs directed against up to two targets. Immunosynthen, Mersana's proprietary STING-agonist ADC platform, is designed to generate systemically administered ADCs that locally activate STING signaling in both tumor-resident immune cells and in antigen-expressing tumor cells, unlocking the anti-tumor potential of innate immune stimulation. Mersana will receive an upfront payment of USD 30 mn and is also eligible to receive reimbursement of certain costs, up to USD 800 mn in potential regulatory, development and commercial milestone payments, and tiered royalties up to the low double-digit percentages on worldwide net sales of any approved ADCs developed under the agreement.

An even broader collaboration deal was signed between Wave Life Sciences and GSK. The collaboration covers Wave's oligonucleotide therapeutics, including the company's preclinical RNA editing program targeting alpha-1 antitrypsin deficiency (AATD), WVE-006. The discovery collaboration has an initial four-year research term. It combines GSK's unique insights from human genetics, as well as its global development and commercial capabilities, with Wave's proprietary discovery and drug development platform, PRISM™. Under the terms of the agreement, Wave will receive an upfront payment of USD 170 mn, which includes a cash payment of USD 120 mn and a USD 50 mn equity investment. For the WVE-006 program, Wave is eligible to receive up to USD 225 mn in development and launch milestone payments and up to USD 300 mn in sales-related milestone payments, as well as tiered sales royalties. Development and commercialization responsibilities will transfer to GSK after Wave completes the first-in-patient study. For each of GSK's eight collaboration programs, Wave will be eligible to receive up to USD 130 to 175 mn in development and launch milestones and USD 200 mn in sales-related milestones, along with tiered sales royalties. Wave will lead all preclinical research for GSK and Wave programs up to investigational new drug (IND) enabling studies. GSK collaboration programs will transfer to GSK for IND-enabling studies, clinical development, and commercialization. The collaboration includes an option to extend the research term for up to three additional years, expanding the number of programs available to both parties.

Agios extended its cash run rate even further by enhancing its balance sheet situation through a monetization of its remaining Tibsovo royalty rate. The company has sold its rights to 5% royalties on U.S. net sales of Servier's TIBSOVO (ivosidenib tablets) to Sagard for a one-time payment of USD 131.8 mn and retains its rights to a potential future milestone payment of USD 200 mn for vorasidenib, as well as 15% royalties on U.S. net sales of vorasidenib.

Selective takeover activity in the fourth quarter

With M&A activity still at low levels and mostly focused towards revenue-generating biotechnology companies, two larger deals being Amgen bidding for Horizon and Pfizer for Biohaven supported the sector somewhat. BB Biotech has not participated in these two large deals but benefited by Sumitomo Pharma announcing an offer for Myovant, initially for USD 22.75 per share followed by a slightly higher bid at USD 27 per share in cash. The transaction is substantially below our internal valuation assumption and will require approval from the minority shareholders.

In contrast to having portfolio companies being taken over, larger and more established companies such as Incyte are continuously looking for companies, assets and technologies to improve their pipeline and product offering. Incyte announced the acquisition of Villaris, a privately held company focused on autoimmune diseases, with its lead molecule auremolimab to be developed for vitiligo. Under the terms of the agreement, Incyte will acquire Villaris and the exclusive global rights to develop and commercialize auremolimab for all uses, including in vitiligo and other autoimmune and inflammatory diseases. Incyte will make an upfront payment of USD 70 mn, and Villaris shareholders will be eligible of up to USD 310 mn upon achievement of certain development and regulatory milestones, as well as up to an additional USD 1.05 bn in commercial milestones on net sales of the product.

