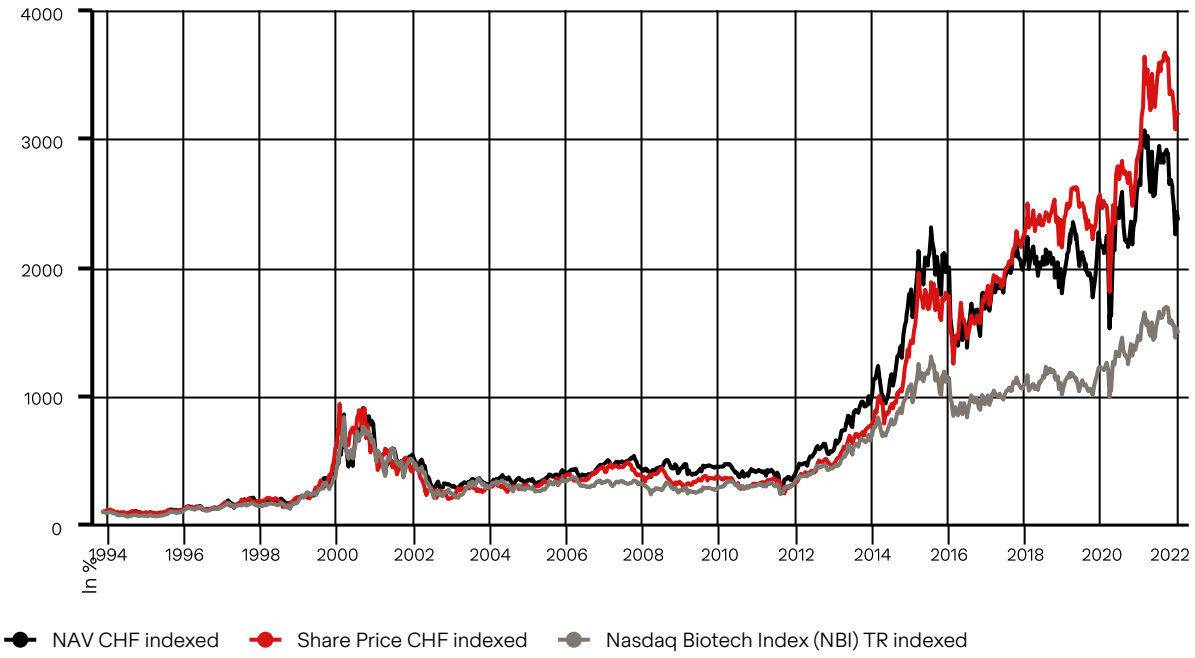
Business report

Performance/Multi-year comparison

Indexed performance since launch

BB Biotech AG (SIX)-CHF



Annual performance

31.12.2021

	SHARE	NAV	NBI TR
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%)
2017	22.9%	23.4%	16.4%

Annualized performance

31.12.2021

	SHARE	NAV	NBI TR
1 year	8.3%	(11.5%)	3.0%
3 years	15.3%	10.7%	13.6%
5 years	12.3%	7.4%	9.4%
since inception [1)]	13.1%	11.9%	10.1%

[1] 09.11.1993

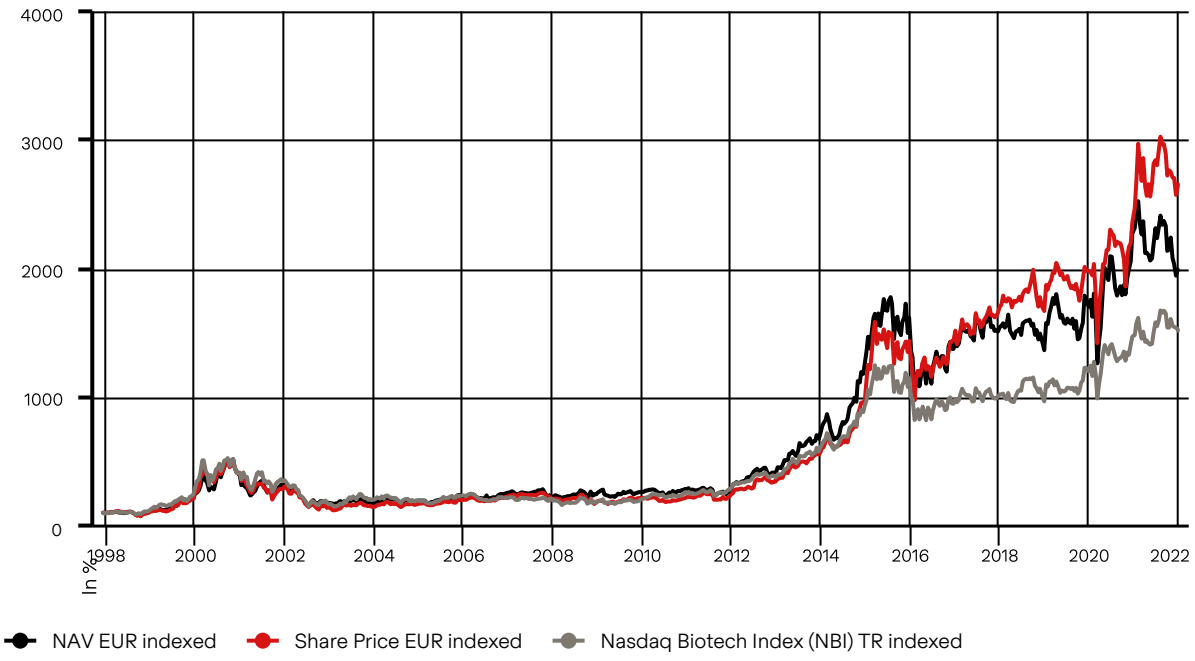
Cumulated performance

31.12.2021

	SHARE	NAV	NBI TR
1 year	8.3%	(11.5%)	3.0%
3 years	53.3%	35.7%	46.7%
5 years	78.6%	43.3%	57.1%
since inception [1)]	3 095%	2 278%	1 397%

