AnGes / 4563

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How to read a Shared Research report: This report begins with the trends and outlook section, which discusses the company's most recent earnings. First-time readers should start at the business section later in the report.

Executive summary

Aims to turn profitable on successful HGF gene therapy drug development overseas

- Since the company's establishment in 1999, HGF gene therapy drug (a new drug candidate; regenerates blood vessels by medicating HGF—hepatocyte growth factor—genes) has been the mainstay pipeline drug for AnGes.
- HGF gene therapy drug, indicated for the improvement of ulcers associated with chronic arterial occlusion, is the first domestic gene therapy product to be approved in Japan. In March 2019, the company obtained conditional and time-limited approval to manufacture and market the product, and Mitsubishi Tanabe Pharma Corporation commenced sales in September 2019.
- Overseas, the company commenced a joint global Phase III clinical trial, mainly in the US, of the HGF gene therapy drug indicated for the treatment of critical limb ischemia (CLI) in October 2014. Regarding this trial, however, the company in June 2016 announced a change in its development strategy, reviewing evaluation criteria and switching to trials that can be completed in a short period of time. A US Phase IIb clinical trial for arteriosclerosis obliterans patients with lower limb ischemic ulcers (assess efficacy of lower limb ulcers, target enrollment of 60 patients, post-administration follow-up period of 12 months) was initiated in February 2020.
- In addition to the HGF gene therapy drug, AnGes is conducting a Phase Ib clinical trial of NF-κB decoy oligonucleotide targeting discogenic low back pain and back pain and Phase I/II clinical trials of a DNA vaccine for high blood pressure. Research is being conducted in new business areas such as genome editing technology (alliance with Emendo Biotherapeutics), microbiome (alliance with MyBiotics Pharma), and cancer diagnosis (alliance with Barcode Diagnostic).
- In its annual securities report submitted in March 2019, AnGes deleted the "Notes regarding Assumption of a Going Concern." As of April 2019, the company believes that the significant uncertainty that prompted the notice no longer exists. Cash and deposits totaled JPY10.0bn at end-December 2019 (JPY5.8bn at end-FY12/18).

Performance

- In FY12/19, AnGes booked operating revenues of JPY327mn (-46.4% YoY), an operating loss of JPY3.3bn (operating loss of JPY3.1bn in FY12/18), recurring loss of JPY3.3bn (recurring loss of JPY3.1bn in FY12/18), and net loss attributable to owners of the parent of JPY3.8bn (net loss attributable to owners of the parent of JPY3.0bn in FY12/18).
- As of February 2020, AnGes has not disclosed its FY12/20 forecast. The company commented that it was difficult at this stage to make a reasonable earnings estimate due to numerous uncertainties that impact on earnings, such as potential for business alliances including out-licensing its HGF gene therapy drug to overseas companies and in-licensing new drug candidates. The company commented that it would disclose its full-year forecast when a reasonable earnings estimate is possible based on business progress.
- AnGes has consistently recorded operating losses with the one exception of FY12/01, prior to being listed. Sources of longer-term growth include expansion of the HGF gene therapy drug business, non-HGF gene therapy pipelines, and creation of new drug candidates. The company aims to increase royalty income and licensing revenue from the HGF gene therapy drug by obtaining approvals in Japan and the US, out-licensing to markets other than Japan and the US, and expanding indications.

Strengths and weaknesses

Strengths include the receipt of conditional and time-limited approval to manufacture and market the company's HGF gene therapy drug, relationships with partner pharmaceutical companies, and prospects for launching the HGF gene therapy drug on overseas markets as well. Weaknesses include the conditional and time-limited nature of approval for the HGF gene therapy drug, ongoing losses, and a lack of capital (see Strengths and weaknesses).

Key financial data

Income statement (JPYmn)	FY12/10 Cons.	FY12/11 Cons.	FY12/12 Cons.	FY12/13 Cons.	FY12/14 Cons.	FY12/15 Cons.	FY12/16 Cons.	FY12/17 Cons.	FY12/18 Cons.	FY12/19 Cons.
Operating revenues	**287**	**243**	**445**	**491**	**910**	**430**	**514**	**365**	**610**	**327**
YoY	-51.0%	-15.2%	82.6%	10.5%	85.2%	-52.7%	19.6%	-29.0%	67.1%	-46.4%
Operating profit	**-2,010**	**-2,101**	**-1,785**	**-1,363**	**-2,274**	**-4,172**	**-4,763**	**-3,289**	**-3,065**	**-3,270**
YoY	-	-	-	-	-	-	-	-	-	-
OPM	-	-	-	-	-	-	-	-	-	-
Recurring profit	**-1,911**	**-1,791**	**-1,716**	**-1,383**	**-2,395**	**-4,089**	**-4,847**	**-3,307**	**-3,096**	**-3,293**
YoY	-	-	-	-	-	-	-	-	-	-
RPM	-	-	-	-	-	-	-	-	-	-
Net income	**-1,967**	**-1,815**	**-1,708**	**-1,410**	**-2,369**	**-4,143**	**-4,777**	**-3,765**	**-2,997**	**-3,751**
YoY	-	-	-	-	-	-	-	-	-	-
Net margin	-	-	-	-	-	-	-	-	-	-
Per share data										
Shares issued (year-end; '000)	23,646	24,467	26,226	31,268	53,544	53,544	70,631	79,724	97,981	106,970
EPS	-83.3	-74.6	-67.7	-46.9	-62.1	-74.5	-75.3	-49.4	-34.5	-35.8
EPS (fully diluted)	-	-	-	-	-	-	-	-	-	-
Dividend per share	-	-	-	-	-	-	-	-	-	-
Book value per share	175.1	125.8	60.3	107.9	142.4	73.8	54.7	42.3	78.4	111.8
Balance sheet (JPYmn)										
Cash and cash equivalents	3,053	1,576	355	2,295	6,017	2,075	996	1,148	5,785	10,041
Total current assets	**4,143**	**2,635**	**1,342**	**3,305**	**7,594**	**4,243**	**3,619**	**3,434**	**7,542**	**10,992**
Tangible fixed assets	72	62	45	23	28	76	76	-	47	49
Investments and other assets	633	1,050	770	506	508	382	789	530	461	1,483
Intangible fixed assets	157	142	103	70	54	51	55	-	-	-
Total assets	**5,004**	**3,889**	**2,260**	**3,904**	**8,184**	**4,752**	**4,539**	**3,964**	**8,051**	**12,525**
Accounts payable	98	60	67	42	207	247	389	201	113	183
Short-term debt	488	417	331	218	116	83	1	1	686	-
Total current liabilities	**716**	**601**	**507**	**345**	**423**	**482**	**631**	**318**	**292**	**443**
Total fixed liabilities	**-**	**17**	**15**	**15**	**26**	**49**	**39**	**24**	**25**	**26**
Total liabilities	**716**	**618**	**522**	**361**	**449**	**531**	**670**	**342**	**316**	**469**
Net assets	**4,288**	**3,271**	**1,739**	**3,544**	**7,734**	**4,221**	**3,869**	**3,622**	**7,734**	**12,055**
Total interest-bearing debt	-	-	-	-	-	-	-	-	-	-
Cash flow statement (JPYmn)										
Cash flows from operating activities	-1,843	-1,706	-1,631	-1,457	-2,704	-4,599	-4,984	-2,991	-2,523	-2,180
Cash flows from investing activities	952	768	7	-27	-52	-69	-830	227	-123	-1,250
Cash flows from financing activities	12	368	387	3,390	6,427	717	4,793	2,916	7,283	7,677
Financial ratios										
ROA (RP-based)	-	-	-	-	-	-	-	-	-	-
ROE	-	-	-	-	-	-	-	-	-	-
Equity ratio	85.7%	84.1%	76.9%	90.8%	94.5%	88.8%	85.2%	91.4%	96.1%	96.3%

Source: Shared Research based on company data
Note: Figures may differ from company materials due to differences in rounding methods.

Recent updates

Highlights

On October 26, 2020, AnGes, Inc. announced earnings results for Q3 FY12/20; see the results section for details.

On October 12, 2020, the company announced the completion of a two-dose vaccination series in all subjects enrolled in the Phase I/II clinical trial of a DNA vaccine against COVID-19 being conducted at Osaka University Hospital.

The company completed the second round of vaccinations (in a two-dose series) as planned in all 30 subjects enrolled in the Phase I/II clinical trial of its DNA vaccine candidate against COVID-19 being conducted at Osaka University Hospital. The purpose of the study is to determine optimal vaccination intervals and frequency. The DNA vaccine development is progressing as planned, and after the completion of the two-dose vaccination series and a post-administration follow-up period, the company plans to announce preliminary results that comprehensively evaluate the outcomes of the Phase I/II clinical trial conducted at Osaka City University Hospital and Osaka University Hospital in Q4 FY12/20.

On October 8, 2020, the company. announced that it had signed a basic out-licensing agreement with Er-Kim Ilac A.S. to market HGF gene therapy Collategene® in Turkey.

The company signed a basic out-licensing agreement with Er-Kim, a specialist pharmaceutical company that supplies treatments for specific diseases based in Turkey, for Collategene®, an HGF gene therapy product developed by AnGes for the treatment of ulcers associated with chronic arterial occlusion.

After obtaining marketing approval from the authorities, Er-Kim will have exclusive rights to market Collategene® in Turkey, and will undertake sales, marketing, and activities related to medical treatment in the country. Prior to approval being granted, AnGes and Er-Kim will begin supplying Collategene® in Turkey via the Named Patient Program.

> Er-Kim Ilac AS is a private company that supports the practical use in Turkey, the Middle East, and Europe of new drug candidates of biotech and pharmaceutical companies with global operations. In its 40-year history, the company has commercialized more than 150 products of over 50 companies.
>
> The Named Patient Program (NPP) provides pharmaceutical products that are yet to be approved by the authorities of the country that they are to be used at the request of a doctor on behalf of a specific patient for humanitarian reasons. This program enables patients to receive treatment with drugs that are in late-stage clinical trials or have been approved in other countries.

On September 24, 2020, the company announced the completion of the first vaccination in the Phase I/II clinical trial of DNA vaccine for COVID-19 being conducted at Osaka University Hospital.

In the Phase I/II clinical trial of DNA vaccine for COVID-19 being conducted at Osaka University Hospital, the company completed administering the first dose of the vaccine in all 30 subjects enrolled in the study as planned, and began administering the second dose. The purpose of the study is to investigate optimal vaccination intervals and frequency. The DNA vaccine development is progressing as planned, and after the completion of the first and second vaccinations and the post-administration follow-up period, the company plans to announce preliminary results that comprehensively evaluate the outcomes of the Phase I/II clinical trial conducted at Osaka City University Hospital and Osaka University Hospital in Q4 FY12/20.

On September 8, 2020, the company announced the conclusion of a joint development agreement with Brickell Biotech, Inc. for the development of DNA vaccine for COVID-19 in the US.

The company entered a joint development agreement with Brickell Biotech (US) in regard to the investigational DNA vaccine for COVID-19. Clinical development of the vaccine in the US is under review, and the company will determine details of the development as appropriate upon consultations with Brickell Biotech.

Overview of Brickell Biotech

- ▷ Company name: Brickell Biotech, Inc.
- ▷ Address: 5777 Central Avenue, Suite 102, Boulder, CO 80301, USA
- ▷ CEO: Robert Brown
- ▷ Business: Pharmaceutical development
- ▷ Capital: USD114,113,000

On September 3, 2020, Shared Research updated the report following interviews with the company.

On August 31, 2020, the company announced that it was selected for the Japan Agency for Medical Research and Development (AMED)'s COVID-19 Vaccine Development Program (second round).

The company and Osaka University submitted their joint development project for a DNA vaccine for COVID-19 to the AMED's public call for the second round of FY2020 COVID-19 Vaccine Development Program, and were selected.

On August 21, 2020, the company announced an outline of the Phase I/II clinical trial for the DNA COVID-19 vaccine to be conducted at Osaka University Hospital.

The Phase I/II clinical trial of the DNA vaccine for COVID-19 that was announced on August 18, 2020 will be conducted at the Osaka University Hospital. The purpose of the trial will be to determine optimal vaccination intervals and frequency. Various preparations will be made with an eye on initiating the vaccinations from early September.

According to the company, development of the vaccine is progressing as planned. AnGes looks to disclose topline results in Q4 FY12/20 after the vaccinations and follow-up observation have been completed and the outcome of the Phase I/II clinical trials conducted at Osaka City University Hospital and Osaka University Hospital have been analyzed. The company is currently reviewing the potential impact the trial results will have on FY12/20 earnings.

Outline of the Phase I/II clinical trial to be conducted at Osaka University Hospital

- ▷ Overview: Assess safety and immunogenicity of investigational vaccine to be administered intramuscularly to healthy adult volunteers.
- ▷ Target number of trial subjects: 30 (dose 2.0mg: (1) 10 subjects to be vaccinated twice at two-week intervals, (2) 10 subjects to be vaccinated twice at four-week intervals, (3) 10 subjects to be vaccinated three times at two-week intervals.)
- ▷ Projected trial completion: By September 30, 2021 (includes 52-week follow-up after first vaccination)

On August 18, 2020, the company announced the completion of vaccination in the Phase I/II clinical trial of a DNA vaccine for COVID-19 at the Osaka City University Hospital and plans for clinical trials going forward.

In the Phase I/II clinical trial of a DNA vaccine for COVID-19 being conducted at the Osaka City University Hospital, the company completed administration of the study vaccine, including high-dose injections, as planned (target enrollment: 30 subjects, low-dose group: 15, high-dose group:15, two administrations separated by an interval of two weeks).

The company plans to conduct another Phase I/II clinical trial to study administration intervals and frequency as initially planned. It will disclose details of the study at another date. After all vaccinations in the Phase I/II clinical trials and follow-up observation have been completed, the company plans to disclose the study results as initial clinical trial data in Q4 FY12/20.

On August 7, 2020, the company announced that it was selected for the Ministry of Health, Labour and Welfare's Emergency Project for the Establishment of Vaccine Manufacturing Systems.

The company has been selected for MHLW's Emergency Project for the Establishment of Vaccine Manufacturing Systems for FY2020.

- ▷ Project overview: Aimed at expedited establishment of practical manufacturing systems (large-scale manufacturing) for COVID-19 vaccines in Japan
- ▷ Grant amount: JPY9.4bn
- ▷ Project duration: August 2020–March 2022

The company is currently analyzing the impact of this event on its full-year earnings.

For previous releases and developments, please refer to the News and topics section.

Trends and outlook

Quarterly trends and results

Quarterly performance

Cumulative (JPYmn)	FY12/19 Q1	Q2	Q3	Q4	FY12/20 Q1	Q2	Q3	Q4
Operating revenues	76	173	324	327	6	17	28	
YoY	2.4%	-1.9%	17.2%	-46.4%	-92.4%	-90.2%	-91.2%	
Operating expenses	994	1,882	2,683	3,597	980	1,783	2,886	
YoY	49.7%	36.2%	6.5%	-2.1%	-1.4%	-5.3%	7.6%	
Operating profit	-918	-1,710	-2,359	-3,270	-974	-1,766	-2,858	
YoY	-	-	-	-	-	-	-	
OPM	-	-	-	-	-	-	-	
Recurring profit	-938	-1,734	-2,386	-3,293	-923	-1,896	-3,151	
YoY	-	-	-	-	-	-	-	
RPM	-	-	-	-	-	-	-	
Net income	-1,184	-1,974	-2,771	-3,751	-920	-1,896	-3,175	
YoY	-	-	-	-	-	-	-	
Net margin	-	-	-	-	-	-	-	

Quarterly (JPYmn)	FY12/19 Q1	Q2	Q3	Q4	FY12/20 Q1	Q2	Q3	Q4
Operating revenues	76	97	151	3	6	11	12	
YoY	2.4%	-5.1%	50.9%	-99.2%	-92.4%	-88.5%	-92.4%	
Operating expenses	994	888	800	914	980	803	1,103	
YoY	49.7%	23.8%	-29.6%	-21.0%	-1.4%	-9.6%	37.8%	
Operating profit	-918	-791	-649	-911	-974	-792	-1,092	
YoY	-	-	-	-	-	-	-	
OPM	-	-	-	-	-	-	-	
Recurring profit	-938	-795	-652	-908	-923	-973	-1,254	
YoY	-	-	-	-	-	-	-	
RPM	-	-	-	-	-	-	-	
Net income	-1,184	-790	-797	-980	-920	-976	-1,279	
YoY	-	-	-	-	-	-	-	
Net margin	-	-	-	-	-	-	-	

Source: Shared Research based on company data
Note: Figures may differ from company materials due to differences in rounding methods.

Quarterly performance (breakdown of operating revenues and expenses)

	FY12/19				FY12/20			
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Operating revenues	76	173	324	327	6	17	28	
YoY	2.4%	-1.9%	17.2%	-46.4%	-92.4%	-90.2%	-91.2%	
Sales of merchandise	73	170	170	170	-	-	-	
YoY	-1.0%	-3.4%	-38.5%	-55.6%	-	-	-	
Sales of finished goods	-	-	1	4	6	17	28	
YoY	-	-	-	-	-	-	-	
R&D revenues	3	3	153	153	-	-	-	
YoY	-	-	-	-32.9%	-	-	-	
Operating expenses	994	1,882	2,683	3,597	980	1,783	2,886	
YoY	49.7%	36.2%	6.5%	-2.1%	-1.4%	-5.3%	7.6%	
Cost of sales	36	84	85	87	3	9	16	
YoY	-0.5%	-3.0%	-37.5%	-53.7%	-90.4%	-89.0%	-81.0%	
Cost ratio	49.2%	49.2%	49.5%	50.0%	60.3%	54.7%	56.8%	
R&D expenses	694	1,130	1,587	2,215	628	1,105	1,881	
YoY	72.3%	40.6%	-3.8%	-12.8%	-9.4%	-2.2%	18.5%	
Salaries and allowances	-	115	-	226	-	124	-	
YoY	-	-15.7%	-	-7.8%	-	8.3%	-	
Outsourcing expenses	-	488	-	1,065	-	578	-	
YoY	-	81.6%	-	-9.3%	-	18.5%	-	
Commission fees	-	101	-	205	-	88	-	
YoY	-	-12.7%	-	-17.7%	-	-12.6%	-	
SG&A expenses	264	668	1,010	1,294	348	669	989	
YoY	17.3%	36.0%	37.8%	36.6%	31.8%	0.1%	-2.1%	
Operating profit	-918	-1,710	-2,359	-3,270	-974	-1,766	-2,858	
YoY	-	-	-	-	-	-	-	

	FY12/19				FY12/20			
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Operating revenues	76	97	151	3	6	11	12	
YoY	2.4%	-5.1%	50.9%	-99.2%	-92.4%	-88.5%	-92.4%	
Sales of merchandise	73	97	-	-	-	-	-	
YoY	-1.0%	-5.1%	-	-	-	-	-	
Sales of finished goods	-	-	1	3	6	11	12	
YoY	-	-	-	-	-	-	730.1%	
R&D revenues	3	0	150	-	-	-	-	
YoY	-	-	-	-	-	-	-	
Operating expenses	994	888	800	914	980	803	1,103	
YoY	49.7%	23.8%	-29.6%	-21.0%	-1.4%	-9.6%	37.8%	
Cost of sales	36	48	1	2	3	6	7	
YoY	-0.5%	-4.8%	-97.7%	-95.6%	-90.4%	-88.0%	500.0%	
Cost ratio	49.2%	49.2%	82.8%	82.8%	60.3%	51.8%	59.8%	
R&D expenses	694	436	457	628	628	476	776	
YoY	72.3%	8.8%	-45.9%	-29.5%	-9.4%	9.2%	69.7%	
SG&A expenses	264	404	342	284	348	321	320	
YoY	17.3%	51.7%	41.5%	32.7%	31.8%	-20.6%	-6.3%	
Operating profit	-918	-791	-649	-911	-974	-792	-1,092	
YoY	-	-	-	-	-	-	-	

Source: Shared Research based on company data
Note: Figures may differ from company materials due to differences in rounding methods.