Portfolio at a glance

Securities as at December 31, 2022

Company	Number of securities	Change since 31.12.2021	Local currency	Share price	Market value in CHF mn	In % of securities	In % of shareholders' equity	In % of company
Ionis Pharmaceuticals	9 635 000	(597 973)	USD	37.77	336.4	11.0%	12.5%	6.8%
Argenx SE	892 503	(78 035)	USD	378.83	312.6	10.2%	11.6%	1.6%
Neurocrine Biosciences	2 730 000	(285 400)	USD	119.44	301.5	9.9%	11.2%	2.8%
Moderna	1 501 951	(161 398)	USD	179.62	249.4	8.2%	9.3%	0.4%
Vertex Pharmaceuticals	930 523	(99 477)	USD	288.78	248.4	8.1%	9.2%	0.4%
Incyte	2 891 077	(5 923)	USD	80.32	214.7	7.0%	8.0%	1.3%
Alnylam Pharmaceuticals	890 000	(220 000)	USD	237.65	195.5	6.4%	7.3%	0.7%
Intra-Cellular Therapies	3 291 479	(246 940)	USD	52.92	161.0	5.3%	6.0%	3.5%
Myovant Sciences	5 872 639	(249 400)	USD	26.96	146.4	4.8%	5.5%	6.1%
Revolution Medicines	4 777 562	1 356 100	USD	23.82	105.2	3.4%	3.9%	5.4%
Agios Pharmaceuticals	4 030 792	(281 500)	USD	28.08	104.6	3.4%	3.9%	7.3%
Sage Therapeutics	2 950 278	(219 826)	USD	38.14	104.0	3.4%	3.9%	5.0%
Celldex Therapeutics	1 800 000	1 800 000	USD	44.57	74.2	2.4%	2.8%	3.8%
Arvinas	2 136 412	(40 491)	USD	34.21	67.6	2.2%	2.5%	4.0%
Relay Therapeutics	4 120 720	34 758	USD	14.94	56.9	1.9%	2.1%	3.4%
Macrogenics	8 929 963	1 654 399	USD	6.71	55.4	1.8%	2.1%	14.5%
Fate Therapeutics	4 839 779	1 138 443	USD	10.09	45.1	1.5%	1.7%	5.0%
Exelixis	2 654 500	(180 500)	USD	16.04	39.4	1.3%	1.5%	0.8%
Crispr Therapeutics	888 605	(60 979)	USD	40.65	33.4	1.1%	1.2%	1.1%
Wave Life Sciences	4 494 458	(108 400)	USD	7.00	29.1	1.0%	1.1%	5.2%
Beam Therapeutics	693 121	86 300	USD	39.11	25.1	0.8%	0.9%	1.0%
Esperion Therapeutics	4 194 064	(283 900)	USD	6.23	24.2	0.8%	0.9%	5.7%
Mersana Therapeutics	4 066 200	(68 800)	USD	5.86	22.0	0.7%	0.8%	4.1%
Kezar Life Sciences	3 000 000	(1 918 148)	USD	7.04	19.5	0.6%	0.7%	4.4%
Essa Pharma	7 879 583	2 863 769	USD	2.52	18.4	0.6%	0.7%	17.9%
Scholar Rock Holding	2 132 725	(142 400)	USD	9.05	17.8	0.6%	0.7%	4.1%
Rivus Pharmaceuticals [1]			USD		16.2	0.5%	0.6%	
Generation Bio Co.	3 608 280	(244 900)	USD	3.93	13.1	0.4%	0.5%	6.1%
Black Diamond Therapeutics	5 377 839	1 937 839	USD	1.80	8.9	0.3%	0.3%	14.8%
Molecular Templates	11 192 003	400 000	USD	0.33	3.4	0.1%	0.1%	19.9%
Homology Medicines	1 622 522	(114 600)	USD	1.26	1.9	0.1%	0.1%	2.8%
Radius Health – Contingent Value Right	8 733 538	8 733 538	USD	0.00	0.0	0.0%	0.0%	
Total securities					**3 051.3**	**100.0%**	**113.6%**	
Other assets					2.0		0.1%	
Other payables					(367.3)		(13.7%)	
Net asset value					**2 686.1**		**100.0%**	

[1] Unlisted company

Exchange rate as at 31.12.2022: USD/CHF: 0.9245

2023: numerous catalysts for the biotech sector

Technological progress is the basis for the transformation of many disease areas, with mRNA, siRNA and ASO-based drugs playing a particularly important role. Antibody drug conjugates or gene therapies are also in the focus of interest, where important development steps are expected. Last but not least, M&A activities and partnerships are likely to increase.