[1] 09.11.1993

BB BIOTECH AG (XETRA)-EUR



Annual performance

31.12.2021

	SHARE	NAV	NBI TR
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%)
2017	12.9%	12.5%	6.7%

Cumulated performance

31.12.2021

	SHARE	NAV	NBI TR
1 year	13.3%	(7.8%)	7.4%
3 years	65.4%	47.4%	59.1%
5 years	82.4%	47.3%	65.5%
since inception [1)]	2 556%	1 889%	1 416%

[1] 10.12.1997

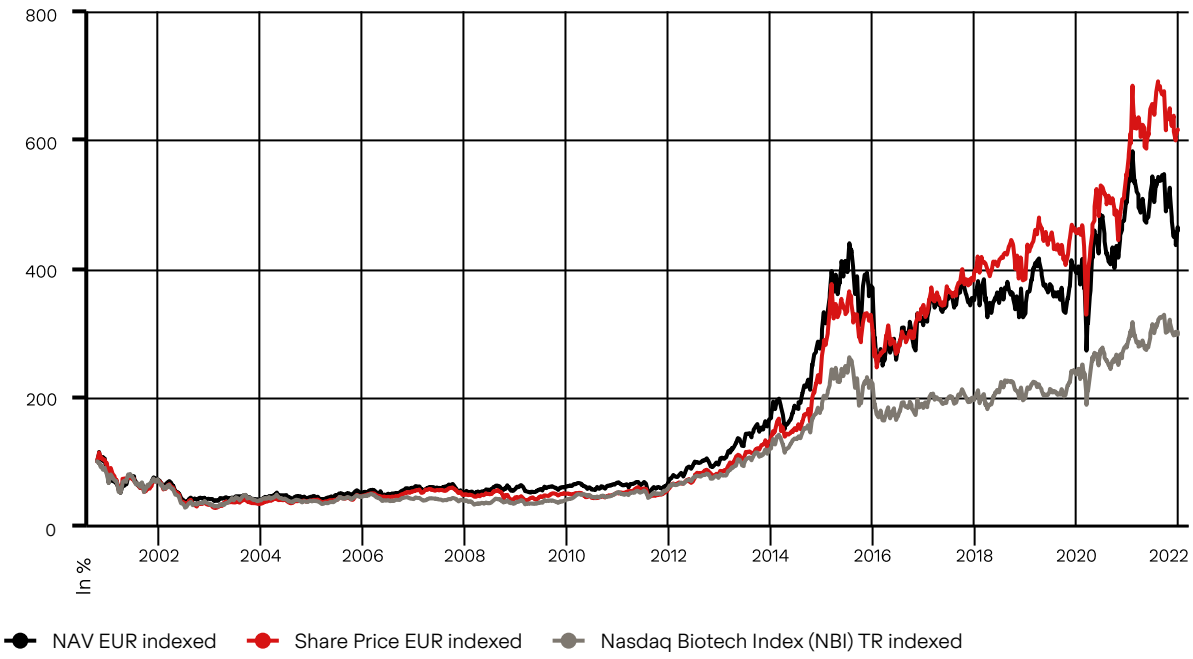
Annualized performance

31.12.2021

	SHARE	NAV	NBI TR
1 year	13.3%	(7.8%)	7.4%
3 years	18.2%	13.8%	16.7%
5 years	12.8%	8.1%	10.2%
since inception [1)]	14.6%	13.2%	12.0%

[1] 10.12.1997

BB BIOTECH AG (MILAN)-EUR



Annual performance

31.12.2021

	SHARE	NAV	NBI TR
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%)
2017	12.2%	12.5%	6.7%

Cumulated performance

31.12.2021

	SHARE	NAV	NBI TR
1 year	13.0%	(7.8%)	7.4%
3 years	65.9%	47.4%	59.1%
5 years	83.7%	47.3%	62.5%
since inception [1)]	516%	359%	197%

[1] 19.10.2000

Annualized performance

31.12.2021

	SHARE	NAV	NBI TR
1 year	13.0%	(7.8%)	7.4%
3 years	18.4%	13.8%	16.7%
5 years	12.9%	8.1%	10.2%
since inception [1)]	8.9%	7.4%	5.3%

[1] 19.10.2000

Multi-year comparison

	2021	2020	2019	2018	2017
Market capitalization at the end of the period (in CHF mn)	4 274.1	4 107.9	3 670.3	3 235.4	3 576.1
Net Asset Value at the end of the period (in CHF mn)	3 283.5	3 887.5	3 393.0	2 884.5	3 538.7
Number of shares (in mn)	55.4	55.4	55.4	55.4	55.4
Trading volume (in CHF mn)	2 101.0	2 315.6	2 004.2	2 610.7	2 864.7
Profit/(loss) (in CHF mn)	(404.8)	691.2	677.4	(471.3)	687.5
Closing price at the end of the period in CHF	77.15	74.15	66.25	58.40	64.55
Closing price (G) at the end of the period in EUR	74.05	68.00	61.40	52.00	55.68
Closing price (I) at the end of the period in EUR	74.40	68.50	61.00	52.00	55.20
Stock performance (incl. distributions) [1)]	8.3%	19.3%	18.5%	(5.2%)	22.9%
High/low share price in CHF	92.20/73.40	74.70/45.44	73.20/59.35	74.10/56.10	67.80/52.10
High/low share price in EUR	86.20/67.80	69.00/43.04	64.70/52.10	64.80/48.60	59.10/48.42
Premium/(discount) (annual average)	19.5%	9.2%	11.8%	9.7%	(2.5%)
Cash distribution / dividend in CHF (*proposal)	3.85*	3.60	3.40	3.05	3.30
Degree of investment (quarterly figures)	108.6%	106.8%	109.1%	108.4%	103.1%
Total Expense Ratio (TER) p.a. [2)]	1.22%	1.25%	1.26%	1.25%	1.27%

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

Shareholder letter

The year 2021 was a volatile market environment for all involved in biotechnology investing, including BB Biotech. The biotech and pharmaceutical sector adapted to the SARS-CoV-2 virus pandemic cycling through Delta and now Omicron variants with offers of booster vaccines, therapeutic antibodies and most recently new antiviral drugs. For human health overall, new modalities such as genetic medicines, cell-based therapies and RNA-based drugs continue to make positive strides and are expected to improve the prognosis of severe and chronic diseases in the coming years.