Cumulative Q3 FY12/20 results

Operating revenues: JPY28mn (-91.2% YoY)

Operating revenues broke down into zero sales of merchandise (JPY170mn in Q3 FY12/19), sales of finished goods of JPY28mn (JPY1mn in Q3 FY12/19), and zero R&D revenue (JPY153mn in Q3 FY12/19).

▷ The company booked zero sales of merchandise, because sales of Naglazyme®, a drug for mucopolysaccharidosis VI (MPS VI), were completed in June 2019.

▷ The company booked sales of HGF gene therapy Collategene® 4mg Intramuscular Injection as sales of finished goods. Mitsubishi Tanabe Pharma Corporation began selling the product in September 2019.

Operating loss: JPY2.9bn (loss of JPY2.4bn in Q3 FY12/19)

Operating expenses: JPY2.9bn (+7.6% YoY)

▷ Cost of sales was JPY16mn (-81.0% YoY) due to sales of Naglazyme® (a drug for mucopolysaccharidosis VI) being completed.

- R&D expenses were JPY1.9bn (+18.5%, +JPY293mn YoY). The company began Phase IIb clinical trials in the US of an HGF gene therapy drug targeting chronic arterial occlusion patients with leg ulcers, as well as developing a COVID-19 vaccine, incurring clinical trial expenses. This led to a JPY302mn increase in outsourcing costs.
- SG&A expenses were JPY989mn (-2.1%, -JPY21mn YoY). Taxes and dues increased by JPY54mn on an increase in the portion of corporate tax determined based on the company's capital. Travel and transport expenses declined by JPY24mn as the company refrained from business travel due to the spread of COVID-19. In Q3 FY12/19, the issue of stock options to directors and employees increased stock-based compensation expenses by JPY73mn; in Q3 FY12/20, the company recorded stock-based compensation expenses of JPY48mn.

Recurring loss: JPY3.2bn (loss of JPY2.4bn in Q3 FY12/19)

- The company booked non-operating profit of JPY39mn (+108.0% YoY), including a JPY22mn forex gain on revaluation of foreign currency deposits (JPY8mn in Q3 FY12/19).
- Non-operating expenses were JPY332mn (+640.5% YoY). Share issuance costs associated with the issue and exercise of stock options were JPY67mn (JPY42mn in Q3 FY12/19). The company also recorded equity-method investment losses of JPY263mn (zero in Q3 FY12/19) as Emendo Biotherapeutics Inc. became an equity-method affiliate in Q1.

Net loss attributable to owners of the parent: JPY3.2bn (net loss of JPY2.8bn in Q3 FY12/19)

- The company booked a JPY5mn gain from the reversal of share subscription rights on the expiry of stock options at the end of the exercise period.
- The company recorded a JPY384mn valuation loss on investment securities in Q3 FY12/19, but none in Q3 FY12/20.
- The company recorded a JPY21mn loss from a change in equity stake in Emendo.

Main pipeline progress

HGF gene therapy drug to treat chronic arterial occlusion

- Regarding the development of its HGF gene therapy drug for chronic arterial occlusion, in January 2018 the company filed an application with the Ministry of Health, Labour and Welfare for approval for the manufacture and marketing of a regenerative medicine product, utilizing the conditional time-limited approval system (a new approval system aiming for the early commercialization of regenerative medicines and other drugs included under the Pharmaceuticals and Medical Devices Law, which went into force in November 2014). In March 2019, the company obtained conditional time-limited approval for the drug Collategene® as Japan's first domestic gene therapy product for improvement of ulcers associated with chronic arterial occlusion, and began sales in September 2019.
- The company signed an agreement with Mitsubishi Tanabe Pharma Corporation regarding exclusive sales rights of HGF gene therapy drug Collategene® targeting peripheral vascular disease in Japan and the US. Mitsubishi Tanabe Pharma is marketing the drug. Since approval is conditional and time-limited, AnGes aims to obtain the full manufacture and marketing approval in March 2024.
- In October 2019, the company began a Phase III clinical trial of Collategene® with chronic arterial occlusion patients who suffer pain when resting with a view to expanding indications of the drug. The company expects the trial to take about two years with around 40 patients enrolled.
- Overseas, the company began a Phase IIb clinical trial in the US in 2020 targeting chronic arterial occlusion with lower limb ischemic ulcers.

- The company also signed a basic agreement with Kamada Ltd. (Israel) regarding the approval of exclusive sales rights of HGF gene therapy drug Collategene® in Israel. Kamada is in talks with the Israeli authorities regarding commercialization.
- In October 2020, the company signed a basic out-licensing agreement with Er-Kim Ilac A.S. to market HGF gene therapy Collategene® in Turkey. The agreement will give Er-Kim exclusive rights to market Collategene® in Turkey. While working toward obtaining marketing approval, the two companies plan to begin supplying Collategene® in Turkey via the Named Patient Program.

NF-κB decoy oligonucleotide DNA treatment to treat lumbar disc disorders and back pain

- The company is progressing with the development of NF-κB decoy oligonucleotide to treat lumbar disc disorders and back pain. The company began Phase Ib clinical trials targeting discogenic low back pain in February 2018 and completed administration of the drug to 25 patients as scheduled in February 2020.
- AnGes has been conducting research on next-generation decoys to follow NF-κB decoy oligonucleotide. The company is making progress on the development of the basic technology for Chimera decoy, which acts to simultaneously suppress STAT6 and NF-κB, two of the key transcription factors. Compared with decoys which only targets NF-kB, it is expected that this decoy would be more effective in suppressing inflammation.

DNA vaccine to treat high blood pressure

AnGes focuses on the development of DNA vaccines as the third pillar of gene medicines in addition to products for gene therapy and nucleic acid medicines. As its first product in this area, the company is developing a DNA vaccine to treat high blood pressure. It began Phase I/IIa clinical trials in April 2018 and completed administration of the drug to 24 patients as scheduled in March 2020.

Alliance with Vasomune

In July 2018, AnGes and Vasomune Therapeutics signed a global co-development agreement of therapeutics targeting diseases associated with severe edema such as acute respiratory failure. The two companies are currently engaged in joint preclinical trials.

Development of novel coronavirus vaccine

In March 2020, AnGes began urgent development of a plasmid DNA vaccine against the novel coronavirus disease spreading worldwide. On June 30, 2020, the company started Phase I/II clinical trials at the Osaka City University Hospital with 30 subjects. The company also started Phase I/II clinical trials at the Osaka University Hospital with 30 subjects to confirm the interval and number of vaccinations required. It plans to conduct larger clinical studies depending on the results of the Phase I/II trials at the two hospitals.

Capital status

The pharmaceutical business is characterized by the need for a large amount of capital and a long period of time to commercialize a product, and the company (a biotech startup) has continuously recorded operating losses and negative cash flows. Accordingly, significant doubt has arisen as to the company's ability to continue as a going concern. At the end of September 2020, cash and deposits totaled JPY12.3bn (JPY10.0bn at end-FY12/19).

Progressing own existing projects and expanding business base

The company is progressing three development projects: HGF gene therapy drug for chronic arterial occlusion, the NF-κB decoy oligonucleotide for treating lumbar disc disorders, and the DNA vaccine for high blood pressure. In March 2019, the company obtained conditional time-limited approval for the manufacturing and sale of HGF gene therapy drug Collategene®, as Japan's first gene therapy product. Sales began in September 2019. Going forward, the company will progress clinical trials in Japan to expand the indication of Collategene® and clinical trials in the US targeting chronic arterial occlusion patients. For the NF-κB

decoy oligonucleotide for treating discogenic low back pain and the DNA vaccine for high blood pressure, clinical trials are currently underway overseas as well.

In addition to these ongoing projects, the company embarked on joint development of a novel coronavirus vaccine with Osaka University in March 2020. It seeks to expand its business base by adding to its pipeline via the following: in-licensing drug candidates, conducting joint development, entering business partnerships to secure drug discovery platform technologies, gaining capital participation of other companies, and acquiring other companies.

Signing up alliance partners for development projects

AnGes adopts an alliance model for development projects, teaming up with pharmaceutical companies to receive upfront and milestone payments and development cooperation payments to reduce financial risk during the development period.

The company signed an agreement with Mitsubishi Tanabe Pharma Corporation regarding exclusive sales rights of HGF gene therapy drug Collategene® in the US and Japan, and expects to receive milestone payments and royalties. The company is also conducting clinical trials of nuclear medicine (NF-κB decoy oligonucleotide DNA) for the treatment of discogenic low back pain and a DNA vaccine for hypertension. If the trials produce promising results, the company plans to out-license these products to pharmaceutical companies at an early stage to reduce its R&D expenses by receiving upfront payments and other fees.

Financing

On March 4, 2020, the company issued the 37th share subscription rights through a third-party allocation to Phillip Securities Japan, Ltd. As of April 2020, all rights had been exercised and the company raised JPY11.5bn from the issue.

For details on previous quarterly and annual results, please refer to the Historical performance section.

Full-year company forecasts

As of February 2020, AnGes has not disclosed its FY12/20 forecasts. The company commented that it was difficult at this stage to make a reasonable earnings estimate due to numerous uncertainties that impact on earnings, such as potential for business alliances including out-licensing its HGF gene therapy drug to overseas companies and in-licensing new drug candidates. The company commented that it would disclose its full-year forecasts when a reasonable earnings estimate is possible based on business progress. That being said, Shared Research believes the following factors could affect earnings.

Thoughts on FY12/20 operating revenues

The operating revenues from sales of mucopolysaccharidosis VI (MPS VI) drug Naglazyme® and upfront payments from partner companies booked in FY12/19 will be absent in FY12/20 but we do expect revenue growth from sales of HGF gene therapy drug Collategene® 4mg Intramuscular Injection (henceforth Collategene®).

- Naglazyme® sales amounted to JPY170mn in FY12/19, but AnGes ended sales of this product in Q2.
- Upfront payments from partner companies: AnGes booked upfront payments of JPY153mn as R&D operating revenues in FY12/19 but is unlikely to book upfront payments in FY12/20.
- Revenue from HGF gene therapy drug sales: In March 2019, the company obtained conditional and time-limited approval for HGF gene therapy drug Collategene® as a treatment for ulcers associated with chronic arterial occlusion. In September 2019, Mitsubishi Tanabe Pharma began distribution of Collategene®, which AnGes sells to Mitsubishi Tanabe Pharma. AnGes began selling the drug to Mitsubishi Tanabe Pharma from 2H FY12/19 and booked JPY4mn in sales of finished goods. Shared Research believes sales will increase in FY12/20 based on full-year contributions.
  - Criteria for booking sales of finished goods: It is our understanding that AnGes' sales of finished goods are based on a set royalty rate of HGF gene therapy drug sales by Mitsubishi Tanabe Pharma and, royalty payments are booked when the product is shipped, not when the drug is administered.
  - NHI reimbursement price for the HGF gene therapy drug: The reimbursement price for Collategene® 4mg is JPY600,360 and a course of treatment is comprised of two 4mg doses given at four-week intervals.
  - Projected number of treated patients: As noted above, Collategene® was given conditional and time-limited approval. To apply for a full manufacture and marketing approval, the company will need to administer the drug to 120 patients and assess the results within a five-year period (beginning from March 2019).
- Potential for out-licensing the HGF gene therapy drug overseas: AnGes concluded an exclusive marketing agreement with Mitsubishi Tanabe Pharma Corporation (TSE1: 4508) for the drug in Japan and the US and with Kamada for Israel. As of February 2020, no marketing partners for other markets had yet been decided, although the company is looking to out-license it in other markets. Conclusion of a marketing agreement with another partner in FY12/20 would likely result in AnGes booking upfront payments.

Thoughts on operating expenses in FY12/20

Operating expenses of JPY3.6bn recorded in FY12/19 included JPY87mn in cost of sales, JPY2.2bn in R&D expenses, and JPY1.3bn in SG&A expenses. Shared Research believes R&D expenses will likely increase YoY based on the following three planned uses of proceeds from the company's fundraising activities. Also, we do not know the outsourcing cost of HGF gene therapy drug API, but think it could inflate costs.

Planned use of proceeds from the 31st, 33rd, and 37th share subscription rights

	Use of funds	Amount (JPYmn)	Timeframe for spending
1.	Conduct post-marketing surveillance of HGF gene therapy drug effective in improving ulcers in chronic arterial occlusion patients in Japan	597 (426)	October 2018–October 2023

2.	Conduct domestic Phase III clinical trial of HGF gene therapy drug to confirm improvement of rest pain in chronic arterial occlusion	621 (621)	March 2020–March 2022
3.	Expenses for conducting US clinical trials of HGF gene therapy drug	3,767 (2,972)	December 2017–December 2025
4.	Outsourcing costs of API for HGF gene therapy drug	1,650	June 2020–December 2024
5.	Working capital	3,200	March 2020–February 2022
6.	Expanding the development pipeline	7,081 (2,725)	October 2018–June 2020
7.	Further expansion of the development pipeline	4,517	March 2020–March 2024

Note: Figures in parentheses in the amount column are unallocated funds as of Feb 2019.
Note: (4), (5), and (6), are estimated expenditures for proceeds of the 37th share subscription rights; the others are estimated expenditures from funds already raised.
Note: The 31st share subscription rights were allocated in September 2017 and exercised in August 2018 (raised JPY5.0bn). The 33rd share subscription rights were allocated in October 2018 and exercised in May 2019 (raised JPY10.5bn). The 37th share subscription rights are scheduled to be allocated in March 2020 (expected to raise JPY9.4bn).

Medium-term outlook

When AnGes reported FY12/19 earnings results, it also presented an outline of the medium-term plan. Projected growth drivers in the plan include expansion of the HGF gene therapy drug business, expansion of other pipeline drugs, and creation of new drug candidates.

Expansion of HGF gene therapy drug business

The company aims to boost royalty payments and licensing revenues of the HGF gene therapy drug through obtaining full manufacture and marketing approval in Japan and approval in the US, out-licensing to other countries, and expanding the label with additional indications.

Approvals for HGF gene therapy drug

The company looks to increase royalty payments and licensing revenues by working to obtain the following approvals in the medium term.

- ▷ Full approval in Japan for treatment of chronic arterial occlusion
- ▷ Full approval in Japan for improvement of rest pain
- ▷ Approval in the US for patients with arteriosclerosis obliterans

Full approval in Japan of the HGF gene therapy drug for chronic arterial occlusion

In March 2019, the company's HGF gene therapy drug was granted conditional and time-limited approval in Japan for improvement of ulcers associated with chronic arterial occlusion. Licensee Mitsubishi Tanabe Pharma began distribution from September 2019.

The conditional and time-limited approval for the drug was granted for five years provided the following conditions are met:

- ▷ Use of this product is limited to facilities where wound management is carried out through collaboration of multiple departments and in cooperation with a physician sufficiently knowledgeable and experienced in treating severe chronic arterial occlusion.
- ▷ Post-marketing surveillance should be conducted on all patients treated (target number of patients: 120, comparator control group: 80) during the conditional and time-limited approval period, and prior to resubmitting an application for manufacture and marketing approval.

Upon subsequent approval, requirements for usage will be relaxed and Shared Research believes this will lead to increased sales volume that generates higher royalty payments.

Approval of HGF gene therapy drug in Japan for improvement of rest pain

In March 2019, the HGF gene therapy drug was granted conditional and time-limited approval in Japan for improvement of ulcers associated with chronic arterial occlusion.

From October 2019, AnGes also initiated a domestic Phase III clinical trial for improvement of rest pain in patients with chronic arterial occlusion. The study is projected to continue for about two years and aims to treat a total of 40 patients. The post-treatment observational period is six months for confirming improvement in rest pain.

Approval for the additional indication of treatment for patients with rest pain would likely increase the target patient base for the HGF gene therapy drug.

Approval of HGF gene therapy drug in the US for arteriosclerosis obliterans

In January 2020, AnGes started a Phase IIb clinical trial of the HGF gene therapy drug in patients with arteriosclerosis obliterans with lower limb ischemic ulcers (assess improvement of lower limb ulcers, target 60 patients, post-treatment follow-up period of

12 months). Once Phase IIb has been completed, Shared Research believes AnGes will advance to Phase III or try to obtain Regenerative Medicine Advanced Therapy (RMAT) designation. If the HGF gene therapy drug is approved in the US, it would likely generate milestone and royalty payments. AnGes has already concluded an agreement with Mitsubishi Tanabe Pharma for exclusive marketing rights in the US back in October 2012.

RMAT was established in the US as part of the 21st Century Cures Act. RMAT designation by the FDA provides for preferential and expedited approval review of regenerative medicines that address serious diseases with unmet medical needs and that have demonstrated some measure of efficacy in clinical trials.

Out-licensing of the HGF gene therapy drug outside Japan and the US

AnGes has licensed exclusive marketing rights for its HGF gene therapy drug in Japan and the US to Mitsubishi Tanabe Pharma (TSE1: 4508) and in Israel to Kamada. As of February 2020, no marketing agreements had been concluded for other markets. In the medium term, the company aims to out-license rights to markets other than Japan, Israel, and the US.

Label expansions for the HGF gene therapy drug

The company looks to promote basic studies and clinical trials for additional indications of the HGF gene therapy drug including for scleroderma, intractable skin ulcers, lymphedema, and chronic obstructive pulmonary disease (COPD).

*Systemic scleroderma: a disease characterized by impaired blood circulation due to fibrosis of the skin and various organs, and vascular endothelial cell proliferation.
*Intractable skin ulcers: lacerations can become intractable ulcers due to factors that prevent normal healing such as infections, vascular disorders, and sensory disturbances.
*Lymphedema: a condition in which lymph fluid accumulates under the skin near cancer treatment sites such as the arms or legs because cancer therapy has impeded accumulation of lymph fluid in lymph vessels.
*Chronic obstructive pulmonary disease (COPD): A lifestyle-related disease of the lungs that causes problems in air passages such as the bronchi and lungs making it difficult to breathe. It is closely linked to smoking.

Expansion of other pipeline drugs (post-HGF gene therapy drug)

As of February 2020, development of pipeline candidates other than the HGF gene therapy drug include a Phase Ib clinical trial of NF-κB decoy oligonucleotide for discogenic low back pain and Phase I/II clinical trials of a DNA vaccine for high blood pressure.

As these candidates have not yet reached Phase III, approval and profit contributions from commercialization are not likely in the near term. The company looks to engage in out-licensing activity for these candidates in the medium term, which if successful could generate upfront revenue and milestone payments.

AnGes also concluded a joint development agreement with Vasomune (Canada) for Tie2 agonists and aims to begin Phase I clinical trial for patients with Acute Respiratory Distress Syndrome (ARDS) from December 2020.