Higher capital costs the new reality

Biotech companies all have gone through, or are in the midst of their life cycle, requiring years of substantial capital investments, first in technology and drug discovery and selection, followed by years of clinical development. If approved, the business model to launch drugs is a capital-intense undertaking and in general takes two to three years to reach profitability following a successful launch. With drug development companies' profits years away and often multiple rounds of intermediate financing required, the hurdle has all the more increased in the current capital environment with Fed fund rates per end of 2022 at 4.5%. This implies that the expected returns on invested capital have increased and thus increasing discount rates are applied to discounting of future cash flow that in aggregate yield a net present value.

With many companies paralyzed by these steep interest rate hikes, the industry is starting to adapt and the upper echelons of quality asset and technology companies are rediscovering the old paths of partnering with larger, profitable and well capitalized biotechnology and pharmaceutical companies.

Dialogue with management teams has become more centric around business models and available options – or alternatives in such an environment. Most companies' executives are planning for many years of higher capital costs despite having seen more takeover activity in mainly revenue-generating companies and a clear acceleration in licensing deals over recent quarters. Hybrid models between partnership and fully owned assets have become a new reality, mostly for the platform companies. Single asset companies can still succeed, but can easily fall into a trap of dwindling valuation in the face of their stable capital demands.

Technology as basis to transform many disease areas

mRNA vaccines have gained the upper hand in the pandemic, both in terms of efficacy and speed to markets as well as scaling of manufacturing capacity. Similarly, recent Phase III data from Moderna for its RSV vaccine are highly promising, at par with the best and newest vaccine candidates. We expect a similar outcome for influenza, with mRNA being on par in terms of efficacy with the potential for superiority in future iterations by leveraging intrinsic advantages of the technology for extension of antigen valency and strain coverage. Combined with the more rapid selection and adoption to new variants and the combinability allowing to cover the two or eventually three largest respiratory virus markets with a single

shot provides the basis for our assumptions on mRNA vaccines' ability to capture substantial market share.

Technologies that are undergoing more classical market cycles, initially starting in orphan indication followed by addressing more prevalent diseases with next generation assets are for example the RNA targeting agents based on short interference RNA (siRNA) and antisense oligonucleotides (ASOs). These companies (e.g. Alnylam or Ionis) are making steady progress, which is most evidently provided by the current and future product offerings in the transthyretin amyloidosis. In hereditary TTR patients with polyneuropathy, both platforms have shown positive late-stage results and the second generation drug of both technologies are in registration or already approved. For the substantially larger indication of TTR cardiomyopathy the same assets are in late-stage clinical development with outcomes trials expected to read out within the next few years. Both companies are developing siRNA and ASO-based drugs for other large patient populations, such as for patients suffering from high triglycerides, high lipids or other cardiovascular risk factors such as liboprotein (a), resistant hypertension and larger neurological indications such as Alzheimer's disease. The basis for targeting these larger patient populations lies within the significantly improved technology, allowing to deliver the drugs less frequently and at lower doses, more convenient administration, with high efficacy and a very good safety margins and few adverse events. We expect substantial progress and further product approvals in 2023 and beyond, with the class to grow substantially in patient reach and revenue potential.

Antibody drug conjugates – again of key interest in oncology

Similar to the progress of new formats, antibody drug conjugates are impacting many solid tumor indications. The successful launch of ADC drugs by large pharma as treatment options for breast cancer patients, and more recently approvals for Immunogen and clinical trial results for Mersana are expected in the second half or 2023. ADCs have become the hot property in the oncology space, not really the new kid on the block given decades of development due to continued challenging situations for other approaches to improve clinical results against or on top of the PD1/PDL1 antibodies. Macrogenics, Incyte and Exelixis are further portfolio companies of BB Biotech that are developing ADCs for different solid tumors. Challenges of the past such as better targeting of tumors, good delivery of the toxin pay-load to the cells and either uptake or proximal killing are being addressed by novel surface targets, improved linker technology and tumor specific toxins. This allows for a broader therapeutic window and potentially for a better outcome. As most drugs have evolved in the cancer field, ADCs are expected to not only be good last line treatment options but to also demonstrate a good efficacy versus tolerability profile in earlier treatment lines for cancer patients, expected to result in a highly attractive business proposition for the drug development industry.