Dear Shareholders

During the last quarter of the year major global equity indices extended their 2021 gains. Many markets achieved new all-time highs even though SARS-CoV-2 infection rates reaccelerated in the last weeks of 2021 due to the rapid spread of the Omicron variant. The Dow Jones (+21.0% in USD), the Dax (+15.8% in EUR), and the SPI (+23.4% in CHF) indices all showed gains for the year in line with the technology dominated Nasdaq Composite (+22.2% in USD). The Nasdaq Biotech Index (NBI) traded flat for the year (0.0% in USD), lagging the broader markets.

Although the SARS-CoV-2 pandemic remained a dominant topic for healthcare authorities in 2021, an impressive array of drug approvals was reported by the US FDA – total drug approvals comprised 50 NDAs and 10 BLAs (vaccines, blood and cell products) for the year. Additionally, multiple SARS-CoV-2 diagnostic tests, vaccines and drugs were granted emergency use authorization (EUA) by the FDA during 2021.

For 2021, BB Biotech's total share return of +8.3% in CHF and +13.3% in EUR trended like European equity indices, better than the biotech indices and deviating from the underlying portfolio performance. Strengthening of the USD versus the CHF and EUR throughout the year created modest support for CHF and EUR-denominated performance. The portfolio Net Asset Value (NAV) declined 11.5% in CHF, 7.8% in EUR and 14.2% in USD for 2021.

For the fourth quarter, BB Biotech's share price declined 8.3% in CHF and 4.7% in EUR. BB Biotech shares proved more resilient than the smaller and mid cap driven correction in the portfolio. BB Biotech's Net Asset Value (NAV) decreased 14.2% in CHF, 10.9% in EUR and 12.5% in USD, while the NBI index decline of 6.9% in USD for the same period.

The consolidated fourth quarter 2021 data for BB Biotech indicates a net loss of CHF 546 mn versus the 2020 fourth quarter net gain of CHF 665 mn. The consolidated full year 2021 data showed a net loss of CHF 405 mn compared to a net gain of CHF 691 mn for 2020.

Proposed expansion of the Board of Directors of BB Biotech

On the background of an increasingly challenging environment for the biotechnology industry BB Biotech is extremely happy to nominate Dr. Pearl Huang, CEO of Cygnal Therapeutics, and Dr. Laura Hamill, former Executive Vice President Worldwide Commercial Operations for Gilead, for election to the Board of Directors of BB Biotech AG. At the scheduled upcoming annual general assembly, all four existing board members will stand for re-election by the shareholders on March 17, 2022. Thus, the Board of Directors of BB Biotech is proposed to be enlarged to six members.

Dividend 2022

CHF 3.85

(Proposed)

A proposed dividend of CHF 3.85 per share

The Board of Directors will propose a regular dividend of CHF 3.85 per share at the AGM on March 17, 2022. Applied to the average share price of December 2021 and consistent with the dividend policy introduced in 2013, and corresponding to a 5% dividend yield.

Portfolio adjustments in the fourth quarter 2021

During the fourth quarter, the investment team made no new investments but focused on careful adjustments of existing portfolio positions. Smaller additions to existing portfolio positions were undertaken in the fourth quarter in oncology-focused companies including Relay Therapeutics, Macrogenics and Fate Therapeutics. Similarly, further shares were acquired in commercial (Neurocrine and Myovant) and in genetic medicines companies (Wave Life Sciences, Generation Bio and Ionis). Some share profits were taken in Intra-Cellular with the FDA's approval for Caplyta to treat bipolar disorder patients. Moderna's valuation experienced significant volatility in the last quarter 2021, as investors analyzed different scenarios for the Omicron variant. The investment team took advantage of these swings with short-term trading activity, realizing further profits. Altogether, additional investments combined with a declining equity base led to an increase in the BB Biotech investment level by around 4% compared to the third quarter, ending 2021 at 111%.

During the fourth quarter, the investment team made no new investments but focused on careful adjustments of existing portfolio positions.

Fourth-quarter portfolio update

The fourth quarter 2021 provided multiple major milestones for our portfolio holdings such as clinical results, regulatory decisions and licensing deals. With the Omicron variant being highly transmissible but less harmful than previous SARS-CoV-2 variants, and the mRNA vaccine boosters providing good protection against Omicron, the focus for investors regarding pipeline updates has shifted back towards chronic and severe diseases.

Outlook for 2022 with exciting sector fundamentals and anticipated M&A activities

We believe that 2022 will include the continued global vaccination strategies to fight the spread of SARS-CoV-2 variants, including Omicron. Expectations that Omicron could be the «final» severe variant may prove to be premature. With the vaccine and drug industry able to adapt quickly, companies such as Moderna are expected to remain responsive to current and future variants, while at the same time widening their focus on longer term pipeline strategies beyond COVID-19.

We continue to strive for a balanced portfolio between more established mid cap companies and technology leading earlier stage companies.