Creation of new drug candidates

As new business areas, the company is conducting research and promoting alliances on genome editing, microbiome, cancer diagnosis, and diagnosis of intractable and rare neonatal diseases.

- ▷ Cancer diagnosis: AnGes entered into a capital tie-up with Barcode Diagnostics (Israel) from November 2019. Barcode is developing diagnostic technology that uses barcode nanoparticles, liposomes containing DNA barcodes (synthetic DNA with a specific base sequence), as a decision-making tool to select the most effective anticancer drugs for individual patients. AnGes plans to work with Barcode Diagnostics to explore the business potential of in vivo diagnostics for selecting anticancer drugs.
- ▷ Genome editing: AnGes invested in Israel-based US firm Emendo Biotherapeutics Inc. (Emendo) in March 2019 and January 2020. Emendo is developing new genome editing technology that can repair and remove genetic abnormalities in cells that cause serious diseases and disorders. AnGes aims to leverage Emendo to develop drugs through genome editing.

▷ Microbiome: AnGes has invested in Israel-based MyBiotics Pharma Ltd. (MyBiotics) four times during the period from July 2018 through June 2019. MyBiotics is engaged in R&D of microbiomes, ecosystems of microorganisms, and pursues cultivation and formulation technologies for gut bacteria to improve the quality and survival rate in the intestines.

Business

Business description

Established to develop gene-based medicines

AnGes was established in 1999 following basic research done at Osaka University. Dr. Ryuichi Morishita, a professor at the Department of Clinical Gene Therapy, Graduate School of Medicine, applied to patent the use of HGF genes (hepatocyte growth factor, see “HGF gene therapy drug”) for medical treatment. Since no company existed to develop gene therapy medicines, Dr. Morishita set up a company to do it.

Gene medicines for intractable and rare diseases

AnGes hopes to commercialize gene medicines—gene therapy drugs and nucleic acid medicines. It is also developing therapeutic vaccines using DNA plasmids.

Reducing risk through partnerships

The company wants to develop new drugs and cut financial risk by selling rights to sell its drugs. Developing a drug takes a lot of money and time, and there’s no guarantee of success. The partnership model, where AnGes gets milestone payments, reduces financial risks on the road to potential commercialization.

Ordinary process and periods of developing new drugs

Process	Period	What is done
Basic research	2-3 years	Creation of new substances and decision on candidates for drugs
Preclinical test	3-5 years	Confirmation of efficacy and safety through experiments on animals
Clinical trials	3-7 years	Phase I: Confirmation of safety and pharmacokinetics with a small number of healthy people
		Phase II: Confirmation of efficacy and safety with a small number of patients
		Phase III: Confirmation of efficacy and safety with many patients in comparison to existing drugs
Application and approval	1-2 years	Examination by the Ministry of Health, Labour and Welfare

Source: Shared Research based on company data

According to the Biotechnology Innovation Organization, in 2006-2015 the success rate by phase of pharmaceutical companies globally was 63.2% for Phase I, 30.7% for Phase II, 58.1% for Phase III and 85.3% for regulatory approval. The success rate for candidates in Phase I reaching regulatory approval was 9.6%.

Key revenue sources—milestone payments and sales of HGF gene therapy drug

The company has posted operating losses every year except for FY12/01, before it began full-scale trials and research. As of March 2020, operating revenues accrue from upfront payments, development cooperation payments, milestone payments from partner companies, and sales of the HGF gene therapy drug. In March 2019, the HGF gene therapy drug was awarded conditional and time-limited approval in Japan for treatment of critical limb ischemia and licensee Mitsubishi Tanabe Pharma began commercialization from September 2019.

Also, through Q2 FY12/19, the company posted revenues of JPY300–400mn per year relating to Naglazyme, a drug for mucopolysaccharidosis VI (in March 2019 AnGes transferred its rights [approval for domestic manufacture and sales, and distribution] for this product to BioMarin Pharmaceutical Japan K.K., BioMarin’s subsidiary in Japan).

- ▷ Upfront payment: conclusion of agreement
- ▷ Development cooperation payment: financial help for R&D
- ▷ Milestone payment: R&D progress at agreed stages
- ▷ Royalty: percentage of sales post product launch

Key pipeline drug—HGF gene therapy drug

The prime pipeline drug is an HGF gene therapy drug for critical limb ischemia (CLI). In March 2019, AnGes obtained conditional and time-limited approval to manufacture and market its HGF gene therapy drug for the indication of critical limb ischemia (CLI) in Japan, and Mitsubishi Tanabe Pharma launched the drug from September 2019. AnGes also initiated domestic Phase III clinical trial for improvement of rest pain from October 2019 to further expand approved indications.

AnGes also began a global Phase III clinical trial in the US in October 2014. AnGes in June 2016 announced that it has discontinued the joint global Phase III clinical trial, to be replaced by another clinical trial. The company is angling to complete the clinical study within a shorter period of time through revising evaluation criteria and selecting study sites exclusively in the US. In January 2020, the company began a Phase IIb clinical trial (assess effectiveness in improvement of lower limb ulcers, target 60 patients, post-treatment follow-up period of 12 months) of HGF gene therapy for arteriosclerosis obliterans patients with lower limb ulcers.

Main pipeline products

The internal development pipeline includes an HGF gene therapy drug, NF-κB decoy oligonucleotide, and DNA vaccine for high blood pressure. Although in pre-clinical and basic research stages of development, the company is also making progress in developing a gene therapy drug for the treatment of chronic hepatitis B in collaboration with Vical Inc., and a compound (Tie2 agonist peptide Vasculotide) targeting diseases caused by vascular dysfunction and destabilization such as acute respiratory failure jointly with Vasomune Therapeutics Inc. In addition, AnGes is pursuing research and alliances in new business areas such as cancer diagnosis, genome editing, microbiome, and early diagnosis of rare and intractable neonatal diseases.

Internal development pipeline

Type	Product/Project	Indications	Area	Development stage	Partner
Medications	HGF gene therapy drug	Improvement of ulcers in chronic arterial occlusion	Japan	Conditional and time-limited approval obtained	Mitsubishi Tanabe Pharma (licensing marketing rights)
		Improvement of rest pain in chronic arterial occlusion	Japan	Phase III clinical trial	
		Arteriosclerosis obliterans with lower limb ulcers	US	Phase IIb clinical trial	Mitsubishi Tanabe Pharma (licensing marketing rights)
	NF-κB decoy oligonucleotide	Atopic dermatitis	Japan	(Ointment) Phase III clinical trial completed*	Shionogi & Company (worldwide licensing marketing rights)
		Discogenic low back pain	US	Phase Ib clinical trial under way	TBD
	DNA vaccine for high blood pressure	High blood pressure	Australia	Phase I/II clinical trials under way	TBD
	Gene therapy drug for chronic hepatitis B	Chronic hepatitis B	Overseas	Basic research	TBD
	Peptide Tie2 agonist Vasculotide	Diseases caused by vascular dysfunction such as acute respiratory failure	Overseas	Pre-clinical studies	TBD

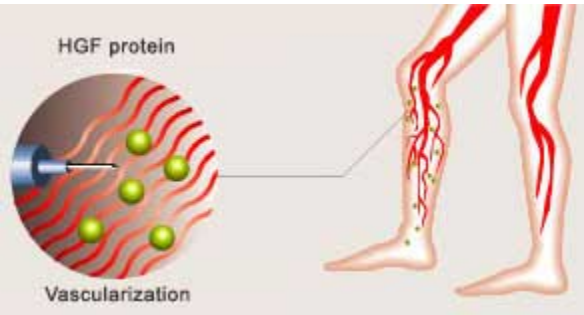
Source: Shared Research based on company data
* In July 2016, AnGes announced that data analysis had not shown a statistically significant difference between the treatment group for this drug and the placebo group in terms of its main efficacy evaluation criterion. The company plans to determine the direction of future drug development based on a detailed evaluation of the results.

Gene drugs

HGF gene therapy drug (chronic arterial occlusion)

HGF discovered in Japan (1984)

HGF (Hepatocyte Growth Factor) was discovered in Japan in 1984 as a factor that increases liver cells, the human organ with the highest regenerative capacity. In 1995, a research group led by Dr. Ryuichi Morishita found a method that regenerates blood vessels through HGF gene transfer. HGF gene therapy can be used to treat chronic arterial occlusion, where blood flow is impeded, by regenerating blood vessels.



Source: Company materials

Severe cases of chronic arterial occlusion—no completely effective treatment

Chronic arterial occlusion includes peripheral vascular diseases (such as arteriosclerosis obliterans and Buerger's disease). These cause blood vessel blockages in human feet and legs on the hardening of arteries, owing to diabetes and other reasons, and ischemic heart diseases (IHD), such as angina and myocardial infarction, due to blood flow problems in coronary arteries. When the peripheral vascular disease conditions worsen, patients' legs can become necrotic and may ultimately require amputation.

> In arteriosclerosis obliterans, damage to the intima of blood vessels causes narrowing of the lumen as platelets accumulate to repair the damage. This narrowing of the blood vessels reduces peripheral blood flow and can cause ischemia of the lower limbs.
> In Buerger's disease, also called thromboangiitis obliterans (TAO), one's arteries and veins in the arms and legs become inflamed, swell and can become blocked with blood clots (thrombi). The specific cause of Buerger's disease remains unknown.

Remedies for severe cases include therapeutic drug treatment, endovascular therapy by balloon catheter (vessel recanalization by catheter) and bypass surgery (connecting other blood vessels to bypass a coronary artery that has become blocked). But these are not always effective. HGF gene therapy can help via an approach that regenerates vessels.

HGF gene therapy drug—interim analysis of Phase III trial in Japan in 2007 demonstrated efficacy

The company completed Phase I/II trials of its HGF gene therapy drug in Japan in 2001–2002. In 2003 it launched a Phase III trial of the drug for peripheral vascular diseases, targeting arteriosclerosis obliterans with CLI and Buerger's disease as indications. In the Phase III trial, in which a total of 120 cases were initially planned, interim analysis of 40 cases in June 2007 showed efficacy.

In the trial target patients were seriously ill with CLI at the stage III (with rest pain) and stage IV (with ischemic ulcers or gangrene), according to the Fontaine classification (see below). Researchers conducted intramuscular injections of the trial drug into the ischemic parts of the patients' limbs twice, with a four-week intermission. They then observed patients for eight weeks. The main criterion for evaluating efficacy: a substantial rate of improvement of rest pain or ischemic ulcers after 12 weeks following the application of the clinical drug.

The rate of improvement for rest pain or ischemic ulcers after 12 weeks was 70.4% (19/27 cases) with patients who were tested with the HGF gene therapy drug. It was 30.8% (4/13 cases) for those given a placebo. The difference between the two groups is statistically significant (p=0.014). For patients at Fontaine stage IV, improvement was 100% (11/11 cases) for those given the HGF gene therapy drug, and 40.0% (2/5 cases) for those given a placebo (p=0.018).

> Fontaine classification: Used to clinically classify arteriosclerosis obliterans. Stage I-asymptomatic, stage II-intermittent claudication, stage III-rest pain, and stage IV-ischemic ulcers or gangrene. Patients at stages III and IV are seriously ill.
>
> P-value: A measure of the probability of a discrepancy from a group or relationship happening randomly, with a p-value of 0.01 suggesting that the probability of a test result occurring randomly is 1 in 100.

Applied for approval of the HGF gene therapy drug in Japan in March 2008; shelved the application in September 2010

Upon receiving the results of interim analysis of the Phase III trial in June 2007, AnGes in March 2008 applied for approval of the manufacture and marketing of its HGF gene therapy drug for arteriosclerosis obliterans and Buerger's disease with CLI as indications. However, following consultations with the Pharmaceuticals and Medical Devices Agency (PMDA), it concluded that

further clinical data were necessary for approval. The company shelved the application in September 2010, intending to make an application again after conducting additional tests.

Joint global Phase III trial launched in October 2014 but discontinued in June 2016; presently preparing a different clinical trial

As flagged, in September 2010 AnGes received PMDA's opinion that further collection of clinical data would be necessary for its HGF gene therapy drug in Japan. Later, with an eye for marketing the drug overseas, the company proceeded with preparations for a global Phase III trial in the US and Europe and in September 2010 got fast-track status in the US.

> Global clinical trial: Clinical trial for worldwide development and approval of a new drug planned by pharmaceutical companies. Medical institutions of several countries participate in a joint trial, which is conducted concurrently based on a common clinical testing plan.
> Fast Track designation: Designed by the FDA to expedite the review of promising drugs for serious diseases.

In October 2014, the company launched global Phase III clinical trials of the drug for CLI and began enrolling patients in the US, and in November 2014 began administering the drug under trial protocols. During the same month, the company began its application to begin trials in six key European countries, including the UK and Germany.

The global Phase III trial targeted some 500 CLI patients in 15 countries in North America, Europe and South America (excluding Japan). The trial compared patients given the HGF gene therapy drug with those given a placebo, and its primary endpoint was determining whether the probability of death/amputation of legs drops within a certain period. According to the company, the whole period was estimated to be three to four years, costing around JPY8bn overall. The trial was scheduled to conclude in the second half of 2017, and the company was aiming to apply for approval in the US in 2018, and then in Europe.

However, AnGes in June 2016 announced that it has discontinued the joint global Phase III clinical trial, to be replaced by another clinical trial. According to the company, analysis and evaluation of the joint global Phase III trial for its HGF gene therapy drug for CLI have revealed that the patient registration rate has been slower than expected. On this basis, it determined that more time and costs would be required to complete the study under the original plan.

Initiated late-stage US Phase II clinical trial from February 2020

Thereafter, the company was creating a new plan for clinical trials in the US involving HGF gene therapy drug for CLI. Aiming to complete the clinical study more quickly, the company has adopted a new development strategy: 1) revision of primary endpoint to ulcer healing from the current endpoint of major amputation or all-cause death, and 2) selection of study sites with experience in CLI treatments in the US to enroll suitable subjects. With these changes, the company is angling to complete the clinical study within a shorter period of time through more efficient registrations of patients for the trial. US Phase IIb clinical trial was started from January 2020 to evaluate HGF gene therapy drug in arteriosclerosis obliterans patients with lower limb ulcers (assess effectiveness in improving lower limb ulcers, target 60 patients, post-treatment follow-up period of 12 months).

Regenerative Medicine Advanced Therapy (RMAT) designation is an option in the US approval review system and, depending on the Phase II results, Shared Research believes AnGes could try to obtain RMAT designation.

> RMAT was established in the US as part of the 21st Century Cures Act. RMAT designation by the FDA provides for preferential and expedited approval review of regenerative medicines that address serious diseases with unmet medical needs and that have demonstrated some measure of efficacy in clinical trials.

Conditional and time-limited approval obtained

Since it had shelved the application for the HGF gene therapy drug for CLI in September 2010, it refrained from testing the drug. However, Osaka University Hospital began conducting investigator-initiated clinical studies for an HGF gene therapy drug to treat CLI in October 2014. In these studies, six new cases of clinical trials utilizing the Japanese Advanced Medical Care B program were conducted. CLI patients enrolled in the study received the HGF gene therapy drug two or three times. After treatment, patients were followed up over three months to assess ulcer reduction and pain improvement.

In regard to the investigator-initiated clinical studies for an HGF gene therapy to treat chronic arterial occlusion, the observation period for the sixth of the six target cases ended in August 2017. In January 2018, the company applied to the Ministry of Health, Labour and Welfare for approval of the manufacture and sale of the HGF gene therapy drug to treat chronic arterial occlusion in Japan as a regenerative medicine product. In March 2019, AnGes obtained conditional and time-limited approval to manufacture and market the HGF gene therapy drug for chronic arterial occlusion in Japan and Mitsubishi Tanabe Pharma started marketing it from September 2019. To further expand the approved indications, AnGes started a Phase III clinical trial in Japan for improvement of rest pain from October 2019.

Conditional time-limited approval system: Allows conditional approval of regenerative medicines and other products, including genetic medicines, based on partial clinical trial data. Full approval will be given when additional clinical data are obtained after the conditional approval. The new system was included in the amended Pharmaceutical Affairs Law enacted in November 2013, with the aim of promoting early approval of regenerative medicines, and was enforced in November 2014.

Advanced Medical Care B program: Under this program, patients may use advanced medical technologies that have been proven safe and effective alongside treatments provided under health insurance. There are two programs, A and B. B applies to technologies that relate to "medical products or devices used in ways that are unapproved or outside their standard indications."

The conditional and time-limited approval for the drug was granted for five years provided that the following conditions are met:

- The product must be administered by physicians with ample knowledge of and experience treating severe chronic arterial occlusive diseases in medical institutions that provide wound care in multiple departments working in collaboration.
- Until the company re-applies for manufacturing and marketing approval for the product after having obtained the conditional and time-limited approval, the company must conduct post-marketing evaluation of how well the product satisfies criteria for approval for all patients using the product (target enrollment of 120 in treatment arm and 80 in control arm).

Estimate of US market size for the HGF gene therapy drug

According to the company, there are an estimated 500,000 patients with CLI in the US. Of these patients, those who are candidates for the HGF gene therapy drug (no-option and poor-option patients) are estimated to be approximately 200,000.

No-option patients refer to patients that are not candidates for existing procedures (balloon, endovascular or external bypass procedures). Poor-option patients refer to patients that are not candidates for endovascular procedures, and for which external bypass procedures would carry too high of a medical risk.

Competitors for the HGF gene therapy drug

Other gene therapy drugs for blood vessel regeneration included Neovasculgen—developed in Russia and the Ukraine and sold by Human Stem Cells Institute OJSC (MCX: ISKJ)—and VM202-PAD (from South Korea's ViroMed Co Ltd, KRX: 084990). Sanofi S.A. (Euronext: SAN) has stopped research on NV1FGF, its regenerative medicine for blood vessels. NV1FGF (riferminogen pecaplasmid) is a non-viral plasmid-based gene local delivery system for human fibroblast growth factor (FGF-1). FGF-1 promotes angiogenesis and induces the formation of new blood vessels that could improve blood flow in the limbs of CLI patients. Other projects include development of cell therapy using bone marrow-derived stem cells.

- Neovasculgen is a genetic drug for treating of peripheral arterial disease (PAD), including CLI. It was approved in Russia by the Ministry of Health and Social Development in September 2011 and was marketed in September 2012. The drug contains the gene of the Vascular Endothelial Growth Factor (VEGF) embedded in a plasmid vector. Approval was obtained in the Ukraine in 2013.
- ViroMed is developing the HGF gene therapy drug VM202-PAD. In 2014, ViroMed completed Phase II clinical trials. In 2014, ViroMed announced completion of Phase II clinical trials, and announced in 2015 that it plans to start Phase III clinical trials in the US focusing on diabetic ischemic ulcer.
- Pluristem Therapeutics Inc. of Israel is developing PLX-PAD, a cell therapy drug for CLI. According to company materials, Phase III trials are under way in the US, and the company reached an agreement with PMDA in December 2015 regarding the implementation plan for clinical trials in Japan required to file for approval under the conditional and time-limited approval

system. PLX-PAD uses technology that enables the culturing of large quantities of placental cells and converting them into placenta-derived, mesenchymal-like adherent stromal cells (PLX cells). These cells release proteins that play an important role in tissue regeneration in response to signals produced by inflamed and ischemic tissue in the patient's body to aid the body's natural healing mechanism.