Similar to the progress of new formats, antibody drug conjugates are impacting many solid tumor indications.

BB Biotech Investment Strategy

BB Biotech's long standing investment strategy is to invest capital in promising technology platforms and promising early clinical assets, follow these companies through their clinical development, regulatory approval, commercial launches, sustainable revenue and profit growth to ultimately become more mature companies. Upon such a long term cycle, BB Biotech would divest and reinvest into the next promising candidates. The same trend will continue to make smaller and mid cap companies attractive licensing partners for large pharmaceutical and large cap biotech companies, either signing attractive business development deals or ultimately through consolidation.

In vivo gene therapies and first ex vivo gene editing approaching reaching the market in 2023

The most advanced platform approaches in gene therapy and in gene editing are starting to impact the healthcare system. Once every few years to even once a lifetime treatments are appealing for patients suffering from monogenetic driven diseases with a high medical burden and costs for the healthcare system. In vivo gene therapy approaches in hemophilia are in the midst of product launches and other diseases with the possibility of replacing dysfunctional genes with a viral delivery system are in late clinical testing. Our portfolio company Generation Bio continues to develop viral free delivery of ceDNA, potentially offering better safety and the possibility for repeat dosing, if required. We expect updates and progress during 2023. Of key interest for the investment team of BB Biotech are initially the ex vivo gene editing products such as CTX001 developed by Crispr Therapeutics and its development and commercialization partner Vertex. FDA and EMA decisions are expected in late 2023, followed by the roll-out of this once-in-a-lifetime functionally curative product for sickle cell disease and beta thalassemia patients. Next generation approaches are testing in vivo delivery of the gene editing enzyme and the required genetic fragments to achieve correction of genetic defects or aberrations. We believe the benefits of avoiding double strand breaks in DNA will enable base editing and as a further iteration prime editing to succeed the vivo setting and we perceive our investment in Beam Therapeutics as the key player in terms of having access, IP and capabilities for these non-nuclease containing approaches. An uncertainty regarding pricing strategies and mostly around patient acceptance of this novel concept and technology remains and will be carefully monitored and gauged by investors over the coming years. Interestingly, most clinical stage assets are being developed by smaller and mid cap biotechnology companies, yet another example of bigger companies initially watching from the sidelines, which may eventually result in an urge to gain access by pricy acquisitions once the visibility on winning assets has improved.

Something is brewing in the business development and M&A world

With M&A activity substantially down over the peak year of 2019, many pharmaceutical companies and large biotechnology company retain flexibility to acquire smaller and mid cap biotechnology companies. Some Wall Street companies quote mid triple digit USD billion capacity, with more or less each company in our portfolio being a potential acquisition candidate. If valuations continue to be attractive, and if smaller and mid cap companies offer promising drugs and platform technologies, we expect a continued takeover activity with an acceleration to be expected in the next years. The core driver of these acquisition remains with the nature of patent cliffs of major revenue and profit contributors of many of the large capitalized companies. It remains to be seen whether large biopharmaceutical companies prefer to consolidate with similar size companies resulting in synergies and costs savings or if they prefer mid cap and smaller cap companies as source to address this top to bottom line looming threat. Many of the larger capitalized companies have experienced a multiple expansion over the past few years, resulting in another source of acquisition currency – offering equity instead of cash. Valuations of smaller and midcap companies continue to be under pressure, as indicated by the fact that the cumulative market cap of the top eight NBI index members is larger than the remaining 265 members.

Healthcare politics with the focus on the IRA implementation

The healthcare sector, and even more so the drug development sectors such as pharma and biotechnology, have always been impacted by political changes in large markets, such as the US. With the midterm election in November 2022 resulting in a split Congress, the Inflation Reduction Act of summer 2022 will start to gain renewed attention in 2023. The companies and investors will carefully monitor how the IRA will be implemented, very importantly when the first drug target list for future price negotiation will be made public, and more specifically which drugs will be on this initial list. Overall, smaller companies with new drug launches will benefit from many exemptions and are expected to be less impacted than pharmaceutical companies with older drug products targeting Medicare and Medicaid patients.