We continue to strive for a balanced portfolio between more established mid cap companies and technology leading earlier stage companies. It anticipates that the industry will continue to deliver significant progress for both. Product launches such as Vyvgart from Argenx for the treatment of gMG patients or Caplyta from Intra-Cellular for the treatment of bipolar disorder patients will be yardsticks not only for these companies but for the sector as a whole. For development stage companies, managing the vast number of clinical trials will continue to be a challenge in the current COVID-19-restricted environment. BB Biotech's exposure to oncology development stage companies will be geared towards many clinical trial read-outs during 2022.

With smaller and mid cap company valuations substantially lower than one year ago, we see compelling re-entry opportunities. Similarly, the more established mid cap portfolio companies such as Neurocrine, Incyte and Ionis own attractive assets and technology, which can trigger renewed interest from new investors – or from strategic partners as M&A targets.

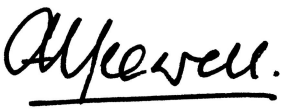
Clinical candidates based on new technologies such as genetic medicines are making progress. Crispr Therapeutics together with its development partner Vertex are planning a regulatory submission by late 2022 for CTX001 to treat beta thalassemia and sickle cell patients. Thus, an ex vivo gene editing product could become available as early as 2023 – reviving investors' interest in the field. Other RNA targeting medicines will be launched in the next 12 to 24 months including products from Alnylam and Ionis. As always, investors will weigh potential implications from US government policymakers associated with midterm elections in late 2022.

Our long-term horizon and structure enables careful investment that does not follow broad market opinions. The highly specialized investment team at BB Biotech believes that the growth case for biotechnology and valuations for portfolio companies are both compelling. We anticipate that following two years dominated by SARS-CoV-2 headlines, 2022 will include advance of the industry to the severe and chronic diseases that continue to demand perennial progress and looks forward to more exciting news flow from our portfolio companies.

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

The Board of Directors of BB Biotech AG

Dr. Erich Hunziker
Chairman



Dr. Clive Meanwell

Prof. Dr. Mads Krogsgaard Thomsen

Dr. Thomas von Planta

Portfolio Update Q4 2021

The fourth quarter 2021 provided multiple major milestones for our portfolio holdings such as clinical results, regulatory decisions and licensing deals. With the Omicron variant being highly transmissible but less harmful than previous SARS-CoV-2 variants, and the mRNA vaccine boosters providing good protection against Omicron, the focus for investors regarding pipeline updates has shifted back towards chronic and severe diseases. The clinical results for the biotechnology industry and our portfolio saw a mixed picture in the last quarter. The negative environment exaggerated market news, with positive updates not necessarily leading to higher valuations.

Many milestones including clinical trial data

Late stage trial read-outs were mixed in the last quarter of 2021. Sage Therapeutics reported further positive data for Zuranolone in the ongoing shoreline study in patients with major depression disorder (MDD). At 50 mg treatment and measured at day 15 following the initial two week treatment, 75% of patients achieved a response (at least 50% reduction from baseline) and 40% achieved a remission. Importantly, the large majority of patients treated for 14 days at 50 mg per day required either no or maximum one additional 14 day course of therapy to maintain an improved status. Sage and its development partner Biogen are planning to file Zuranolone for MDD in the US in late 2022, allowing for a potential market launch in late 2023.

Biogen reported results from its pivotal Phase III VALOR study of tofersen (BIIB067), an investigational antisense drug being evaluated for people with superoxide dismutase 1 (SOD1) amyotrophic lateral sclerosis (ALS). Tofersen did not meet the primary endpoint of change from baseline to week 28 in the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R). Due to trends favoring tofersen across multiple secondary and exploratory measures of biologic activity and clinical function, Biogen announced to invest in the clinical study called ATLAS testing tofersen in pre-symptomatic individuals with a SOD1 genetic mutation and to broaden early access to ALS patients in expanded access program.

Radius Health reported on three Phase III studies in the fourth quarter of 2021. The ATOM study met its primary endpoint – the percentage change in lumbar spine (LS) bone mineral density (BMD) compared to placebo – demonstrating statistical significance after 12 months in male osteoporosis patients. The more important wearable study did not meet its primary endpoint of non-inferiority for the transdermal delivered abaloparatide 300 micrograms versus the subcutaneous delivered and approved Tymlos 80 micrograms in the percent change from baseline in lumbar spine (LS) bone mineral density (BMD) at 12 months. The patch demonstrated a 7.1% increase in lumbar spine bone mineral density versus subcutaneous Tymlos achieving 10.9%. Thus the patch, albeit its anabolic activity, missed the non-inferiority margin of 2.0%.

Radius partner Menarini for the company's oncology asset elacestrant reported positive results for the EMERALD study. Both primary endpoints, showing statistically significant PFS

in the overall population and ESR1 mutation subgroup were met. The safety profile of elacestrant exhibited in EMERALD was similar to that of the previous clinical trial. Given these results, Menarini and Radius plan on proceeding with regulatory submissions in both the US and in EU in 2022.

Promising proof-of concept data was reported by Relay Therapeutics and by Fate Therapeutics. Relay Therapeutics announced interim clinical data for RLY-4008, a highly selective irreversible and oral small molecule inhibitor of FGFR2, in a first-in-human trial in patients with FGFR2-altered cholangiocarcinoma and multiple other solid tumors. The data suggests that RLY-4008 is the first investigational therapy designed to selectively bind to FGFR2, and importantly, avoiding off-isoform toxicities for the treatment of patients with FGFR2-altered tumors. In pan-FGFRi treatment-naïve cholangiocarcinoma patients, RLY-4008 demonstrated tumor shrinkage in all six patients, with three achieving confirmed partial responses. Three of these six patients remain on study and a fourth patient went on to surgery with curative intent. Further data from dose expansion cohorts can be expected during 2022.