- ▷ UK company Rexgenero Ltd. initiated Phase III clinical trials of REX-001 in January 2018. REX-001 is a novel autologous cell therapy for CLI that restores blood supply by stimulating growth of new blood vessels to relieve the symptoms of the disease. The company plans to enroll 138 patients in the study, which is scheduled for completion in 2020.

Alliances involving the HGF gene therapy drug: Exclusive marketing agreement with Mitsubishi Tanabe Pharma for Japan and US sales

AnGes made agreements with Mitsubishi Tanabe Pharma (TSE1: 4508) granting the pharmaceutical giant the exclusive marketing rights for its HGF gene therapy drug in Japan as well as in the US. As of February 2020, the company did not have any sales partners in Europe or Asia.

Under this exclusive marketing agreement for Japan and the US, AnGes is set to receive an upfront and development milestone payments from Mitsubishi Tanabe Pharma. It is also set to receive a percentage of sales (royalties) once the HGF gene therapy drug is brought to the market.

- ▷ The agreement with Daiichi Sankyo for exclusive marketing rights in Japan for AnGes' HGF gene therapy drug for peripheral vascular diseases and ischemic heart diseases came to an end in June 2015. AnGes announced that it had reached an agreement with Mitsubishi Tanabe Pharma for these rights on its HGF gene therapy drug for peripheral vascular diseases.
- ▷ In the US, AnGes entered into an agreement with Mitsubishi Tanabe Pharma in October 2012 that gave Mitsubishi Tanabe Pharma exclusive marketing rights in the US for its HGF gene therapy drug for peripheral vascular diseases.
- ▷ In February 2019, AnGes entered into an agreement with Kamada Ltd. of Israel, granting Kamada exclusive commercialization rights to the HGF gene therapy drug in the Israeli market.

Nucleic acid medicines

Types of genetic medicines: 1) using genes themselves as is the case with HGF non-viral genetic therapy; and 2) using short artificial nucleic acids made by synthesizers to regulate gene expression, known as nucleic acid medicines (includes decoy oligodeoxynucleotide).

NF-κ(kappa)B decoy oligonucleotide

AnGes has designed NF-κB decoy oligonucleotide as a specific inhibitor for NF-κB that acts as a switch to a gene cluster involved in the immune inflammatory response in the body. The company has been conducting research and development of NF-κB decoy oligonucleotide as a new pharmaceutical product for immune and inflammatory diseases. Specifically, AnGes is conducting trials to treat discogenic low back pain. Further, the company is looking to begin product development of its Chimera decoy, which simultaneously suppresses transcription factors STAT6 and NF-κB.

NF-κB decoy oligonucleotide injection for treating discogenic low back pain

In February 2018, AnGes began Phase Ib clinical trials for NF-κB decoy oligonucleotide targeting treatment of discogenic low back pain in the US and administration was completed in February 2020. Twenty-five patients were enrolled in the study, which will confirm safety and efficacy over a 12-month follow-up period after administration. The company plans to release clinical trial results around Q4 FY12/20.

The company stated that NF-κB decoy oligonucleotide for treating discogenic low back pain is injected directly into the affected area. The drug can therefore be more efficiently delivered to the targeted area than NF-κB decoy oligonucleotide ointment for atopic dermatitis (discussed later), which is applied to the skin.

As of March 2020, AnGes has yet to conclude a development and marketing agreement for NF-κB decoy oligonucleotide with a pharmaceutical company.

NF-κB decoy oligonucleotide ointment for atopic dermatitis

In March 2015, the company launched domestic Phase III clinical trials. The company aimed to confirm the safety and efficacy of the drug in this trial, which covers about 200 patients with at least medium facial atopic dermatitis. Subsequently, however, it announced in July 2016 that results of the trials did not yield a statistically significant difference versus the placebo group. While the company continues a detailed analysis of the trials, it states that it is not in a position to apply for approval to market the product targeting patients with atopic dermatitis.

The company has a worldwide exclusive sales agreement in place with Shionogi & Co., Ltd. (TSE1: 4507) for the topical use of NF-κB decoy oligonucleotide for patients with skin diseases.

Other: Examining applications of Chimera decoy and new DDS technology for pharmaceutical drugs to treat inflammatory diseases

AnGes has been conducting research on next-generation decoys to follow NF-κB decoy oligonucleotide. In July 2016, the company announced that it had completed the development of the basic technology for Chimera decoy, which acts to simultaneously suppress STAT6 and NF-κB, two of the key transcription factors, and would begin product development.

> STAT6 is a transcription factor that controls gene expression. Excessive activation of STAT6 has been shown to aggravate allergies (including atopic dermatitis and asthma) and immunological disorders.

AnGes stated that this Chimera Decoy is expected to be significantly more effective in suppressing inflammation than current decoys that only target NF-κB. Other advantages of Chimera Decoy include high biological stability and low production costs compared to NF-κB decoys.

Therapeutic vaccines

AnGes is developing a DNA vaccine for high blood pressure as a therapeutic vaccine that uses gene drugs. There are two types of therapeutic vaccines; preventive vaccines, which are vaccines that prevent a certain illness, and therapeutic vaccines, which are used as treatment to combat an existing illness. AnGes aims to develop therapeutic vaccines. A DNA vaccine introduces DNA (contains the blueprint for proteins) into the body. Major benefits are a strong vaccine effect induced by producing the target antigen in the body and lasting effectiveness. Such vaccines have possible applications for treating cancer, allergies, and certain chronic diseases.

In addition to development of a DNA vaccine for hypertension, in March 2020 AnGes and Osaka University embarked on joint development of a preventive DNA vaccine against the novel coronavirus, COVID-19.

In December 2016, AnGes signed an agreement to exclusively reassign all rights it had possessed for the CIN therapeutic vaccine to Morishita Jintan, which has become the main developer of the vaccine and will pay royalties to AnGes once it has been commercialized.

DNA vaccine for high blood pressure

Australian Phase I/II clinical trials of DNA vaccine for high blood pressure started from April 2018

In July 2016, the company announced that it launched a DNA therapeutic vaccine business, with plans to start clinical trials for a DNA vaccine for high blood pressure. It has been developing this DNA vaccine for high blood pressure in partnership with Osaka University. After confirming efficacy in animal testing and in view of the completion of various pre-clinical trials in sight, the company began Phase I/II clinical trials of a DNA vaccine for high blood pressure in Australia in April 2018. Twenty-four patients with mild to moderate high blood pressure are enrolled for the study, which will confirm safety and efficacy over a 12-month follow-up period after administration. The planned length of the study is approximately two years.

AnGes in August 2016 made an additional investment of JPY816mn in Vical Incorporated (Vical)—a US company involved in DNA vaccine development—which raised its equity from 2.4% to 18.6%. The company plans to use this to strengthen and expand its base for the DNA vaccine business.

Vical Inc, which entered into a strategic alliance with AnGes from December 2016, concluded a merger agreement with Brickell Biotech in August 2019 and the company name was changed to Brickell Biotech. AnGes is reviewing future collaborations with Brickell Biotech.

Special features of high blood pressure DNA vaccine

In the field of high blood pressure treatment, there are already numerous orally administered drugs on the market. However, they need to be taken on a daily basis and the adherence rate (how conscientiously the patient takes the medication) is not very high. The basic technology for the DNA therapeutic vaccine the company has been developing was developed by a research group led by Professor Morishita at Osaka University, and has a longer hypotensive effect than current high blood pressure treatment drugs. By targeting angiotensin II, this DNA vaccine for high blood pressure is able to achieve a long-lasting and stable hypotensive effect. It is therefore expected to have certain advantages over existing high blood pressure treatment drugs, including suppressing excessive diurnal variations in blood pressure and as an indication for patients that have difficulty taking medicine as prescribed.

Market for high blood pressure DNA vaccine

The domestic drug market for high blood pressure surpasses JPY800bn including the core drug ARB (angiotensin II receptor blocker, with market size around JPY500bn). As the DNA vaccine business aims to cut into this market as an alternative to existing products, its potential is high. Especially promising are developing nations, where the consumption of ARB is limited due to its high medical costs despite its demonstrated efficacy.

Partnerships for DNA vaccine to treat high blood pressure

As of March 2020, AnGes has yet to conclude a development and marketing agreement for the DNA vaccine for high blood pressure with a pharmaceutical company.

Vaccine against novel coronavirus, COVID-19

In March 2020, AnGes and Osaka University embarked on joint development of a preventive DNA vaccine against the novel coronavirus, COVID-19, leveraging the company's experience in commercializing DNA plasmid-based HGF gene therapies. In the same month, the company completed production of the plasma DNA vaccine and initiated preclinical studies (animal testing). The preclinical studies will be conducted to evaluate antibody productivity in animals, after which the plan is to commence clinical trials in humans.

According to AnGes, the manufacturing process can be established more safely and in a shorter period of time with the manufacture of DNA vaccines, compared with vaccines using inactivated viruses (attenuated vaccines) or vaccines using genetically modified virus protein.

Overview of project for development and manufacture of preventive DNA vaccine against novel coronavirus, COVID-19, using plasmid DNA manufacturing technology

- ▷ AnGes and Osaka University (Department of Clinical Gene Therapy; Department of Health Development and Medicine) will engage in joint development of a preventive DNA vaccines against the novel coronavirus, COVID-19, capitalizing on previous experience in developing plasmid DNA products.
- ▷ Manufacturing will be undertaken by Takara Bio Inc. (TSE1: 4974), which possesses plasmid DNA manufacturing technology and production facilities.
- ▷ Daicel Corp. (TSE1: 4202) is developing an intradermal gene transfer method using a new drug delivery device, and is undertaking research with Osaka University (Impulse Science for Medicine; Department of Health Development and

Medicine), with a view to adoption in clinical settings. Use of this new drug delivery device is expected to increase intradermal gene expression efficiency and antibody production capability, enabling the development of more effective DNA vaccines.

- ▷ EPS Holdings Inc. (TSE1: 4282) will participate also, as an organization providing drug development support. It will run the trials involving humans, in order to advance clinical development.
- ▷ Peptide Institute Inc. (unlisted) will undertake research on peptide synthesis for antibody titer measurement.
- ▷ Shin Nippon Biomedical Laboratories, Ltd. (TSE1: 2395) is involved also, with the main role of planning and conducting preclinical safety studies for the DNA vaccine.
- ▷ Human Metabolome Technologies Inc. (TSE Mothers: 6090) will employ metabolomics technology to analyze changes over time in the body's metabolic profile post-inoculation, along with analyzing antibody titer values and other biometric information. Human Metabolome Technologies also will investigate biomarkers for gauging the vaccine's efficacy.

Pipeline drugs in pre-clinical and basic research stages of development

Drugs in pre-clinical and basic research stages of development include a gene therapy drug targeting chronic hepatitis B being developed in collaboration with Vical, and a compound (Tie2 agonist peptide Vasculotide) targeting diseases caused by vascular dysfunction and destabilization such as acute respiratory failure being developed jointly with Vasomune.

Gene therapy drug targeting chronic hepatitis B

After AnGes became the largest shareholder of the US-based Vical Incorporated (Vical) by purchasing additional shares in August 2016, the company concluded a strategic business alliance agreement with Vical. As part of the business alliance, the two companies agreed to jointly develop a gene therapy drug targeting chronic hepatitis B in April 2017. By signing the joint development agreement, AnGes acquired preferential negotiating rights for the development and marketing rights of the drug in Japan.

Hepatitis B is a viral infection caused by hepatitis B virus. There are more than 1.3mn people infected with hepatitis B virus (carriers) in Japan alone, and roughly 350mn people worldwide. Although majority of infected individuals do not develop any symptoms, in some cases the infection may develop into chronic hepatitis, which can cause severe complications such as cirrhosis or hepatocellular carcinoma in worst cases. Current standard treatment involves administering antiviral agents that suppress the activity of the hepatitis B virus, but because the virus cannot be completely eradicated, patients need to take medications for their lifetime.

The gene therapy drug being developed jointly by the company and Vical aims to treat chronic hepatitis B rather than merely keeping it under control. By taking advantage of Vical's gene transfer technology, the two companies aim to insert a specific DNA fragment into the liver cell to eradicate hepatitis virus from the liver. If favorable results are obtained from a jointly conducted study using mice, the two companies will discuss progressing to the next stage of development.

Tie2 agonist peptide, Vasculotide

In July 2018, AnGes concluded a joint development agreement with a Canada-based biomedical company Vasomune Therapeutics Inc. regarding a compound (Vasculotide) targeting diseases caused by vascular dysfunction and destabilization such as acute respiratory failure. Based on the agreement, the two companies will jointly promote development of the compound discovered by Vasomune worldwide, and will halve the development cost and future earnings. The company will pay an upfront payment (on concluding the agreement) and milestone payments in accordance with development progress to Vasomune.

Vasomune is a biomedical, drug discovery startup founded in 2012 as a spinoff of the University of Toronto's medical research institute Sunnybrook Research Institute. It is working on developing a Tie2 receptor agonist targeting diseases caused by vascular dysfunction and destabilization.

The agreement targets not only acute respiratory failure but all diseases associated with vascular dysfunction, and the scope of joint development may be expanded to cover other diseases including asthma. The company has accumulated much knowledge and expertise in vascular diseases through development of its mainstay product HGF gene therapy drug (targeting critical limb ischemia), and plans to leverage that strength in developing Vasculotide in collaboration with Vasomune.

Tie2 agonist peptide, Vasculotide

Although vascular permeability is usually maintained at a low level in normal cells, it increases in response to inflammation as part of the body's defense mechanism, allowing immune cell to move through and out of the blood vessels to the site of inflammation and causing plasma contents to leak out of the vessels. Endothelial cells have a mechanism for regulating vascular permeability, and failure of that mechanism is said to be closely related to various diseases such as sepsis, acute respiratory distress syndrome (ARDS), asthma, edema, anaphylactic shock, cancer, diabetic retinopathy, and chronic inflammation.

Research has found that vascular structure stabilizes when angiopoietin-1 (Ang1), a glycoprotein that promotes angiogenesis, binds to a molecule known as Tie2 receptor expressed on vascular endothelial cells. Hence, administering Ang1 can prevent vascular permeability from increasing. However, according to the company, Ang1 is difficult to manufacture and doing so is costly. A Tie2 agonist peptide Vasculotide discovered by Vasomune can also bind to Tie2 receptors and activate the mechanism for stabilizing vascular structure, preventing blood vessels from becoming leaky just as Ang1 can. Further, compared with Ang1, Vasculotide can be manufactured at a lower cost and in large volume.

According to AnGes, Vasculotide, with its unique mechanism of action, can be used to treat various diseases, and its contribution to earnings will be significant if development succeeds.

Develop Vasculotide for the treatment of acute respiratory distress syndrome (ARDS)

The company plans to conduct a pre-clinical study of Vasculotide for the initial target indication of ARDS, a severe respiratory insufficiency, with an aim of starting clinical trials in two years. Upon acquiring a proof of concept (POC—evidence of certain degree of effectiveness shown in patients) from the clinical trials, the company expects to out-license manufacturing and marketing rights to pharmaceutical companies.

ARDS is a severe respiratory insufficiency caused by various reasons including trauma, pneumonia, and blood transfusion. There is no fundamental treatment for ARDS, and hence discovering an effective therapeutic agent is highly anticipated. Symptoms of ARDS mainly result from the leakage of plasma contents from lung capillaries and interference with gas exchange in the alveoli. Binding of Vasculotide to Tie2 receptors can prevent blood vessels from becoming leaky.

According to the company, successful development of an effective therapeutic agent for ARDS could potentially generate business opportunities worth more than USD2.5bn worldwide.

New business areas

AnGes is pursing research and alliances in the new business areas of genome editing, microbiome, cancer diagnosis, and early diagnosis of rare and intractable neonatal diseases.

Target	Alliance partner	Start of partnership
Genome editing	Emendo Biotherapeutics	March 2019
Cultivation, formulation of microbiome ecosystem	MyBiotics Pharma	July 2018
Diagnosis technology for anticancer drug selection	Barcode Diagnostic	August 2019

Genome editing

In March 2019**,** the company made an investment in US biotech firm Emendo Biotherapeutics, which is based in Israel.

Emendo is developing novel genome editing technology, including those with zero off-target effect. AnGes commented that it seeks to leverage Emendo's safe genome editing technology to establish a competitive edge in gene therapy medicine development.

Genome editing entails cutting specific DNA sequences (targeted genome sequences) to modify the targeted gene. However, cutting a sequence that is similar to the target sequence by mistake can affect non-targeted genes and is a safety risk (off-target effect). To minimize the off-target effect, the target sequence should be one with as few similar sequences as possible. Emendo has developed a highly precise DNA-cleaving enzyme (nuclease) that cannot cut non-target sequences. It is hoped that this not only makes genome editing much safer, but also allows free choice of target without being constrained by the existence of similar sequences.

> Genome editing is a technology that uses a DNA-cleaving enzyme (nuclease) that only cuts a specific DNA sequence (target sequence) to modify genes as required. Known nucleases include zinc-finger nucleases (ZFN), transcription activator-like effector nuclease (TALEN), and CRISPR (clustered regularly interspaced short palindromic repeats)/Cas9. Emendo Biotherapeutics uses CRISPR/Cas9, which is composed of two separate molecules (guide RNA and Cas9 protein). The target sequence is defined by the DNA sequence of the target site and guide RNA with a complementary RNA base, and the Cas9 protein specifically cuts the target location defined by the guide RNA.

Additional investment in Emendo

Following initial investment in Emendo from March 2019, AnGes invested USD50mn to increase its equity stake by 3,760,000 shares and made Emendo an equity-method affiliate from December 2019. In January 2020, it acquired 1,880,000 shares, raising its total holdings to 2,222,000 shares (26.8% equity stake). Management plans to acquire the remaining 1,880,000 shares in June 2020.

Microbiome: formulation of indigenous bacteria

AnGes entered into a capital alliance with Israeli biotechnology company MyBiotics Pharma Ltd. (MyBiotics) in July 2018. MyBiotics is engaged in R&D of microbiomes and has developed technology that improves the quality and survival rate of indigenous bacteria, including gut bacteria through its cultivation and formulation processes. It has already signed a licensing agreement with a major pharmaceutical company to commercialize candidates for gastrointestinal and women's health diseases. AnGes aims to explore the commercial potential of microbiome through the partial equity stake in MyBiotics.

Human intestinal flora within the microbiome, typically called intestinal flora, have been reported to be associated with not only gastrointestinal diseases, but also infectious diseases, inflammatory diseases, obesity, diabetes, autoimmune diseases, and even psychiatric disorders such as autism. Microbiome research can also be widely applied to not only pharmaceuticals, but health foods and supplements.

Diagnostic technology for anticancer drug selection

In August 2019, AnGes entered into a capital alliance with Barcode Diagnostics Ltd.

When treating cancer with anticancer drugs, it is currently difficult to identify which drug is most effective for an individual patient. Doctors must administer a drug to confirm its efficacy. It takes a certain length of time after administration to determine whether or not a drug is effective, with the risk of the patient suffering adverse effects of an anticancer drug that may not be effective. This process may have to be repeated before an effective anticancer drug is identified.