Fate Therapeutics, another of our oncology portfolio companies, presented promising interim dose-escalation clinical data from its FT596 program in relapsed refractory B-cell lymphoma. The data presented demonstrates that off-the-shelf, iPSC-derived CAR NK cells can bring substantial therapeutic benefit to heavily pre-treated patients in urgent need of therapy. Over half of the patients treated with a higher single dose of FT596 in combination with rituximab achieved a complete response with a favorable safety profile that is clearly differentiated from CAR T-cell therapy. The company is expected to provide data for patients treated at yet a higher dose and for patients earlier in care, most importantly data on duration of response in 2022.

Moderna disclosed important updates for its mRNA vaccine candidates. Most importantly, the company presented reassuring data for its SARS-CoV-2 authorized booster, with the 50 microgram dose of mRNA-1273 increased Omicron specific neutralizing antibody levels by approximately 37 fold, versus the 100 microgram dose increasing the neutralizing antibody levels by 83 fold. Thus, the company plans to use mRNA-1273 as first line of defense against Omicron but at the same time develop an Omicron-specific variant vaccine (mRNA-1273.529), which has entered the clinic in January 2022. Next to the pandemic vaccine efforts, Moderna updated investors on its quadrivalent influenza vaccine (mRNA-1010) effectively boosted titers against all four strains in older and younger adults, with no significant safety concerns observed. The quadrivalent mRNA-1010 encodes for the hemagglutinin (HA) protein from four seasonal influenza viruses based on the recommendations of the World Health Organization (WHO), including seasonal influenza A/H1N1, A/H3N2 and influenza B/Yamagata- and B/Victoria-lineages. Importantly, Moderna is expected to present data in 2022 for mRNA-1011 that includes one additional hemagglutinin (HA) antigen and mRNA-1012 with two additional HA antigens. Separately, the company is also developing two next-generation flu candidates that incorporate neuraminidase antigens to broaden immunity beyond hemagglutinin (mRNA-1020, mRNA-1030), all being part of the company's strategy to ultimately develop a pan-respiratory annual booster vaccine.

One of our pre-clinical companies, Generation Bio, is developing gene therapies devoid of viral packaging and viral vector biology. The company unfortunately updated investors in the fourth quarter that the latest generation of LNPs in combination with ceDNA plasmids did not maintain and translate expression levels from mice to nonhuman primate models. Thus, the company is back to the drawing board to develop functional LNP/ceDNA combinations that will translate into higher expression levels in NHPs and only then will move into human clinical trials. Strategically, this could lead to the ophthalmology programs jumping ahead of the liver targeting application, with further updates regarding the pre-clinical progress expected for 2022.

Numerous milestones with regard of regulatory decisions

BB Biotech's portfolio holdings updated on multiple regulatory decisions in the fourth quarter 2021 such as

- Vyvgart (efgartigimod alfa-fcab) from Argenx was approved by the FDA for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.
- Caplyta (lumateperone) from Intra-Cellular was approved by FDA to treat depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults as monotherapy and as adjunctive therapy with lithium or valproate.
- Leqvio (inclisiran) from Novartis/Alnylam was approved by FDA an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of lowdensity lipoprotein cholesterol (LDL-C).

Beneficial collaboration in the last quarter of 2021

With M&A activity close to a standstill and no deals within the industry and our portfolio holdings, business development activities were of interest. AstraZeneca has entered into a new global development and commercialization agreement with Ionis Pharmaceuticals for eplontersen, formerly known as IONIS-TTR-LRX. Eplontersen is a ligand-conjugated antisense (LICA) investigational medicine currently in Phase III clinical trials for amyloid transthyretin cardiomyopathy (ATTR-CM) and amyloid transthyretin polyneuropathy (ATTR-PN). It is designed to reduce the production of transthyretin (TTR protein) to treat both hereditary and non-hereditary forms of TTR amyloidosis (ATTR). The companies will jointly develop and commercialize eplontersen in the US, while AstraZeneca will develop and commercialize it in the rest of the world, except in Latin America. Ionis will receive an upfront payment of USD 200 mn and additional conditional payments of up to USD 485 mn following regulatory approvals and up to USD 2.9 bn of sales-related milestones based on sales thresholds between USD 500 mn and USD 6 bn, plus royalties in the range of low double-digit to mid-twenties percentage depending on the region.

Portfolio at a glance

Securities as at December 31, 2021

Company	Number of securities	Change since 31.12.2020	Local currency	Share price	Market value in CHF mn	In % of securities	In % of shareholders' equity	In % of company
Moderna	1 663 349	(1 191 614)	USD	253.98	385.7	10.6%	11.7%	0.4%
Argenx SE	970 538	49 206	USD	350.19	310.3	8.5%	9.5%	1.9%
Ionis Pharmaceuticals	10 232 973	2 012 973	USD	30.43	284.3	7.8%	8.7%	7.2%
Neurocrine Biosciences	3 015 400	(19 600)	USD	85.17	234.5	6.4%	7.1%	3.2%
Vertex Pharmaceuticals	1 030 000	130 000	USD	219.60	206.5	5.7%	6.3%	0.4%
Fate Therapeutics	3 701 336	1 671 336	USD	58.51	197.7	5.4%	6.0%	3.9%
Incyte	2 897 000	(3 000)	USD	73.40	194.1	5.3%	5.9%	1.3%
Alnylam Pharmaceuticals	1 110 000	(45 000)	USD	169.58	171.8	4.7%	5.2%	0.9%
Intra-Cellular Therapies	3 538 419	–	USD	52.34	169.1	4.6%	5.1%	4.3%
Arvinas	2 176 903	–	USD	82.14	163.2	4.5%	5.0%	4.1%
Agios Pharmaceuticals	4 312 292	153 390	USD	32.87	129.4	3.6%	3.9%	7.9%
Sage Therapeutics	3 170 104	1 630 000	USD	42.54	123.1	3.4%	3.7%	5.4%
Relay Therapeutics	4 085 962	2 676 605	USD	30.71	114.6	3.1%	3.5%	3.8%
Biogen	500 000	(37 000)	USD	239.92	109.5	3.0%	3.3%	0.3%
Macrogenics	7 275 564	2 460 000	USD	16.05	106.6	2.9%	3.2%	11.9%
Myovant Sciences	6 122 039	1 365 000	USD	15.57	87.0	2.4%	2.6%	6.6%
Revolution Medicines	3 421 462	3 421 462	USD	25.17	78.6	2.2%	2.4%	4.6%
Kezar Life Sciences	4 918 148	385 000	USD	16.72	75.1	2.1%	2.3%	9.2%
Crispr Therapeutics	949 584	48 700	USD	75.78	65.7	1.8%	2.0%	1.2%
Essa Pharma	5 015 814	5 015 814	USD	14.20	65.0	1.8%	2.0%	11.4%
Scholar Rock Holding	2 275 125	19 474	USD	24.84	51.6	1.4%	1.6%	6.5%
Radius Health	7 705 714	250 000	USD	6.92	48.7	1.3%	1.5%	16.3%
Exelixis	2 835 000	–	USD	18.28	47.3	1.3%	1.4%	0.9%
Beam Therapeutics	606 821	210 000	USD	79.69	44.1	1.2%	1.3%	0.9%
Molecular Templates	10 792 003	4 411 672	USD	3.92	38.6	1.1%	1.2%	19.2%
Nektar Therapeutics	2 620 676	–	USD	13.51	32.3	0.9%	1.0%	1.4%
Generation Bio Co.	3 853 180	1 520 000	USD	7.08	24.9	0.7%	0.8%	6.8%
Mersana Therapeutics	4 135 000	2 250 000	USD	6.22	23.5	0.6%	0.7%	5.8%
Esperion Therapeutics	4 477 964	530 000	USD	5.00	20.4	0.6%	0.6%	7.1%
Black Diamond Therapeutics	3 440 000	2 050 000	USD	5.33	16.7	0.5%	0.5%	9.5%
Wave Life Sciences	4 602 858	2 000 000	USD	3.14	13.2	0.4%	0.4%	7.8%
Homology Medicines	1 737 122	–	USD	3.64	5.8	0.2%	0.2%	3.0%
Alder Biopharmaceuticals – Contingent Value Right	2 766 008	–	USD	0.88	2.2	0.1%	0.1%	
Total securities					**3 641.1**	**100.0%**	**110.9%**	
Other assets					3.0		0.1%	
Other payables					(360.6)		(11.0%)	
Net asset value					**3 283.5**		**100.0%**	

Exchange rate as at 31.12.2021: USD/CHF: 0.9129

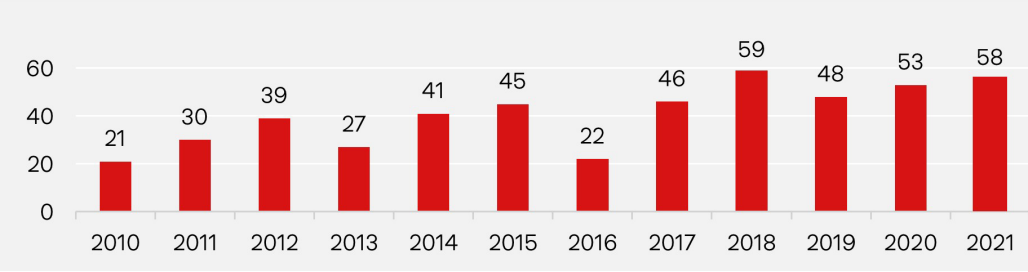
The focus is shifting

Biotech companies often specialize in rare disease treatments but, as a result of the pandemic, they have displayed a greater interest in applying their cutting-edge technologies to treat disease indications that are significantly more prevalent. Meanwhile chronic and serious diseases are attracting more investor attention again. SARS-CoV2 vaccines and drugs are fading away from the spotlight. The biotech industry is sure to regain its momentum from past years and chances are that investors will start showing greater interest in the sector as well.

Positive momentum to continue

The momentum of the biotech industry will likely remain strong, but we expect a shift away from SARS-CoV-2 vaccines and therapeutics back towards the high unmet medical needs of patients with chronic and severe disorders. Prevalent diseases have gained recognition due to the pandemic, and we observe an increased willingness of the biotechnology industry to dare to tackle these disorders. Major technological advancements, focusing mostly on rare diseases, are expected to make many more inroads into broader indications than in the past. Overall, a growing number of products have been approved. Approvals have dramatically increased from the 20s range per year in the early 2000s, to 30 to 40 products approved per year in the last decade to around 50 in recent years. Despite the pandemic's effects on the industry and regulatory authorities, 50 approvals were awarded in 2021 by FDA's CDER division in addition to 10 products by FDA's CBER division (vaccines and cell-based products). 2022 should be no exception to this trend, as regulatory authorities balance their COVID-19 response while supporting innovative technology progress, surveying clinical projects and reviewing important registration filings. Following regulatory approval, access to healthcare systems remains another core hurdle for success. The recent controversial approval of Aduhelm by the FDA was challenged by CMS with their draft coverage guidance restricting its reimbursement for the product. In an unusual move and disputably not within their usual mandate, CMS is asking Biogen to run further clinical trials to prove the efficacy of the product. Although the critical stance towards Aduhelm is not a real surprise, many investors worry that this CMS decision can set precedence and have far-reaching consequences for the drug industry.