Barcode provides diagnostic technology called Barcode Nanoparticle (liposome that contains a DNA barcode, i.e., synthetic DNA with specific nucleotide sequence) as a tool to determine the most effective anticancer drug for an individual patient. Barcode's diagnostic technology entails manufacturing multiple liposomes that encapsulate anticancer drugs expected to be effective for a patient and a DNA barcode. These liposomes are used to administer minute doses of multiple anticancer drugs to a patient to measure the DNA barcode volume, which will indicate the drug most effective for the patient. Barcode Diagnostics has successfully identified the most effective anticancer drug from a number of drugs in laboratory tests with mice and plans to begin clinical trials with breast cancer patients going forward.

Earnings structure

Earnings structure

(JPYmn)	FY12/10	FY12/11	FY12/12	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19
Operating revenue	287	243	445	491	910	430	514	365	610	327
Sales of merchandise	181	181	242	271	309	350	347	365	383	170
Sales of finished goods	-	-	15	8	-	-	-	-	-	4
R&D revenues	106	63	187	212	601	80	167	0	227	153
Operating expenses	2,297	2,344	2,230	1,854	3,184	4,602	5,278	3,654	3,675	3,597
Cost of sales	83	81	129	131	151	180	175	178	188	87
% of sales of goods	45.8%	44.9%	53.5%	48.4%	48.9%	51.3%	50.3%	48.8%	49.2%	51.3%
R&D expenses	1,440	1,444	1,200	1,025	2,339	3,533	4,189	2,600	2,540	2,215
Salaries and allowances	420	348	312	247	309	456	441	364	245	226
Outsourcing expenses	315	348	374	274	1,194	2,145	2,769	1,370	1,174	1,065
SG&A expenses	775	819	901	699	694	890	915	876	947	1,294
Directors' compensations	123	123	121	72	74	83	78	91	90	76
Salaries and allowances	217	230	224	139	125	155	148	140	127	147
Commission fee	135	145	197	197	163	240	265	179	232	373
Operating profit	-2,010	-2,101	-1,785	-1,363	-2,274	-4,172	-4,763	-3,289	-3,065	-3,270

Source: Shared Research based on company data
Note: Figures may differ from company materials due to differences in rounding methods.

Sales to major clients

(JPYmn)	FY12/10	FY12/11	FY12/12	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19
Mitsubishi Tanabe Pharma	-	-	-	-	500	50	-	-	-	154
Daiichi Sankyo	102	42	159	35	92	-	-	-	-	-
TS Alfresa (former Seiwa Sangyo)	97	90	132	151	148	160	176	179	196	91
Alfresa	83	91	110	120	161	190	171	186	186	79
Shionogi	-	-	26	113	8	-	-	-	-	-
Ishihara Sangyo	-	-	2	50	-	-	-	-	-	-
Morishita Jintan	-	-	-	-	-	-	155	-	-	-
Other	-	-	-	-	-	-	-	-	227	-

Source: Shared Research based on company data
Note: Figures may differ from company materials due to differences in rounding methods.

Operating revenues

Operating revenues comprise sales of merchandise (52.0% of the FY12/19 total), sales of finished goods (1.3%), and research and development revenues (46.7%).

Sales of merchandise

Under sales of merchandise, AnGes booked sales of Naglazyme in FY12/19. The company procures Naglazyme from BioMarin Pharmaceuticals Inc., and sells to TS Alfresa Corporation (formerly SEIWA SANGYO CO., LTD.), and Alfresa Corporation.

The agreement for the development and sale of this product in Japan ended in March 2019, at which point the company transferred its rights (approval for domestic manufacture and sales, and distribution) to BioMarin Pharmaceutical Japan K.K., BioMarin's subsidiary in Japan. AnGes ended sales of Naglazyme in 1H FY12/19.

Sales of finished goods

Sales of finished goods are revenues booked from the sale of HGF gene therapy drug Collategene® 4mg Intramuscular Injection. AnGes procures the HGF gene therapy drug from Boehringer Ingelheim and sells it to Mitsubishi Tanabe Pharma.

R&D

Upfront payments, development cooperation payments and milestone payments from partner companies.

▷ In FY12/13, AnGes received milestone payment from Shionogi for NF-κB decoy oligonucleotide ointment for atopic dermatitis and an upfront payment from Nippon Zoki Pharmaceutical Co., Ltd.

- In FY12/14, AnGes recorded an upfront payment from Mitsubishi Tanabe Pharma for use of its HGF gene therapy drug to treat peripheral vascular disease in the US.
- In FY12/15, the company booked a milestone payment following the conclusion of an exclusive licensing agreement with Mitsubishi Tanabe Pharma for use of its HGF gene therapy drug in Japan for patients afflicted with peripheral vascular diseases.
- In FY12/16, the company signed an agreement that reassigned exclusive development, manufacturing, use and marketing rights for its CIN therapeutic vaccine in Japan, the US, UK and China to Morishita Jintan. In exchange, AnGes received upfront payments.
- In FY12/18, the company booked R&D revenue of JPY227mn from the transfer of its pre-clinical trial data to an overseas pharmaceutical company.
- In FY12/19, we understand AnGes booked a milestone payment from Mitsubishi Tanabe Pharma as a result of the conditional and time-limited approval of HGF gene therapy drug Collategene® in Japan.

Operating expenses

Cost of sales, research and development expenses, and SG&A expenses.

Cost of sales

In FY12/19, costs related to Naglazyme were incurred in 1H while costs for HGF gene therapy drug were booked in 2H.

The cost ratio for sales of finished goods in 2H FY12/19 was 82.8%. AnGes procures the HGF gene therapy drug from Boehringer Ingelheim and sells it to Mitsubishi Tanabe Pharma. The high cost ratio in FY12/19 is attributable to small lot production, but costs will likely go down over the medium term as production lot volumes increase.

R&D

Mainly salaries, allowances and outsourcing expenses.

- Salaries and allowances rose to JPY615mn in FY12/07 on more personnel but decreased from FY12/08 onward, due partly to the departure of employees via an early retirement program in January 2013, reaching JPY247mn in FY12/13. Salaries and allowances have remained in the JPY200mn to JPY500mn range since FY12/14.
- Outsourcing expenses comprise those for clinical trials entrusted to contract research organizations (CROs). These expenses vary depending on the clinical trial status of pipeline candidates

SG&A

Mainly directors' compensation, salaries and allowances—and fixed. Due to cost rationalization, such as a reduction in rewards to directors, in Q3 FY12/12 and beyond, SG&A expenses fell from JPY901mn in FY12/12 to JPY694mn in FY12/14. Expenses were also down as a result of a reduction in employee count from an early retirement program implemented in January 2013. SG&A increased to roughly JPY900mn from FY12/15 due to higher commissions paid, owing mainly to higher business compensation. In FY12/19, SG&A expenses were JPY1.3bn as stock compensation and commissions paid increased.

Strengths and weaknesses

Strengths

- **Receipt of conditional and time-limited approval to manufacture and sell HGF gene therapy drug:** In March 2019, AnGes obtained conditional and time-limited approval to manufacture and market its main pipeline product—the HGF gene therapy drug for improvement of ulcers associated with chronic arterial occlusion —in Japan. This marks the first gene therapy product approved in Japan. Mitsubishi Tanabe Pharma began marketing it from September 2019.
- **Partnerships with pharmaceutical companies**: AnGes has entered into partnerships with some major domestic pharmaceutical companies (Daiichi Sankyo, Mitsubishi Tanabe Pharma and Shionogi), which we think attests to its high development capabilities. The company has reduced development risk by getting development cooperation payments, milestone payments and royalties from partners.
- **Prospects for launching the HGF gene therapy drug on overseas markets as well:** The company has an agreement with Mitsubishi Tanabe Pharma Corporation, granting the latter exclusive rights to sell the HGF gene therapy drug in Japan and the US. As of February 2020, AnGes has yet to identify a sales partner for the European and Asian markets. As noted above, in March 2019 the company obtained conditional and time-limited approval to manufacture and market the HGF gene therapy drug in Japan. Over the medium term, Shared Research believes earnings opportunities will increase, as the company also seeks approval in the US, where the number of CLI patients is greater than in Japan, and is looking to sign up sales partners in Europe and Asia.

Weaknesses

- **Approval to manufacture and sell the HGF gene therapy drug is conditional and time-limited:** In March 2019 the company obtained conditional and time-limited approval to manufacture and market the HGF gene therapy drug in Japan. However, for five years after this conditional and time-limited approval, the company must conduct post-marketing evaluation of how well the product satisfies criteria for approval for all patients using the product (target enrollment of 120 in treatment arm and 80 in control arm), and apply for formal approval using this additional data.
- **Ongoing losses:** The company has posted operating losses every year except for FY12/01, before it listed. Although AnGes has obtained conditional and time-limited approval to manufacture and market the HGF gene therapy drug in Japan, Shared Research believes that as of February 2020 there is still a lack of visibility over the timing of a medium-term transition to profitability as well as its sustainability.

Historical performance

1H FY12/20 results

Operating revenues: JPY17mn (-90.2% YoY)

Operating revenues broke down into zero sales of merchandise (JPY170mn in 1H FY12/19), sales of finished goods of JPY17mn (JPY0mn in 1H FY12/19), and zero R&D revenue (JPY3mn in 1H FY12/19).

- ▷ The company booked zero sales of merchandise, because sales of Naglazyme®, a drug for mucopolysaccharidosis VI (MPS VI), were completed in June 2019.
- ▷ The company booked sales of HGF gene therapy Collategene® 4mg Intramuscular Injection as sales of finished goods. Mitsubishi Tanabe Pharma Corporation began selling the product in September 2019.

Operating loss: JPY1.8bn (loss of JPY1.7bn in 1H FY12/19)

Operating expenses: JPY1.8bn (-5.3% YoY)

- ▷ The company booked costs for Collategene® as cost of sales, which came to JPY9mn (-89.0% YoY). Operating expenses declined YoY due to sales of Naglazyme® (a drug for mucopolysaccharidosis VI) being completed.
- ▷ R&D expenses were JPY1.1bn (-2.2%, -JPY25mn YoY). Research material costs fell JPY122mn, because the company booked a smaller loss from reassessment of research materials. The company began Phase IIb clinical trials in the US of an HGF gene therapy drug targeting chronic arterial occlusion patients with leg ulcers, incurring clinical trial expenses. This led to a JPY90mn increase in outsourcing costs.
- ▷ SG&A expenses were JPY669mn (+0.1%, +JPY1mn YoY). Taxes and dues increased by JPY16mn on an increase in the portion of corporate tax determined based on the company's capital. Travel and transport expenses declined by JPY15mn as the company refrained from business travel due to the spread of COVID-19.

Recurring loss: JPY1.9bn (loss of JPY1.7bn in 1H FY12/19)

- ▷ The company booked non-operating profit of JPY50mn (+248.6% YoY), including a JPY36mn forex gain on revaluation of foreign currency deposits (JPY7mn in 1H FY12/19).
- ▷ Non-operating losses were JPY180mn (+367.7% YoY). Equity-method investment losses were JPY121mn (zero in 1H FY12/19) as Emendo Biotherapeutics Inc. became an equity-method affiliate in 1H.

Net loss attributable to owners of the parent: JPY1.9bn (net loss of JPY2.0bn in 1H FY12/19)

- ▷ The company booked a JPY5mn gain from the reversal of share subscription rights on the expiry of stock options at the end of the exercise period.
- ▷ The company recorded a JPY243mn valuation loss on investment securities in 1H FY12/19, but none in 1H FY12/20.

Main pipeline progress

Main pipeline progress in 1H FY12/20

The most notable advances in the pipeline since end-FY12/19 are as follows.

- ▷ In August 2020, AnGes announced the outline of Phase I/II clinical trials of a DNA vaccine targeting the novel coronavirus disease (COVID-19) conducted at the Osaka University Hospital. The purpose of the trial will be to determine optimal vaccination intervals and frequency. Target enrollment is 30 subjects, with plans to begin the vaccinations in early September.
- ▷ In the same month, the company announced that it had completed Phase I/II clinical trials of a DNA vaccine targeting COVID-19 conducted at Osaka City University Hospital, with target enrollment of 30 subjects (15 receiving a low dose and 15 receiving a high dose; two fortnightly vaccinations given).

- Also in the same month, the company was chosen among the applicants for the Ministry of Health, Labour and Welfare's 2020 subsidy program for urgent provision of vaccine production facilities. The standard subsidy amount is JPY9.4bn and the facility construction period is August 2020–March 2022.

- In March 2020, AnGes and Osaka University completed production of a plasmid DNA vaccine targeting COVID-19, also commencing preclinical studies (animal testing).
- In March 2020, AnGes announced that administration of a DNA vaccine for hypertension was completed for 24 patients in a Phase I/IIa clinical trial in Australia. Going forward, investigators will evaluate safety, tolerability, and efficacy over a follow-up period of 12 months, with the data scheduled for release in Q4 FY12/20 or thereabouts.
- In February 2020, enrollment of 25 patients was completed in a Phase Ib clinical trial in the US of NF-κB decoy oligonucleotide DNA for discogenic lumbar back pain. Moving forward, investigators will evaluate safety, tolerability, and efficacy over a follow-up period of 12 months, with the data scheduled for release in Q4 FY12/20 or thereabouts.
- In January 2020, a US Phase IIb clinical trial for arteriosclerosis obliterans patients with lower limb ulcers was initiated (assess effectiveness in alleviating lower limb ulcers, target enrollment of 60 patients, post-administration follow-up period of 12 months).

HGF gene therapy drug to treat chronic arterial occlusion

- Regarding the development of its HGF gene therapy drug for chronic arterial occlusion, in January 2018 the company filed an application with the Ministry of Health, Labour and Welfare for approval for the manufacture and marketing of a regenerative medicine product, utilizing the conditional time-limited approval system (a new approval system aiming for the early commercialization of regenerative medicines and other drugs included under the Pharmaceuticals and Medical Devices Law, which went into force in November 2014). In March 2019, the company obtained conditional time-limited approval for the drug Collategene® as Japan's first domestic gene therapy product for improvement of ulcers associated with chronic arterial occlusion, and began sales in September 2019.
- The company signed an agreement with Mitsubishi Tanabe Pharma Corporation regarding exclusive sales rights of HGF gene therapy drug Collategene® targeting peripheral vascular disease in Japan and the US. Mitsubishi Tanabe Pharma is marketing the drug. Since approval is conditional and time-limited, AnGes aims to obtain the full manufacture and marketing approval in March 2024.
- In October 2019, the company began a Phase III clinical trial of Collategene® with chronic arterial occlusion patients who suffer pain when resting with a view to expanding indications of the drug. The company expects the trial to take about two years with around 40 patients enrolled.
- Overseas, the company began a Phase IIb clinical trial in the US in 2020 targeting chronic arterial occlusion with lower limb ischemic ulcers.
- The company also signed a basic agreement with Kamada Ltd. (Israel) regarding the approval of exclusive sales rights of HGF gene therapy drug Collategene® in Israel. Kamada is in talks with the Israeli authorities regarding commercialization.

NF-κB decoy oligonucleotide DNA treatment to treat lumbar disc disorders and back pain

- The company is progressing with the development of NF-κB decoy oligonucleotide to treat lumbar disc disorders and back pain. The company began Phase Ib clinical trials targeting discogenic low back pain in February 2018 and completed administration of the drug to 25 patients as scheduled in February 2020.
- AnGes has been conducting research on next-generation decoys to follow NF-κB decoy oligonucleotide. The company is making progress on the development of the basic technology for Chimera decoy, which acts to simultaneously suppress

STAT6 and NF-κB, two of the key transcription factors. Compared with decoys which only targets NF-kB, it is expected that this decoy would be more effective in suppressing inflammation.

DNA vaccine to treat high blood pressure

▷ AnGes focuses on the development of DNA vaccines as the third pillar of gene medicines in addition to products for gene therapy and nucleic acid medicines. As its first product in this area, the company is developing a DNA vaccine to treat high blood pressure. It began Phase I/II clinical trials in April 2018 and completed administration of the drug to 24 patients as scheduled in March 2020.

Alliance with Vasomune

▷ In July 2018, AnGes and Vasomune Therapeutics signed a global co-development agreement of therapeutics targeting diseases associated with severe edema such as acute respiratory failure. The two companies are currently engaged in joint preclinical trials.

Development of novel coronavirus vaccine

▷ In March 2020, AnGes began urgent development of a plasmid DNA vaccine against the novel coronavirus disease spreading worldwide. DNA vaccines do not use any pathogens. By immunizing harmless, circular DNA (plasmids) to which a protein of the target pathogen is attached, the protein is produced in the body to provide immunity against the pathogen. Unlike attenuated vaccines, they are very safe, because they have no pathogenicity.

> The COVID-19 vaccines currently at the most advanced stage of developments are virus vector vaccines and nucleic acid vaccines. DNA plasmid vaccines being developed by AnGes belong to the nucleic acid vaccine category. These vaccines are safe, because they use genetic information instead of the virus itself. It can also be developed relatively quickly, because it can be manufactured using the genetic information of the virus instead of attenuating the virus.
>
> Compared with virus vector vaccines, nucleic acid vaccines that use the RNA and DNA of viruses produce a smaller amount of spike protein that allows the virus to infect its host. They are also extremely safe, because they do not use viruses. Virus vector vaccines use adenoviruses, which produce a large quantity of antigens in the body that facilitate the production of antibodies. However, adenoviruses are themselves toxic and can cause liver toxicity. The vaccines cannot be given more than once, because the body produces adenovirus antigens.

▷ DNA vaccines can be cultured quickly in large quantities by inserting genes into circular plasmid DNA that exist in bacteria such as bacillus coli and transferred to bacterial cells.

▷ On June 30, 2020, the company started Phase I/II clinical trials at the Osaka City University Hospital with 30 subjects and completed all immunizations in August 2020. The company plans to begin a separate Phase I/II clinical trial at the Osaka University Hospital to determine optimal vaccination intervals and frequency. Preliminary results of the Phase I/II clinical trials at the Osaka University Hospital and Osaka City University Hospital are scheduled to be released in Q4 FY12/20.

- Phase I/II clinical trials at the Osaka City University Hospital: Target enrollment of 30 subjects (15 receiving a low dose and 15 receiving a high dose; two fortnightly vaccinations given).
- Phase I/II clinical trials at Osaka University Hospital: 30 subjects (receiving 2.0mg dose). Ten will receive two vaccinations two weeks apart, 10 will receive two immunizations four weeks apart, and 10 will receive three immunizations at two-week intervals.

▷ The project to develop and manufacture a DNA vaccine targeting COVID-19 involves AnGes and Osaka University, as well as Takara Bio Inc. (TSE1: 4974), which is responsible for manufacturing, Daicel Corp. (TSE1: 4202), which is developing a drug delivery mechanism, and EPS Holdings Inc. (TSE1: 4282), which is providing drug development support. Other partners include Peptide Institute Inc. (unlisted), Shin Nippon Biomedical Laboratories, Ltd. (TSE1: 2395), Human Metabolome Technologies Inc. (TSE Mothers: 6090), and 3-D Matrix, Inc. (JASDAQ Growth: 7777).

Financial status

- ▷ Total assets ended the quarter at JPY22.1bn (up JPY9.6bn from end-FY12/19). Cash and deposits and investments and other assets increased.
- ▷ Cash and deposits ended the quarter at JPY13.6bn (down JPY3.5bn from end-FY12/19). Although cash and deposits were buoyed by JPY11.5bn in proceeds from the issuance and exercise of the 37th share subscription rights, there were also outflows associated with the acquisition of Emendo shares and operating expenses.
- ▷ Investments and other assets ended the quarter at JPY6.9bn (up JPY5.4bn from end-FY12/19). For the most part, the increase was due to the acquisition of Emendo shares, resulting in an increase in investment securities. As a consequence, fixed assets rose JPY5.4bn YoY to JPY6.9bn.
- ▷ Net assets ended the quarter at JPY21.7bn (up JPY9.6bn from end-FY12/19). Capital and capital surplus each increased by JPY5.7bn, while retained earnings decreased due to the booking of a JPY1.9bn net loss attributable to owners of the parent.

Capital status

The pharmaceutical business is characterized by the need for a large amount of capital and a long period of time to commercialize a product, and the company (a biotech startup) has continuously recorded operating losses and negative cash flows. Accordingly, significant doubt has arisen as to the company's ability to continue as a going concern. At the end of June 2020, cash and deposits totaled JPY13.6bn (JPY10.0bn at end-FY12/19).

Progressing own existing projects and expanding business base

The company is progressing three development projects: HGF gene therapy drug for chronic arterial occlusion, the NF-κB decoy oligonucleotide for treating lumbar disc disorders, and the DNA vaccine for high blood pressure. In March 2019, the company obtained conditional time-limited approval for the manufacturing and sale of HGF gene therapy drug Collategene®, as Japan's first gene therapy product. Sales began in September 2019. Going forward, the company will progress clinical trials in Japan to expand the indication of Collategene® and clinical trials in the US targeting chronic arterial occlusion patients. For the NF-κB decoy oligonucleotide for treating discogenic low back pain and the DNA vaccine for high blood pressure, clinical trials are currently underway overseas as well.

In addition to these ongoing projects, the company embarked on joint development of a novel coronavirus vaccine with Osaka University in March 2020. It seeks to expand its business base by adding to its pipeline via the following: in-licensing drug candidates, conducting joint development, entering business partnerships to secure drug discovery platform technologies, gaining capital participation of other companies, and acquiring other companies.

Signing up alliance partners for development projects

AnGes adopts an alliance model for development projects, teaming up with pharmaceutical companies to receive upfront and milestone payments and development cooperation payments to reduce financial risk during the development period.

The company signed an agreement with Mitsubishi Tanabe Pharma Corporation regarding exclusive sales rights of HGF gene therapy drug Collategene® in the US and Japan, and expects to receive milestone payments and royalties. The company is also conducting clinical trials of nuclear medicine (NF-κB decoy oligonucleotide DNA) for the treatment of discogenic low back pain and a DNA vaccine for hypertension. If the trials produce promising results, the company plans to out-license these products to pharmaceutical companies at an early stage to reduce its R&D expenses by receiving upfront payments and other fees.

Financing

On March 4, 2020, the company issued the 37th share subscription rights through a third-party allocation to Phillip Securities Japan, Ltd. As of end-1H FY12/29, the company raised JPY11.5bn from the issue.

Q1 FY12/20 results

Operating revenues: JPY6mn (-92.4% YoY)

Operating revenues broke down into zero sales of merchandise (JPY73mn in Q1 FY12/19), sales of finished goods of JPY6mn (JPY0mn in Q1 FY12/19), and zero R&D revenue (JPY3mn in Q1 FY12/19).

- The company booked zero sales of merchandise, because sales of Naglazyme®, a drug for mucopolysaccharidosis VI (MPS VI), were completed in June 2019.
- The company booked sales of HGF gene therapy Collategene® 4mg Intramuscular Injection as sales of finished goods. Mitsubishi Tanabe Pharma Corporation began selling the product in September 2019. Sales of finished goods amounted to JPY1mn in Q3 FY12/19 (Jul–Sep 2019), JPY3mn in Q4 FY12/19 (Oct–Dec 2019), and JPY6mn in Q1 FY12/20 (Jan–Mar 2020).

Operating loss: JPY974mn (loss of JPY918mn in Q1 FY12/19)

Operating expenses: JPY980mn (-1.4% YoY)

- Cost of sales was JPY3mn (-90.4% YoY) due to sales of Naglazyme® (a drug for mucopolysaccharidosis VI) being completed.
- R&D expenses were JPY628mn (-9.4%, -JPY65mn YoY). Research material costs fell JPY106mn, because the company booked a smaller loss from reassessment of research materials. The company began Phase IIb clinical trials in the US of an HGF gene therapy drug targeting chronic arterial occlusion patients with leg ulcers, incurring clinical trial expenses. This led to a JPY50mn increase in outsourcing costs.
- SG&A expenses were JPY348mn (+31.8%, +JPY84mn YoY). Commissions paid increased by JPY39mn due to expenses associated with evaluation of approval conditions after manufacture and sales of its HGF gene therapy drug Collategene®. Advertising expenses were up JPY10mn due to a rise in IR-related expenses. Taxes and dues increased by JPY10mn on an increase in the portion of corporate tax determined based on the company's capital.

Recurring loss: JPY923mn (loss of JPY938mn in Q1 FY12/19)

- The company booked a JPY71mn forex gain on revaluation of foreign currency current account balances under non-operating profit.
- Share issuance expenses were JPY22mn, down JPY1mn YoY, due to the issuance of shares on the exercise of share subscription rights, which were booked as a non-operating loss.

Net loss attributable to owners of the parent: JPY920mn (net loss of JPY1.2bn in Q1 FY12/19)

- The company booked a JPY5mn gain from the reversal of share subscription rights on the expiry of stock options at the end of the exercise period.
- The company recorded a JPY243mn valuation loss on investment securities in Q1 FY12/19, but none in Q1 FY12/20.

Main pipeline progress

Main pipeline progress in Q1 FY12/20

The most notable advances in the pipeline since end-FY12/19 are as follows.

- In March 2020, AnGes and Osaka University completed production of a plasmid DNA vaccine targeting the novel coronavirus, COVID-19, also commencing preclinical studies (animal testing).
- In March 2020, AnGes announced that administration of a DNA vaccine for hypertension was completed for 24 patients in a Phase I/IIa clinical trial in Australia. Going forward, investigators will evaluate safety, tolerability, and efficacy over a follow-up period of 12 months, with the data scheduled for release in Q4 FY12/20 or thereabouts.

▷ In February 2020, enrollment of 25 patients was completed in a Phase Ib clinical trial in the US of NF-κB decoy oligonucleotide DNA for discogenic lumbar back pain. Moving forward, investigators will evaluate safety, tolerability, and efficacy over a follow-up period of 12 months, with the data scheduled for release in Q4 FY12/20 or thereabouts.
In January 2020, a US Phase IIb clinical trial for arteriosclerosis obliterans patients with lower limb ulcers was initiated (assess effectiveness in alleviating lower limb ulcers, target enrollment of 60 patients, post-administration follow-up period of 12 months).

HGF gene therapy drug to treat chronic arterial occlusion

▷ Regarding the development of its HGF gene therapy drug for chronic arterial occlusion, in January 2018 the company filed an application with the Ministry of Health, Labour and Welfare for approval for the manufacture and marketing of a regenerative medicine product, utilizing the conditional time-limited approval system (a new approval system aiming for the early commercialization of regenerative medicines and other drugs included under the Pharmaceuticals and Medical Devices Law, which went into force in November 2014). In March 2019, the company obtained conditional time-limited approval for the drug Collategene® as Japan's first domestic gene therapy product for improvement of ulcers associated with chronic arterial occlusion, and began sales in September 2019.

▷ The company signed an agreement with Mitsubishi Tanabe Pharma Corporation regarding exclusive sales rights of HGF gene therapy drug Collategene® targeting peripheral vascular disease in Japan and the US. Mitsubishi Tanabe Pharma is marketing the drug. Since approval is conditional and time-limited, AnGes plans to conduct post-marketing evaluation of how well the product satisfies criteria for approval for all patients using the product within five years with a view to having the conditions removed.

▷ In October 2019, the company began a Phase III clinical trial of Collategene® with chronic arterial occlusion patients who suffer pain when resting with a view to expanding indications of the drug. The company expects the trial to take about two years with around 40 patients enrolled.

▷ Overseas, the company began a Phase IIb clinical trial in the US in 2020 targeting arteriosclerosis obliterans patients with lower limb ulcers (assess effectiveness in alleviating lower limb ulcers, target enrollment of 60 patients, post-administration follow-up period of 12 months).

▷ The company also signed a basic agreement with Kamada Ltd. (Israel) regarding the approval of exclusive sales rights of HGF gene therapy drug Collategene® in Israel.

NF-κB decoy oligonucleotide DNA treatment to treat lumbar disc disorders and back pain

▷ The company is progressing with the development of NF-κB decoy oligonucleotide to treat lumbar disc disorders and back pain. The company began Phase Ib clinical trials in February 2018 and completed administration of the drug to 25 patients as scheduled in February 2020. Looking ahead, investigators will evaluate safety, tolerability, and efficacy over a follow-up period of 12 months, with the data scheduled for release in Q4 FY12/20 or thereabouts.

▷ AnGes has been conducting research on next-generation decoys to follow NF-κB decoy oligonucleotide. The company is making progress on the development of the basic technology for Chimera decoy, which acts to simultaneously suppress STAT6 and NF-κB, two of the key transcription factors. Compared with decoys which only targets NF-kB, it is expected that this decoy would be more effective in suppressing inflammation.

DNA vaccine to treat high blood pressure

▷ AnGes focuses on the development of DNA vaccines as the third pillar of gene medicines in addition to products for gene therapy and nucleic acid medicines. As its first product in this area, the company is developing a DNA vaccine to treat high blood pressure. In July 2017, AnGes submitted to the Therapeutic Goods Administration (TGA), the regulatory authority in Australia, a CTN for a clinical trial of its DNA vaccine for high blood pressure. It began Phase I/II clinical trials in April 2018 and completed administration of the drug to 24 patients as scheduled in March 2020. Going forward, investigators will evaluate safety, tolerability, and efficacy over a follow-up period of 12 months, with the data scheduled for release in Q4 FY12/20 or thereabouts.

Alliance with Vasomune

▷ In July 2018, AnGes and Vasomune Therapeutics signed a global co-development agreement of therapeutics targeting diseases associated with blood vessel dysfunction and destabilization such as acute respiratory distress syndrome (ARDS). The two companies are currently engaged in joint preclinical trials.

Development of novel coronavirus vaccine

▷ In March 2020, AnGes began urgent development of a plasmid DNA vaccine against the novel coronavirus disease (COVID-19) that is spreading worldwide. In the same month, the company completed production of the plasma DNA vaccine and initiated preclinical studies (animal testing). The preclinical studies will be conducted to evaluate antibody productivity in animals, after which the plan is to commence clinical trials in humans at the earliest possible juncture.

▷ The project to develop and manufacture a DNA vaccine targeting COVID-19 involves AnGes and Osaka University, as well as Takara Bio Inc. (TSE1: 4974), which is responsible for manufacturing, Daicel Corp. (TSE1: 4202), which is developing a drug delivery mechanism, and EPS Holdings Inc. (TSE1: 4282), which is providing drug development support. Other partners include Peptide Institute Inc. (unlisted), Shin Nippon Biomedical Laboratories, Ltd. (TSE1: 2395), and Human Metabolome Technologies Inc. (TSE Mothers: 6090).

Financial status

▷ Total assets ended the quarter at JPY14.6bn (up JPY2.1bn from end-FY12/19). Cash and deposits decreased, while investments and other assets increased.

▷ Cash and deposits ended the quarter at JPY9.3bn (down JPY722mn from end-FY12/19). Although cash and deposits were buoyed by JPY3.1bn in proceeds from the issuance and exercise of the 37th share subscription rights, there were also outflows associated with the acquisition of Emendo shares and operating expenses.

▷ Investments and other assets ended the quarter at JPY4.1bn (up JPY2.7bn from end-FY12/19). For the most part, the increase was due to the acquisition of Emendo shares, resulting in an increase in investment securities. As a consequence, fixed assets rose JPY2.8bn YoY to JPY4.3bn.

▷ Net assets ended the quarter at JPY14.3bn (up JPY2.2bn from end-FY12/19). Capital and capital surplus each increased by JPY1.5bn, while retained earnings decreased due to the booking of a JPY919mn net loss attributable to owners of the parent.

Capital status

The pharmaceutical business is characterized by the need for a large amount of capital and a long period of time to commercialize a product, and the company (a biotech startup) has continuously recorded operating losses and negative cash flows. Accordingly, significant doubt has arisen as to the company's ability to continue as a going concern. At the end of March 2020, cash and deposits totaled JPY9.3bn (JPY10.0bn at end-FY12/19).

Progressing own existing projects and expanding business base

The company is progressing three development projects: HGF gene therapy drug for critical limb ischemia (CLI), the NF-κB decoy oligonucleotide for treating lumbar disc disorders, and the DNA vaccine for high blood pressure. In March 2019, the company obtained conditional time-limited approval for the manufacturing and sale of HGF gene therapy drug Collategene®, as Japan's first gene therapy product. Sales began in September 2019. Going forward, the company will progress clinical trials in Japan to expand the indication of Collategene® and clinical trials in the US targeting chronic arterial occlusion patients. AnGes has started clinical trials for the second and third drugs, and plans to license-out to pharmaceutical companies at an early stage to earn upfront/milestone payments and reduce R&D spending if results are favorable.

In addition to these ongoing projects, the company seeks to expand its business base by adding to its pipeline via the following: in-licensing drug candidates, conducting joint development, entering business partnerships to secure drug discovery platform technologies, gaining capital participation of other companies, and acquiring other companies.

Signing up alliance partners for development projects

AnGes adopts an alliance model for development projects, teaming up with pharmaceutical companies to receive upfront and milestone payments and development cooperation payments to reduce financial risk during the development period.

The company signed an agreement with Mitsubishi Tanabe Pharma Corporation regarding exclusive sales rights of HGF gene therapy drug Collategene® in the US and Japan, and expects to receive milestone payments and royalties. The company is also conducting clinical trials of nuclear medicine (NF-κB decoy oligonucleotide DNA) for the treatment of discogenic low back pain and a DNA vaccine for hypertension. If the trials produce promising results, the company plans to out-license these products to pharmaceutical companies at an early stage to reduce its R&D expenses by receiving upfront payments and other fees.

Financing

On March 4, 2020, the company issued the 37th share subscription rights through a third-party allocation to Phillip Securities Japan, Ltd. As of end-Q1 FY12/29, the company raised JPY3.1bn from the issue.

Full-year FY12/19 results

Operating revenues: JPY327mn (-46.4% YoY)

Operating revenues included JPY170mn in sales of merchandise (-55.6% YoY), sales of finished goods of JPY4mn (JPY0mn in FY12/18), and JPY153mn in R&D revenues (-32.9% YoY).

- ▷ The company booked sales of Naglazyme® (sales completed in 1H), a drug for mucopolysaccharidosis VI (MPS VI) as sales of merchandise.
- ▷ The company booked sales of HGF gene therapy drug Collategene® 4mg Intramuscular Injection as sales of finished goods. Mitsubishi Tanabe Pharma Corporation began selling the product in September 2019. Sales of finished goods was JPY1mn in Q3 (July–September) and JPY3mn in Q4 (October–December).
- ▷ The company booked upfront payments from partner companies as R&D revenue.

Operating loss: JPY3.3bn (loss of JPY3.1bn in FY12/18)

Operating expenses: JPY3.6bn (-2.1% YoY)

- ▷ Cost of sales dropped to JPY87mn (-53.7% YoY) due to the termination of Naglazyme® (a drug for mucopolysaccharidosis VI) sales.
- ▷ R&D expenses were JPY2.2bn (-12.8%, -JPY324mn YoY). The company booked expenses such as upfront payment to Vasomune Therapeutics last term while R&D spending declined YoY. Research material costs decreased by JPY195mn because

the quantity of materials that the company reassessed and disposed of was reduced. Outsourcing costs were down by JPY108mn, mainly due to a decline in joint development costs paid to overseas partners.

▷ SG&A expenses were JPY1.3bn (+36.6%, +JPY347mn YoY). Commissions paid increased by JPY141mn due to consulting contracts for new businesses and expenses related to sales of its HGF gene therapy drug Collategene®. Granting of stock options increased stock-based compensation expenses by JPY70mn. Taxes and dues increased by JPY45mn on an increase in the portion of corporate tax determined based on the company's capital.

Recurring loss: JPY3.3bn (loss of JPY3.1bn in FY12/18)

▷ The company booked a JPY9mn forex gain on revaluation of foreign currency current account balances under non-operating profit.

▷ Share issuance expenses were JPY42mn (-JPY1mn YoY) due to the issuance of shares on the exercise of share subscription rights, booked as a non-operating loss.

Net loss attributable to owners of the parent: JPY3.8bn (net loss of JPY3.0bn in FY12/18)

▷ The company booked JPY469mn in valuation losses on investment securities.

Main pipeline progress

Main pipeline progress in FY12/19

Main pipeline progress from end-FY12/18 is described below.

▷ In February 2020, administration of NF-κB decoy oligonucleotide for treatment of discogenic low back pain to the 25 patients in the US Phase Ib clinical trial was completed. Patients will be monitored for safety, tolerability, and efficacy over the next 12-month period.

▷ In January 2020, the (assess efficacy on lower limb ulcers, target enrollment of 60 patients, post-administration follow-up period of 12 months) was initiated.

▷ In October Phase IIb clinical trial of HGF gene therapy drug for patients with arteriosclerosis obliterans with lower limb ischemic ulcers 2019, the company commenced a Phase III clinical trial in Japan to test the effects of HGF gene therapy drug Collategene® on rest pain in patients with chronic arterial occlusion. The clinical trial is being conducted on approximately 40 patients over a two-year period.

▷ In March 2019, the company obtained conditional and time-limited approval for its HGF gene therapy drug targeting critical limb ischemia (CLI) in Japan.

▷ In February 2019, the company signed a basic agreement with Kamada Ltd. (Israel) regarding the approval of exclusive sales rights of HGF gene therapy drug in Israel.

HGF gene therapy drug to treat chronic arterial occlusion

▷ Regarding the development of its HGF gene therapy drug for chronic arterial occlusion, in January 2018 the company filed an application with the Ministry of Health, Labour and Welfare for approval for the manufacture and marketing of a regenerative medicine product, utilizing the conditional time-limited approval system (a new approval system aiming for the early commercialization of regenerative medicine products included under the Pharmaceuticals and Medical Devices Law, which went into force in November 2014). In March 2019, the company obtained conditional time-limited approval for the drug Collategene® as Japan's first domestic gene therapy product for improvement of ulcers associated with chronic arterial occlusion, and began sales in September 2019.

- The company signed an agreement with Mitsubishi Tanabe Pharma Corporation regarding exclusive sales rights of HGF gene therapy drug Collategene® targeting peripheral vascular disease in Japan and the US. Mitsubishi Tanabe Pharma is marketing the drug. Since approval is conditional and time-limited, AnGes plans to conduct post-marketing evaluation of how well the product satisfies criteria for approval for all patients using the product within five years with a view to having the conditions removed.
- In October 2019, the company began a Phase III clinical trial of Collategene® with chronic arterial occlusion patients who suffer pain when resting with a view to expanding indications of the drug. The company expects the trial to take about two years with around 40 patients enrolled.
- Overseas, the company plans to begin a Phase IIb clinical trial in the US in 2020 targeting chronic arterial occlusion patients with leg ulcers.
- The company also signed a basic agreement with Kamada Ltd. (Israel) regarding the approval of exclusive sales rights of HGF gene therapy drug Collategene® in Israel.