Number of FDA drug approvals



Source: FDA, Evaluate Pharma February 2022

Overall, as a pure quantitative measure, the number of trials and patients enrolled in clinical trials is now well ahead of pre-pandemic levels. Many disease areas will have a flurry of trial readouts throughout 2022. Examples of important readouts for our portfolio throughout 2022 are Moderna's updates regarding its Omicron specific booster and for its influenza vaccine mRNA-1010 with pending Phase II readout in the first half of 2022. This trial is directly controlled by a trial arm of standard conventional flu shot and aiming for non-inferiority on immunogenicity, tolerability and safety. The next generations of Moderna's influenza vaccines are aiming for superiority on immunogenicity as well as consequentially vaccine efficacy and effectiveness by incorporating additional antigens (mRNA-1020/1030) or additional strains beyond the four selected by the WHO (mRNA-1011/1012) on a faster and shorter timeline than the currently used seasonal influenza protocol. Ultimately, Moderna's vision entails combination vaccines with a single annual injection covering multiple respiratory pathogens (e.g. SARS-CoV-2, influenza, RSV, hMPV, PIV3, etc.; depending on regional and geographic risks) for high risk populations such as elderly and pediatrics.

Overall, as a pure quantitative measure, the number of trials and patients enrolled in clinical trials is now well ahead of pre-pandemic levels.

Other RNA based or RNA targeting drugs in development of importance for 2022 include the TTR lowering agents from Alnylam and Ionis. Alnylam will report highly anticipated P3 results for Onpattro to treat TTR amyloidosis patients with cardiomyopathy, while Ionis together with its development and commercial partner AstraZeneca will report data for the TTR-LICA drug eplontersen for TTR amyloidosis patients with polyneuropathy.

In oncology, a highly anticipated clinical result is expected from Nektar Therapeutics for bempegaldesleukin, a pegylated interleukin 2, in metastatic melanoma patients. The company will report on its cytokine drug in combination with today's standard of care, a PD1 antibody. If positive, we expect more focus on the cytokine class in general and for many other combination trials to become a bigger focus for the oncology field. In addition to the continued efforts around immune oncology and cytokines, many targeted oncology pipeline candidates will report proof of concept studies throughout 2022, such as our portfolio companies Relay Therapeutics and Revolution Medicines.

New technologies are expected to prove their disruptive potential

Progress for the newest generation of drug technologies will continue to be a focal point for biotech investors in 2022 and beyond. Important data points have been presented throughout the past year and further proof of concept for different approaches of gene editing, next generation gene therapy and cell therapy are expected. A recent example of a groundbreaking breakthrough is the ex vivo gene editing treatment CTX001 by Crispr Therapeutics and Vertex to treat sickle cell disease (SCD) and transfusion-dependent beta thalassemia (TDT). Designed as a one-time treatment that incorporates the fairly invasive procedure of bone marrow transplantation, CTX001 has so far resulted in functional cures for all treated patients. Crispr Therapeutics and Vertex have guided that the registrational data will be filed in the second half of 2022 implying a potential launch in 2023. This represents the first approval and major product launch of a gene-editing product.

The manifold of challenges posed by high doses of viral vector delivered gene therapies have offered a key point of differentiation for *non-viral gene therapies* and our investment

hypotheses on Generation Bio. The company's technology utilizes cell-targeting lipid nanoparticles (ctLNP) to encapsulate closed-ended DNA (ceDNA) as cargo, which typically encodes for the respective protein of interest or need. During preclinical experimentation between different species, this approach unfortunately did not translate with sufficient expression levels from mice to non-human primates, with the latter providing the most important proximity to human physiology and clinical studies. Generation Bio now has to redesign this liver targeting construct, reduce the inter-subject variability and improve the inter-species translatability before moving into human clinical trials. An update on progress on the next generation is expected in 2022. Many biotechnology companies are working to solve the challenge of organ or tissue-specific delivery of genetic material. We believe that Moderna as one of our largest holdings is at the forefront of such endeavors developing LNPs with tropism for muscle and lymphatic tissue as deployed for their SpikeVax SARS-CoV-2 vaccine and further LNP formulations for one-time or repeat delivery to the liver, lung or hematopoietic compartment.

In the cell-based therapies space, our portfolio company Fate Therapeutics is developing induced pluripotent stem cell products. The company's pipeline candidates FT516 and FT596 targeting CD20 and CD19/CD20 with different mechanisms of action are making continuous progress. Promising early results demonstrating robust anti-tumor efficacy have been disclosed in hematological cancers. For 2022, we expect further demonstration of efficacy in patients treated at even higher doses, and most importantly to gain insight regarding the durability of these responses. Vertex announced an early but intriguing result for VX-880, an investigational allogeneic human stem cell-derived islet cell therapy evaluated for patients with type 1 diabetes with impaired hypoglycemic awareness and sever hypoglycemia. Although these infused functional islet cells require co-concomitant immunosuppressive therapy, the results for the first patient at the low dose indicate a transformative potential. The patient was able to substantially reduce exogenous insulin and simultaneously achieved rapid improvement in glycemic control. More patients are being treated with this approach as well as progress on the next generation free of immunosuppression and instead including a protective device for the cell graft will be presented in 2022.

RNA-based medicines, such as siRNA and ASO, are making substantial progress in moving from rare and specialty to more prevalent diseases. In mid-2022, Alnylam is expected to announce results for its clinical study APOLLO-B, treating ATTR Amyloidosis patients with cardiomyopathy with Onpattro (patisiran). If successful, it could expand Onpatto's market potential substantially, with the current approved indication targeting hereditary TTR amyloidosis patients with polyneuropathy from around 50–000 patients globally to the 200 000 to 300 000 patients with wild type or hereditary TTR cardiomyopathy. Additionally, Novartis – Alnylam's development and commercialization partner for Leqvio (inclisiran) – is targeting the large hypocholesteremia market and has launched commercial efforts for the product in the US in early 2022.

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.