NF-κB decoy oligonucleotide DNA treatment to treat discogenic low back pain

- The company is progressing with the development of NF-κB decoy oligonucleotide to treat discogenic low back pain. The company began Phase Ib clinical trial in February 2018. Despite some slight delays compared with the initial forecast, there were no serious issues and the company completed the trial in February 2020.
- AnGes has been conducting research on next-generation decoys to follow NF-κB decoy oligonucleotide. The company is making progress on the development of the basic technology for Chimera decoy, which acts to simultaneously suppress STAT6 and NF-κB, two of the key transcription factors. Compared with decoys which only targets NF-kB, it is expected that this decoy would be more effective in suppressing inflammation.

DNA vaccine to treat high blood pressure

- AnGes focuses on the development of DNA vaccines as the third pillar of gene medicines in addition to products for gene therapy and nucleic acid medicines. As its first product in this area, the company is developing a DNA vaccine to treat high blood pressure. In July 2017, AnGes submitted to the Therapeutic Goods Administration (TGA), the regulatory authority in Australia, a CTN for a clinical trial of its DNA vaccine for high blood pressure. It began Phase I/II clinical trials in April 2018 and is currently enrolling patients as planned.

Strategic alliance with Vical

- In December 2016, AnGes concluded a strategic business alliance with Vical, Inc. for co-development. Vical announced in June 2019 that it had entered into a merger agreement with Brickell Biotech, Inc. (new company name: Brickell Biotech Inc.). AnGes and Brickell Biotech are currently reviewing the prospects for the alliance.

Alliance with Vasomune

- In July 2018, AnGes and Vasomune Therapeutics signed a global co-development agreement of therapeutics targeting diseases associated with blood vessel dysfunction and destabilization such as acute respiratory distress syndrome (ARDS). The two companies are currently engaged in joint preclinical trials.

Capital status

The pharmaceutical business is characterized by the need for a large amount of capital and a long period of time to commercialize a product, and the company (a biotech startup) has continuously recorded operating losses and negative cash flows. Accordingly, significant doubt had previously arisen as to the company's ability to continue as a going concern. At the end of December 2019, cash and deposits totaled JPY10.0bn (JPY5.8bn at end-FY12/18).

Progressing own existing projects and expanding business base

The company is progressing three development projects: HGF gene therapy drug for critical limb ischemia (CLI), the NF-κB decoy oligonucleotide for treating discogenic low back pain, and the DNA vaccine for high blood pressure. In March 2019, the company obtained conditional time-limited approval for the manufacturing and sale of HGF gene therapy drug Collategene®, as Japan's first gene therapy product. Sales began in September 2019. AnGes has started clinical trials for the second and third drugs, and plans to out-license to pharmaceutical companies at an early stage to earn upfront/milestone payments and reduce R&D spending if results are favorable.

In addition to these ongoing projects, the company seeks to expand its business base by adding to its pipeline via the following: in-licensing of drug candidates, joint development, business partnerships to secure drug discovery platform technologies, and capital participation in and acquisition of other companies.

Financing

In October 2018, the company issued the 33rd share subscription rights through a third-party allocation to Mita Securities. All of these rights were exercised by May 2019, raising JPY7.7bn in FY12/19 (JPY10.6bn in total).

Cumulative Q3 FY12/19 results

Operating revenues: JPY324mn (+17.2% YoY)

Operating revenues included JPY170mn in sales of merchandise (-38.5% YoY), sales of finished goods of JPY1mn (JPY0mn in cumulative Q3 FY12/18) and JPY153mn in R&D revenue (JPY0mn in cumulative Q3 FY12/18).

- ▷ The company booked sales of Naglazyme® (sales completed in 1H), a drug for mucopolysaccharidosis VI (MPS VI) as sales of merchandise.
- ▷ The company booked Q3 (July–September 2019) sales of HGF gene therapy Collategene® 4mg Intramuscular Injection as sales of finished goods. Mitsubishi Tanabe Pharma Corporation began selling the product in September 2019.
- ▷ The company booked upfront payments from partner companies as R&D revenue.

Operating loss: JPY2.4bn (loss of JPY2.2bn in cumulative Q3 FY12/18)

- ▷ Operating expenses: JPY2.7bn (+6.5% YoY)
- ▷ Cost of sales: JPY85mn (-37.5% YoY) due to sales of Naglazyme® (a drug for mucopolysaccharidosis VI) being completed in 1H.
- ▷ R&D expenses were JPY1.6bn (-3.8% YoY). Expenses fell YoY on the absence of an upfront payment to Vasomune booked in Q3 FY12/18 (July–September 2018). Research material costs increased by JPY75mn because the company reassessed the value of materials and some materials were used for clinical trials. Outsourcing costs were down by JPY120mn, mainly due to a decline in joint development costs paid to overseas partners.
- ▷ SG&A expenses were up 37.8% YoY at JPY1.0bn. Commissions paid increased by JPY116mn due to consulting contracts for new businesses and expenses related to sales of its HGF gene therapy drug Collategene®. Granting of stock options increased stock-based compensation expenses by JPY61mn. Taxes and dues increased by JPY42mn on an increase in the portion of corporate tax determined based on the company's capital.

Recurring loss: JPY2.4bn (loss of JPY2.3bn in cumulative Q3 FY12/18)

- The company booked a JPY8mn forex gain on revaluation of foreign currency current account balances under non-operating profit.
- Share issuance expenses were JPY41mn (+JPY17mn YoY) due to the issuance of shares on the exercise of share subscription rights, booked as a non-operating loss.

Net loss attributable to owners of the parent: JPY2.8bn (net loss of JPY2.2bn in Q3 FY12/18)

- The company booked JPY384mn in valuation losses on investment securities.

Main pipeline progress

Main pipeline progress in cumulative Q3 FY12/19

Main pipeline progress from end-FY12/18 is described below.

- In November 2019, the company initiated a clinical trial for HGF gene therapy drug Collategene® to treat arteriosclerosis obliterans based on new US guidelines. It aims to obtain approval by conducting a trial on US patients with a lower risk of lower limb amputation. The small clinical trial (conducted prior to a Phase III trial) is intended to confirm the effectiveness of the drug for improving leg ulcers in these patients. The company plans on an enrollment of approximately 60 patients.
- In October 2019, the company commenced a Phase III clinical trial in Japan to test the effects of HGF gene therapy drug Collategene® on rest pain in patients with chronic arterial occlusion. The clinical trial will be conducted on approximately 40 patients over a two-year period.
- In March 2019, the company obtained conditional and time-limited approval for its HGF gene therapy drug targeting critical limb ischemia (CLI) in Japan.
- In February 2019, the company signed a basic agreement with Kamada Ltd. (Israel) regarding the approval of exclusive sales rights of HGF gene therapy drug in Israel.

HGF gene therapy drug to treat CLI

- Regarding the development of its HGF gene therapy drug for CLI, in January 2018 the company filed an application with the Ministry of Health, Labour and Welfare for approval for the manufacture and marketing of a regenerative medicine product, utilizing the conditional time-limited approval system (a new approval system aiming for the early commercialization of regenerative medicines and other drugs included under the Pharmaceuticals and Medical Devices Law, which went into force in November 2014). In March 2019, the company obtained conditional time-limited approval for the drug Collategene® as Japan's first domestic gene therapy product for improvement of ulcers associated with chronic arterial occlusion, and began sales in September 2019.
- The company signed an agreement with Mitsubishi Tanabe Pharma Corporation regarding exclusive sales rights of HGF gene therapy drug Collategene® targeting peripheral vascular disease in Japan and the US. Mitsubishi Tanabe Pharma is marketing the drug. Since approval is conditional and time-limited, AnGes plans to conduct post-marketing evaluation of how well the product satisfies criteria for approval for all patients using the product within five years with a view to having the conditions removed.
- As for overseas development, AnGes is conducting clinical trials in the US as mentioned above.
- The company also signed a basic agreement with Kamada Ltd. (Israel) regarding the approval of exclusive sales rights of HGF gene therapy drug Collategene® in Israel.

NF-κB decoy oligonucleotide DNA treatment to treat discogenic low back pain and back pain

▷ The company is progressing with the development of NF-κB decoy oligonucleotide to treat lumbar disc disorders and back pain. The company's Investigational New Drug application (IND) with the FDA was approved in April 2017. The company began Phase Ib clinical trials in February 2018. Despite some slight delays compared with the initial forecast, there were no serious issues and the company completed administering drugs to 25 patients as of February 2020.

▷ AnGes has been conducting research on next-generation decoys to follow NF-κB decoy oligonucleotide. The company is making progress on the development of the basic technology for Chimera decoy, which acts to simultaneously suppress STAT6 and NF-κB, two of the key transcription factors. Compared with decoys which only targets NF-kB, it is expected that this decoy would be more effective in suppressing inflammation.

DNA vaccine to treat high blood pressure

▷ AnGes focuses on the development of DNA vaccines as the third pillar of gene medicines in addition to gene therapy drugs and nucleic acid medicines. As its first product in this area, the company is developing a DNA vaccine to treat high blood pressure. In July 2017, AnGes submitted to the Therapeutic Goods Administration (TGA), the regulatory authority in Australia, a CTN for a clinical trial of its DNA vaccine for high blood pressure. It began Phase I/II clinical trials in April 2018 and is currently enrolling patients as planned.

Strategic alliance with Vical

▷ In December 2016, AnGes concluded a strategic business alliance with Vical, Inc. for co-development. As the first project, the two companies signed an agreement to co-develop a gene therapy drug that completely cures chronic hepatitis B in April 2017. Under the terms of the agreement, AnGes has first refusal rights on development and sales in Japan. Vical announced in June 2019 that it had entered into a merger agreement with Brickell Biotech, Inc. (new company name: Brickell Biotech Inc.), and the impact of this merger on the company is currently under investigation.

Alliance with Vasomune

▷ In July 2018, the company and Vasomune Therapeutics signed a global co-development agreement of therapeutics targeting diseases associated with blood vessel dysfunction and destabilization such as acute respiratory distress syndrome (ARDS). The two companies are currently engaged in joint preclinical trials.

Capital status

▷ The pharmaceutical business is characterized by the need for a large amount of capital and a long period of time to commercialize a product, and the company (a biotech startup) has continuously recorded operating losses and negative cash flows. Accordingly, significant doubt has arisen as to the company's ability to continue as a going concern. At the end of September 2019, cash and deposits totaled JPY10.8bn (JPY5.8bn at end-FY12/18).

Progressing own existing projects and expanding business base

The company is progressing three development projects: HGF gene therapy drug for critical limb ischemia (CLI), the NF-κB decoy oligonucleotide for treating discogenic low back pain, and the DNA vaccine for high blood pressure.

▷ In March 2019, the company obtained conditional time-limited approval for the manufacturing and sale of HGF gene therapy drug Collategene®, as Japan's first gene therapy product. Sales began in September 2019.

- ▷ AnGes has started clinical trials for the second and third drugs, and plans to license-out to pharmaceutical companies at an early stage to earn upfront/milestone payments and reduce R&D spending if results are favorable.
- ▷ In addition to these ongoing projects, the company seeks to expand its business base by adding to its pipeline via the following: in-licensing drug candidates, conducting joint development, entering business partnerships to secure drug discovery platform technologies, gaining capital participation of other companies, and acquiring other companies.

Financing

In October 2018, the company issued the 33rd share subscription rights through a third-party allocation to Mita Securities. All of these rights were exercised by May 2019, raising JPY7.7bn in cumulative Q3 FY12/19 (JPY10.6bn in total).

Other information

History

Month/Year	Events
December 1999	Founded as MedGene Co Ltd in Izumi, Osaka Prefecture, for research and development of gene and nucleotide based drugs and reagents for use in functional analyses of genetic medication.
August 2000	Formed partnership with Ishihara Sangyo Kaisha Ltd on the manufacture and marketing of HVJ envelope non-viral vectors.
January 2001	Formed partnership with Daiichi Pharmaceutical Co Ltd (now Daiichi Sankyo Co Ltd) on the domestic sale of HGF gene-based drugs for peripheral vascular diseases.
October 2001	Changed corporate name to AnGes MG Inc.
October 2001	Founded AnGes, Inc, a consolidated US unit, for clinical development in the US.
April 2002	Formed partnership with Daiichi Pharmaceutical (presently Daiichi Sankyo) on the domestic sale of HGF gene-based drugs for ischemic heart diseases.
June 2002	Founded AnGes, Euro Ltd, a consolidated UK subsidiary, for clinical development in Europe
July 2002	Founded GenomIdea Inc, a consolidated subsidiary, in Toyonaka, Osaka Prefecture, for discovery of genes for medical treatment and diagnosis, and formulation of drugs.
September 2002	AnGes MG achieved listing on the Mothers section of the Tokyo Stock Exchange.
September 2003	Conducts organizational restructuring, integrated HVJ envelope non-viral vectors business, which had been dispersed in AnGes MG and GenomIdea, into GenomIdea.
May 2006	Formed partnership with Vical Inc. of the US, on R&D of Allovectin-7, a gene therapy drug, for melanoma and funding Vical's clinical trials of the drug.
December 2006	Formed partnership with BioMarin Pharmaceutical Inc. of the US on the sale of Naglazyme, a drug for mucopolysaccharidosis VI (MPS VI), in Japan.
April 2008	Launched Naglazyme for the treatment of MPS VI in Japan.
November 2009	Reached agreement with US FDA (Food and Drug Administration) regarding SPA (Special Protocol Assessment) for a Phase III clinical trial of HGF gene therapy drug in the US.
September 2010	Obtained Fast Track status from FDA for a Phase III clinical trial of HGF gene therapy drug in the US.
October 2012	Formed partnership with Mitsubishi Tanabe Pharma Corporation for the exclusive US marketing right for HGF gene therapy drug peripheral vascular diseases.
January 2013	Transferred shares in GenomIdea to Ishihara Sangyo.
October 2014	Started global Phase III trials of HGF gene therapy drug.
June 2015	Agreed to sell exclusive licensing rights for its HGF gene therapy drug for peripheral vascular diseases in Japan to Mitsubishi Tanabe Pharma
March 2019	Obtained conditional and time-limited approval to market HGF gene therapy drug for CLI in Japan

News and topics

July 2020

On July 22, 2020, the company announced the completion of low-dose vaccination in the Phase I/II clinical trials of a DNA vaccine for COVID-19.

In the Phase I/II clinical trials of a DNA vaccine for COVID-19 being conducted at the Osaka City University Hospital, the company completed administering low-dose injections of the vaccine. Currently, it is administering high-dose injections. After completing administration of all injections of the vaccine, the company plans to disclose initial results of the trial in Q4 FY12/20 after a follow-up monitoring period.

June 2020

On June 30, 2020, the company announced the commencement of Phase I/II clinical trials of a DNA vaccine for COVID-19.

The company commenced Phase I/II clinical trials of a DNA vaccine for COVID-19 at the Osaka City University Hospital.

Phase I/II clinical trials

- Summary: Evaluate the safety and immunogenicity of the drug in healthy adult volunteers administered through intramuscular injection
- Estimated enrollment: 30 (low dose group: 15; high dose group: 15; two administrations at a two-week interval for each group)
- Trial period: Through July 31, 2021

May 2020

On May 25, 2020, the company announced that it confirmed a rise in antibody titer through pre-clinical testing conducted jointly with Osaka University with the aim of developing a DNA vaccine for the novel coronavirus disease (COVID-19).

As announced on March 5, 2020, the company has been conducting joint development of a DNA vaccine for COVID-19 along with Osaka University. Since March 26, the two parties had been conducting pre-clinical animal testing of the vaccine and were able to confirm a rise in antibody levels (antibody titer). After toxicological testing results have been confirmed, the company plans to begin clinical testing of the vaccine.

On May 22, 2020, the company announced that the bid it made in response to a public call for the development of a vaccine for COVID-19 was successfully approved by the Japan Agency for Medical Research and Development (AMED).

AMED approved a bid from the company to jointly develop a vaccine for the novel coronavirus pandemic (COVID-19) with Osaka University. The bid was made in response to a public call made by AMED for FY2020 drug discovery business targeting the development of a vaccine for the virus.

- Title of the R&D project: Development of vaccines targeting COVID-19 aimed at preparing them for practical use
- R&D period: May 2020–March 2023
- R&D expenses eligible for subsidies: JPY2.0bn (direct expenses)

March 2020

On March 26, 2020, the company announced the commencement of pre-clinical studies (animal testing) of a DNA vaccine against the novel coronavirus jointly developed with Osaka University.

In the joint development of a DNA vaccine against the novel coronavirus (2019-nCoV) with Osaka University announced on March 5, 2020, the company launched pre-clinical trials in which the plasmid DNA vaccine would be administered to animal models.

On March 24, 2020, the company announced that it completed the manufacture of a plasmid DNA vaccine for the novel coronavirus 2019-nCoV jointly developed with Osaka University for use in pre-clinical trials (animal testing).

In collaboration with Osaka University to develop a DNA vaccine against the novel coronavirus 2019-nCoV as announced on March 5, 2020, the company completed manufacturing the active ingredient for a plasmid DNA vaccine and made preparations to administer it to animal models in pre-clinical trials. Animal testing is set to commence soon.

On March 16, 2020, the company announced that the final patient was treated with its DNA vaccine for hypertension in an Australian Phase I/IIa clinical study.

AnGes has completed administering the drug to 24 patients as planned, in a Phase I/IIa clinical study in Australia investigating its DNA vaccine for hypertension. The company will now evaluate the vaccine's safety and efficacy over a six-month period using the double-blind method, which will be followed by a six-month open-label observational period during which it will evaluate the vaccine's long-term safety and efficacy.

Australian Phase I/IIa clinical trial of DNA vaccine for hypertension

- ▷ Study overview: A double-blind, placebo-controlled clinical trial aimed at evaluating the safety and efficacy of the DNA vaccine in hypertension patients
- ▷ Number of patients: 24
- ▷ Observation period: 12 months

The company plans to announce the results of the clinical trial in Q4 FY12/20.

On March 13, 2020, the company announced the participation of Daicel Corp. in the joint development for a DNA vaccine against the novel coronavirus disease (COVID-19).

The company announced that Daicel Corp. will join the joint development project between the company and Osaka University for a DNA vaccine against the novel coronavirus 2019-nCoV (announced on March 5, 2020). Daicel will contribute to the project with its novel drug delivery device technology that enables intracellular drug delivery.

Using Daicel's novel drug delivery device Actranza™ lab. to deliver drugs can increase the antibody production capability of DNA vaccines through enhancing their gene expression efficiency, and hence lead to the development of highly effective DNA vaccines. The joint development covers all stages from the vaccine development through manufacturing, and parties involved in the development aim to initiate a clinical trial as soon as possible within the next six months.

Daicel's new drug delivery device Actranza™ lab.: A technology that delivers a drug solution into a specific tissue powered by pyro combustion without using a needle. Studies using animal models have shown that the pyro-driven intracellular drug delivery delivers drugs with better precision to target areas and exhibits enhanced efficiency of gene expression compared to conventional needle injections. Since there are more immunocompetent cells in the skin than in the muscle, the technology is expected to improve the efficiency of administering vaccines.

On March 5, 2020, the company announced it would start joint development of a DNA vaccine against the novel coronavirus disease (COVID-19) with Osaka University.

Capitalizing on its expertise from commercializing DNA plasmid-based HGF gene therapies, AnGes decided to develop a prophylactic DNA vaccine targeting COVID-19 in partnership with Osaka University.

Development of DNA vaccine for COVID-19 that utilizes DNA plasmid manufacturing technology

- ▷ AnGes and Osaka University will leverage their expertise in DNA plasmid products to jointly develop a DNA vaccine for COVID-19.
- ▷ DNA vaccines can be produced in a shorter timeframe than vaccines based on inactivated viruses (attenuated vaccines) or recombinant viral proteins.
- ▷ Production will be consigned to Takara Bio Inc., which has plasmid DNA production technology and equipment.

February 2020

On February 28, 2020, the company announced the completion of drug administration in the US-based Phase Ib clinical trial of NF-κB decoy oligonucleotide targeting discogenic low back pain.

In the US-based Phase Ib clinical trial of NF-κB decoy oligonucleotide DNA ("NF-κB decoy") for the treatment of discogenic low back pain, AnGes completed administering drugs to 25 patients as planned. The company will evaluate safety and efficacy of NF-κB decoy in the patients who were administered the drugs for six months using a double-blind method, and in the following six months of an open-label observational period, it will evaluate the long-term safety, tolerability, and efficacy of the drug.

Phase Ib clinical trial of NF-κB decoy oligonucleotide in the US

- ▷ Study overview: A double-blind, multicenter, placebo-controlled clinical trial of NF-κB decoy for the treatment of discogenic low back pain, aimed at evaluating safety, tolerability, and efficacy of NF-κB decoy using a dose escalation method (intradiscal administration)
- ▷ Number of patients: 25
- ▷ Observation period: 12 months

The company plans to announce the results of the clinical trial around Q4 FY12/20.

Due to its ability to suppress inflammatory cytokines (biologically active substances released from cells), NF-κB decoy has the potential to become an effective drug against disorders caused by excessive inflammation and immune responses. As of February 2020, only symptomatic treatment such as antiphlogistic analgesics were available for the treatment of discogenic low back pain. NF-κB decoy differs from these conventional analgesics in that its analgesic effect is derived from its ability to suppress the causative agents. Basic research has shown that NF-κB decoy is effective in treating lumbar disc disorders, and it is also expected to suppress progression of these disorders and stimulate lumbar disc regeneration, which were not available with the conventional drugs.

On February 17, 2020, the company announced the issue of the 37th share subscription rights with price revision provisions through third-party allocation.

Overview of issue

Allotment date	March 4, 2020
Total number of share subscription rights	160,000 units
Issue price	JPY457 per subscription right (total: JPY73.1mn)
Number of residual securities associated with the issue	16.0mn (100 securities per subscription right, dilution of 14.96% of shares on issue as of end-December 2019) No maximum exercise price. Even at minimum exercise price, number of residual securities is 16.0mn.
Amount to be raised	JPY9.4bn (estimated net proceeds)
Exercise price and exercise price revision provisions	JPY584 (initial price) If the price calculated by multiplying the closing price of the company's common shares during regular trading on the Tokyo Stock Exchange on the trading day immediately prior to the exercise request date ("price revision date") by 0.92 (with fractional amounts less than one yen rounded up) is one or more yen higher or lower than the effective exercise price immediately prior to the price revision date, the price calculated in that manner shall become the new exercise price on and following the price revision date. However, if the revised price on the price revision date is less than JPY292 (minimum exercise price) the minimum exercise price shall be the revised price.

Subscription or allocation method (allottee)	Third-party allotment to Phillip Securities

Specific uses of funds to be raised

- ▷ Adding to pipeline: The company plans to spend JPY4.5bn from March 2020 through March 2024 by in-licensing and joint development of drug candidates, business alliances to secure drug development platform technologies, capital participation in other companies, and acquisitions of other companies. It plans to allocate a portion of the proceeds toward the search for, evaluation of, and negotiations regarding drug candidates, upfront and milestone payments, direct and indirect investments in shares, considerations for shares, and R&D expenses.
- ▷ Cost for contract manufacture of active ingredients for its HGF gene therapy: The company plans to spend JPY1.7bn from June 2020 through December 2024. It received conditional approval in March 2019 in Japan for its mainstay HGF gene therapy product, which Mitsubishi Tanabe Pharma Corporation started marketing in September 2019. However, royalty revenue over the roughly five-year conditional approval period is likely to be negligible. Meanwhile, the company has a long-term supply contract with the manufacturer of active ingredients for its HGF gene therapy, and is scheduled to purchase a set amount of supply. This means that it incurs payments for contract manufacturing ahead of full approval which is expected in the future. Separate to sales in Japan, the company started conducting clinical trials for arteriosclerosis obliterans in the US in January 2020. The company is also looking for overseas partners similar to Israeli company Kamada Ltd. (with which it signed a basic out-licensing agreement in February 2019, granting Kamada exclusive sales rights in Israel). The company said that these initiatives required securing high inventories of HGF gene therapy product under contract manufacture.
- ▷ Working capital: The company plans to spend JPY3.2bn from March 2020 through February 2022. The company is still in the stage of early investments in developments, with ongoing losses. The situation is likely to persist for some time, so the company plans to allocate a portion of the funding proceeds to working capital (including expenses for personnel, fee payments, travel and transport, and rent) from FY03/20 onward.

On February 4, 2020, the company announced the launch of Phase IIb clinical trial in the US to evaluate its HGF gene therapy product in patients with arteriosclerosis obliterans with lower limb ischemic ulcers.

The company began patient enrollment for a US-based clinical trial to study the efficacy of HGF gene therapy product, beperminogene perplasmid, in patients with arteriosclerosis obliterans with lower limb ischemic ulcers.

Overview of Phase IIb clinical trial in the US

- ▷ A small clinical trial aimed at assessing the efficacy on lower limb ulcer treatments
- ▷ Target enrollment of 60 patients
- ▷ Post-administration follow-up period of 12 months

In March 2019, the company received conditional approval in Japan for the use of Collategene® (beperminogene perplasmid) intramuscular injection 4mg to treat ulcers in patients with chronic arterial occlusive diseases. In September 2019, Mitsubishi Tanabe Pharma Corporation began distribution of the drug. To further expand its indications, the company is also conducting a Phase III trial for the treatment of patients with rest pain from October 2019.

January 2020

On January 23, 2020, the company announced a revision to its FY12/19 full-year earnings forecast and the recording of an extraordinary loss.

Revised FY12/19 full-year earnings forecast

- Operating revenues: JPY335mn (previous forecast: JPY335mn)
- Operating loss: JPY3.3bn (JPY3.3bn)
- Recurring loss: JPY3.3bn (JPY3.3bn)
- Net loss attributable to owners of the parent: JPY3.8bn (JPY3.7bn)
- Loss per share: JPY35.90 (JPY35.33)

Reasons for revision

The company made no changes to its previous forecasts for operating revenues, operating loss, and recurring loss, but revised its previous forecast for net loss attributable to owners of the parent and now expects a larger loss. The revision to net loss forecast was due mainly to the recording of a loss on valuation of investment securities resulting from a decline in the market value of investment securities the company held.

Recording of extraordinary loss

In Q4 FY12/19 (October–December 2019), the company recorded a loss of JPY84mn on valuation of investment securities due to impairment of investment securities it held; for the full-year, it expects the loss to amount to JPY469mn.

December 2019

On December 12, 2019, the company announced that Emendo Biotherapeutics, which has advanced genome editing technology, would become an affiliate after additional investments by the company.

On the same day, the company resolved to make additional investments in Israel based US biotech firm Emendo Biotherapeutics. Emendo will become an equity-method affiliate as a result of the additional investments. The company said that the impact on FY12/19 results would be minimal.

Aim in making Emendo an affiliate

The company aims to build close relationships with Emendo, which has safe genome editing technology that affords greater flexibility in gene targeting. The company is also considering becoming involved in some of the target diseases that Emendo is developing technologies for.

Israel based US biotech firm Emendo is developing novel genome editing technologies to repair or eliminate genetic cell abnormalities that cause serious diseases or disorders.

Genome editing entails cutting only specific nucleotide sequences (target sequences) to modify the targeted gene. However, cutting a sequence that is similar to the target sequence by mistake can affect non-targeted genes, thereby posing a safety risk (off-target effect). To lessen the off-target effect, it is necessary to choose a target sequence with as few similar sequences as possible. Emendo has a different approach. It is developing a DNA-cleaving enzyme (nuclease) that does not cut DNA at sites other than the target sequence. According to Emendo, this will lead to much safer genome editing and allow free choice of target, unconstrained by the presence of similar sequences.

The company said that making Emendo an affiliate and developing therapies based on genome editing will enable it to expand its development pipeline in a fourth area in addition to HGF gene therapy drugs, nucleic acid medicines, and DNA vaccines.

Overview of investee: Emendo

- Establishment date: December 2015
- Capital and capital reserves: USD7.7mn (as of August 2019)
- Business: Development of genome editing technology to enable repair and elimination of genetic cell abnormalities that cause serious diseases or disorders

Investment

- Amount: USD50.0mn (JPY5.5bn converted at JPY109/USD)
- Company shareholding: Approximately 32% (following investment of total amount, fully diluted)
- Payment date (planned): January and June 2020

November 2019

On November 22, 2019, the company announced initiation of clinical trials for HGF gene therapy Collategene® to treat arteriosclerosis obliterans based on new US guidelines.

AnGes will start a US clinical trial of HGF gene therapy beperminogene perplasmid (Collategene® 4mg Intramuscular Injection) for the treatment of arteriosclerosis obliterans patients with leg ulcers.

Global guidelines for treatment of comprehensive advanced chronic limb ischemia, a type of arteriosclerosis obliterans, were published in June 2019 through collaboration of societies for vascular surgery in Europe, the US, Asia, and Oceania; the guidelines call for treatments to be tailored to disease progression from the perspective of patient QOL.

In line with the global guidelines, AnGes aims to obtain US approval by conducting clinical trials on patients with lower risk of lower limb amputation than those previously targeted. Efficacy in improving leg ulcers will be confirmed in a small clinical trial before starting a Phase III study. The company looks to recruit about 60 patients for the trial. AnGes had consulted with the FDA (Food and Drug Administration) and reached an agreement on a development plan.

AnGes obtained conditional and time-limited approval for Collategene® in Japan on March 26, 2019 for the improvement of ulcers associated with chronic arterial occlusive disease (arteriosclerosis obliterans and Buerger's disease); Collategene® was launched by Mitsubishi Tanabe Pharma on September 10, 2019.

October 2019

On October 28,2019, the company announced a revision to its FY12/19 full-year earnings forecast.

Revised FY12/19 full-year earnings forecast

- Operating revenues: JPY335mn (previous forecast: JPY335mn)
- Operating loss: JPY3.3bn (previous forecast: JPY2.8bn)
- Recurring loss: JPY3.3bn (previous forecast: JPY2.8bn)
- Net loss attributable to owners of the parent: JPY3.7bn (previous forecast: JPY2.8bn)
- Net loss per share: JPY35.33 (previous forecast: JPY26.74)

Reasons for revision

- No change in full-year forecast for operating revenues.
- The company revised down its operating loss and recurring loss forecasts to reflect an increase in expenses for Phase III clinical trial of HGF gene therapy drug Collategene® targeting patients with rest pain associated with chronic arterial occlusion in Japan and operating expenses such as preparations for setting up new trials of HGF gene therapy drugs in the US.
- The company expects net loss attributable to owners of the parent to widen due to worse-than-expected recurring loss and booking a valuation loss on investment securities whose market value has fallen.

On October 7, 2019, the company announced the launch of a Phase III clinical trial of HGF gene therapy Collategene® targeting rest pain associated with chronic arterial occlusion in Japan.

The company began a Phase III clinical trial of HGF gene therapy drug beperminogene perplasmid (Collategene® 4mg Intramuscular Injection) targeting patients with rest pain associated with chronic arterial occlusion in Japan.

The clinical trial will be conducted with patients suffering from rest pain resulting from chronic arterial occlusion. After patients are administered the drug, they will be observed over a period of six months for improvement in rest pain. The trial is scheduled to run for about two years, with a total of roughly 40 patients enrolled.

HGF gene therapy Collategene® obtained conditional and time-limited manufacturing and marketing approval for improvement of ulcers associated with chronic arterial occlusion in March 2019; Mitsubishi Tanabe Pharma began selling the product in September 2019.

Major shareholders

Top shareholders	Shares held	Shareholding ratio
Nomura Securities Co., Ltd.	2,278,562	2.13%
Shionogi & Co., Ltd.	1,186,800	1.10%
SBI Securities Co., Ltd.	964,400	0.90%
Daiwa Securities Co. Ltd.	840,800	0.78%
Teruo Isohata	835,700	0.78%
Ryuichi Morishita	691,600	0.64%
Matsui Securities Co., Ltd.	553,400	0.51%
Rakuten Securities, Inc.	543,100	0.50%
kabu.com Securities Co., Ltd.	492,000	0.45%
STATE STREET BANK WEST CLIENT - TREATY 505234	490,900	0.45%
SUM	8,877,262	8.29%

Source: Shared Research based on company data
(As of December 31, 2019. Excludes treasury shares.)

Company profile

Company Name	Head Office
AnGes, Inc.	Saito Bio-Incubator 4F 7-7-15, Saito-asagi, Ibaraki Osaka, Japan, 567-0085
Phone	**Listed On**
+81-72-643-3590	Mothers
Established	**Exchange Listing**
December 17, 1999	September 25, 2002
Website	**Financial Year-End**
https://www.anges.co.jp/en/index.php	December
IR Contact	**IR Web**
-	https://www.anges.co.jp/en/ir/index.php
IR Mail	**IR Phone**
-	+81-3-5730-2641

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Bell-Park Co., Ltd.
Benefit One Inc.
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Canon Marketing Japan Inc.
Career Design Center Co., Ltd.
Carna Biosciences, Inc.
CARTA HOLDINGS, INC
CERES INC.
Chiyoda Co., Ltd.
Chori Co., Ltd.
Chugoku Marine Paints, Ltd.
cocokara fine Inc.
COMSYS Holdings Corporation
COTA CO.,LTD.
CRE, Inc.
CREEK & RIVER Co., Ltd.
Daiichi Kigenso Kagaku Kogyo Co., Ltd.
Daiseki Co., Ltd.
Demae-Can CO., LTD
DIC Corporation
Digital Arts Inc.
Digital Garage Inc.
DIP Corporation
Doshisha Corporation
Dream Incubator Inc.
Earth Corporation
Edion Corporation
Elecom Co., Ltd.
en-Japan Inc.
Estore Corporation.
euglena Co., Ltd.
FaithNetwork Co., Ltd.
Ferrotec Holdings Corporation
FIELDS CORPORATION
Financial Products Group Co., Ltd.
First Brothers Col, Ltd.
FreeBit Co., Ltd.
Fujita Kanko Inc.
Gamecard-Joyco Holdings, Inc.
GameWith, Inc.
GCA Corporation
Good Com Asset Co., Ltd.
Grandy House Corporation
Hakuto Co., Ltd.
Hamee Corp.
Happinet Corporation
Harmonic Drive Systems Inc.
HENNGE K.K.
Hope, Inc.
HOUSEDO Co., Ltd.
H2O Retailing Corporation
IDOM Inc.
IGNIS LTD.
i-mobile Co.,Ltd.
Inabata & Co., Ltd.
Infocom Corporation
Infomart Corporation
Intelligent Wave, Inc.
ipet Insurance CO., Ltd.
Itochu Enex Co., Ltd.
JAFCO Co.,Ltd.
JMDC Inc.
JSB Co., Ltd.
JTEC Corporation
J Trust Co., Ltd
Japan Best Rescue System Co., Ltd.
JINS HOLDINGS Inc.
JP-HOLDINGS, INC.
KAMEDA SEIKA CO., LTD.
Kanamic Network Co.,LTD
Kawanishi Holdings, Inc.
KFC Holdings Japan, Ltd.
KI-Star Real Estate Co., Ltd.
KLab Inc.
Kondotec Inc.
Kumiai Chemical Industry Co., Ltd.
Lasertec Corporation
Locondo, Inc.
LUCKLAND CO., LTD.
MATSUI SECURITIES CO., LTD.
Media Do Co., Ltd.
Medical System Network Co., Ltd.
MEDINET Co., Ltd.
MedPeer,Inc.
Mercuria Investment Co., Ltd.
Micronics Japan Co., Ltd.
MIRAIT Holdings Corporation
Monex Goup Inc.
MORINAGA MILK INDUSTRY CO., LTD.
Mortgage Service Japan Limited.
NAGASE & CO., LTD
NAIGAI TRANS LINE LTD.
NanoCarrier Co., Ltd.
Net Marketing Co., Ltd.
Net One Systems Co.,Ltd.
Nichi-Iko Pharmaceutical Co., Ltd.
Nihon Denkei Co., Ltd.
Nippon Koei Co., Ltd.
NIPPON PARKING DEVELOPMENT Co., Ltd.
NIPRO CORPORATION
Nisshinbo Holdings Inc.
NS TOOL CO., LTD.
OHIZUMI MFG. CO., LTD.
Oisix ra daichi Inc.
Oki Electric Industry Co., Ltd
ONO SOKKI Co., Ltd.
ONWARD HOLDINGS CO.,LTD.
Pan Pacific International Holdings Corporation
PARIS MIKI HOLDINGS Inc.
PIGEON CORPORATION
QB Net Holdings Co., Ltd.
RACCOON HOLDINGS, Inc.
Raysum Co., Ltd.
RESORTTRUST, INC.
ROUND ONE Corporation
RYOHIN KEIKAKU CO., LTD.
SanBio Company Limited
SANIX INCORPORATED
Sanrio Company, Ltd.
SATO HOLDINGS CORPORATION
SBS Holdings, Inc.
Seikagaku Corporation
Seria Co.,Ltd.
Serverworks Co.,Ltd.
SHIFT Inc.
Shikigaku Co., Ltd
SHIP HEALTHCARE HOLDINGS, INC.
SIGMAXYZ Inc.
SMS Co., Ltd.
Snow Peak, Inc.
Solasia Pharma K.K.
SOURCENEXT Corporation
Star Mica Holdings Co., Ltd.
Strike Co., Ltd.
SymBio Pharmaceuticals Limited
Synchro Food Co., Ltd.
TAIYO HOLDINGS CO., LTD.
Takashimaya Company, Limited
Take and Give Needs Co., Ltd.
Takihyo Co., Ltd.
TEAR Corporation
Tenpo Innovation Inc.
3-D Matrix, Ltd.
The Hokkoku Bank,Ltd.
TKC Corporation
TKP Corporation
Tsuzuki Denki Co., Ltd.
TOCALO Co., Ltd.
TOKAI Holdings Corporation
Tokyu Construction Co., Ltd.
TOYOBO CO., LTD.
Toyo Ink SC Holdings Co., Ltd
Toyo Tanso Co., Ltd.
Tri-Stage Inc.
TSURUHA Holdings
VISION INC.
VISIONARY HOLDINGS CO., LTD.
World Holdings Co., Ltd.
YELLOW HAT LTD.
YOSHINOYA HOLDINGS CO., LTD.
YUMESHIN HOLDINGS CO., LTD.
ZAPPALLAS, INC.

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