Computational capabilities influencing the drug industry

Computational power and the digital transformation of the biotechnology industry are becoming a focus on all levels of the drug development industry. Advanced analytics, artificial intelligence (AI) and machine learning (ML) approaches are being applied from target identification over drug discovery and candidate selection all the way to better trial design and patient selection. There are many early stage companies applying such methodologies, but the clinical proof of concept is still sparse and will require more time to be proven. Relay Therapeutics has proven in a first instance with its FGFR2 specific inhibitor RLY-4008 that its Dynamo platform approach to modelling and studying protein motion in order to dynamically understand drug-target interactions at highest fidelity in early clinical trials can result in superior drug candidate properties. Most companies are working towards this goal, with a few select projects in clinical development. Established drug companies are increasingly investing in such internal capabilities as well as in external collaborations to learn from AI/ML frontrunners. Most of these technology companies are still privately held, so we expect more IPOs and market listings in the coming years. This will increase both visibility and scrutiny regarding the promise of developing drugs faster, cheaper and with a higher success rate.

Ownership of assets will matter, at some point

The biotechnology business model has radically changed over the last decade, moving away from an innovation provider for large pharma and large biotech companies as more and more companies become fully integrated biopharmaceutical companies. Retaining assets through clinical development, regulatory approvals up to commercialization, even globally, is more capital intense but leads to higher ROICs (return on invested capital) for companies that are successful in clinical trial development and once commercial launches are capital efficient and successful. This requires a better understanding of a product's profile, pricing power, and value proposition for all healthcare stakeholders in order to grasp the long-term prospects of a product in the context of the established standard of care as well as future competition.

Important product launches in biotechnology are rare, thus investors monitor early launch metrics and project the prescription ramp to peak sales assumptions and cumulative cash flows that can be generated by individual products. A negative example in 2021 was Aduhelm (aducanumab) with a highly disappointing launch driven by controversial product data, a cost-ineffective pricing strategy and barred access to the US Medicare population. This has cast a shadow not just on Biogen but on the whole industry. As a hopefully positive counterexample, the ongoing global launch of Argenx' Vyvgart for the treatment of myasthenia gravis patients will be of utmost importance for our portfolio and the industry in general. Further, the US roll-out of Intra-Cellular's Caplyta will be in focus now that its label has been expanded to bipolar patients as a second indication after its approval in schizophrenia.

We expect that the broad investor base will regain appetite for the biotech sector as soon as successful drug launches can prove that the fully integrated biotech business model still can provide positive and competitive returns on invested capital, a measure that seems to have fallen by the wayside during times of low interest rates and excess capital.

Politics and healthcare reform – US midterm elections

The Biden Administration has proposed Robert Califf as new FDA commissioner. The Senate committee has advanced the nomination, but a full Senate vote and confirmation is still pending. We expect Califf to replace Janet Woodcock and maintain FDA's innovation mindset.

Of high importance to the US healthcare system are the midterm elections in November of 2022. A substantial focus will be potential shifts in congressional majorities. If Republicans win control of both houses of Congress, this would deal a significant blow to the Democrats' agenda of pushing for the individual mandate implying limits to the cost of healthcare insurance all the way to the lowering of prescription drug prices by changing laws currently banning Medicare from negotiating lower drug prices with manufacturers.

With the biotechnology industry dominated by the US, China is making great strides due to a rapidly evolving regulatory landscape and a maturing biotech industry. The high growth of Chinese firms in contract research, development and manufacturing is fostering a move away from the former focus on generics towards innovation in general.

Artificial intelligence

Artificial intelligence (AI) is not a new theme, but it has gained considerable momentum during the past decade. AI has already led to groundbreaking success, two examples of which are speech recognition (Siri) and text analysis (Google Translate). The dynamic pace of change in the field of IT and innovation in the field of machine learning have fueled this strong momentum. Using AI in the healthcare industry for drug research and development purposes is particularly interesting and AI-driven projects are underway throughout the drug development process, from preclinical toxicology and pharmacology to clinical trial design and the regulatory approval process, and even in post-approval product launch campaigns.

Artificial intelligence can be used, for example, to identify the most suitable development candidates more quickly and at less cost. Collaborative interaction between humans and machines is vital here, and a balance must be found between in silico experimentation and in vitro experiments. The objective is to support the efforts of scientists through the use of AI.

The two promising AI players in BB Biotech's portfolio are Relay Therapeutics and Black Diamond Therapeutics.

Companies large and small are trying to establish a foothold in this business and there is a risk of them rushing into the field without careful forethought. It would be quite sobering, also for investors, if early wins don't materialize. An additional hurdle big corporations face is that AI is not one of their core business areas, so relatively few resources are allocated to it. Consequently, the top talent in these hybrid areas where computer science and life sciences overlap often elect to work for innovation leaders who are entirely focused on AI and for whom tech expertise is just as important as sound knowledge of biology and medicine. Developing a drug for human use is a complex and highly regulated process, which is why even giant tech companies such as Apple, IBM and Amazon have difficulties entering the fields of digital health and AI in healthcare. When screening investment candidates, BB Biotech AG is mostly interested in companies offering solutions that can alleviate or even completely cure a patient's ailments; the approach or method used to achieve that is of less importance. BB Biotech is most likely to find such innovation in the US, but China and Europe, the latter led by the UK, have also produced some innovation leaders.

There are two promising AI players in BB Biotech's portfolio. One is Relay Therapeutics, which has access to the world's fastest computer. Researchers use it to run dynamic simulations of known protein structures and identify the smallest of differences. The technology is being used for drug discovery purposes. Black Diamond Therapeutics is the other AI player in BB Biotech's portfolio. It uses machine learning to understand and classify the effects of various mutations on a protein relevant in oncology and then selectively block those mutations with a single agent. BB Biotech itself uses AI in its investment process. «Advanced analytics» plays an important role in its investment decisions. Large sets of data such as EHRs (electronic health records) or health insurance data are mined to provide a better understanding of specific markets from a medical as well as commercial point of view. Tools that help BB Biotech track and process new data inputs and news reports have also been developed to give it a broad and solid understanding of complex topics.