AnGes / 4563

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INDEX

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, hepatocyte growth factor (HGF) gene therapy drugs (new drug candidates; regenerate blood vessels by medicating HGF genes) have been the mainstay pipeline drugs for AnGes. HGF gene therapy drug Collategene®, indicated for the improvement of ulcers associated with chronic arterial occlusion, is the first domestic gene therapy product 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 US-based late Phase II clinical trial of the HGF gene therapy drug for arteriosclerosis obliterans patients with lower limb ischemic ulcers (assess effectiveness in alleviating lower limb ulcers, target enrollment of 60 patients, post-administration follow-up period of 12 months) in February 2020.
- In addition to the HGF gene therapy drug, AnGes is conducting a Phase Ib clinical trial of NF-κB decoy oligo DNA targeting discogenic low back pain, Phase I/II clinical trials of a DNA vaccine for high blood pressure, and development of a vaccine against the novel coronavirus (SARS-CoV-2) as well as novel coronavirus treatments. 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 February 2021, the company believes that the significant uncertainty that prompted the notice no longer exists. Cash and deposits totaled JPY11.5bn at end-December 2020 (JPY10.0bn at end-FY12/19).

Performance

- In FY12/20, AnGes reported operating revenues of JPY40mn (-87.8% YoY), an operating loss of JPY5.6bn (an operating loss of JPY3.3bn in FY12/19), a recurring loss of JPY6.6bn (a recurring loss of JPY3.3bn in FY12/19), and a net loss attributable to owners of the parent of JPY4.2bn (a net loss of JPY3.8bn in FY12/19).
- As of May 2021, AnGes had not disclosed its FY12/21 forecast. The company is developing a DNA vaccine for COVID-19. The scope and methodology of clinical trials are yet to be determined, and it is unclear what sort of government subsidies would be provided at future development stages and what form calls for participants may take. Thus, the company commented that it was difficult to make a reasonable earnings estimate at the start of the fiscal year, and said it would disclose its full-year forecast when 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. As noted above, as of February 2021 the company is also developing a DNA vaccine for COVID-19. Shared Research understands that the scale of clinical trials going forward, government and other subsidies, and earnings contribution if the vaccine goes on the market will have a substantial impact on the company' performance in the medium term.

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 and ongoing losses (see Strengths and weaknesses).

Key financial data

Income statement (JPYmn)	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.	FY12/20 Cons.
Operating revenues	**243**	**445**	**491**	**910**	**430**	**514**	**365**	**610**	**327**	**40**
YoY	-15.2%	82.6%	10.5%	85.2%	-52.7%	19.6%	-29.0%	67.1%	-46.4%	-87.8%
Operating profit	**-2,101**	**-1,785**	**-1,363**	**-2,274**	**-4,172**	**-4,763**	**-3,289**	**-3,065**	**-3,270**	**-5,599**
YoY	-	-	-	-	-	-	-	-	-	-
OPM	-	-	-	-	-	-	-	-	-	-
Recurring profit	**-1,791**	**-1,716**	**-1,383**	**-2,395**	**-4,089**	**-4,847**	**-3,307**	**-3,096**	**-3,293**	**-6,618**
YoY	-	-	-	-	-	-	-	-	-	-
RPM	-	-	-	-	-	-	-	-	-	-
Net income	**-1,815**	**-1,708**	**-1,410**	**-2,369**	**-4,143**	**-4,777**	**-3,765**	**-2,997**	**-3,751**	**-4,210**
YoY	-	-	-	-	-	-	-	-	-	-
Net margin	-	-	-	-	-	-	-	-	-	-
Per-share data										
Shares issued (year-end; '000)	24,467	26,226	31,268	53,544	53,544	70,631	79,724	97,981	106,970	133,059
EPS	-74.6	-67.7	-46.9	-62.1	-74.5	-75.3	-49.4	-34.5	-35.8	-35.3
EPS (fully diluted)	-	-	-	-	-	-	-	-	-	-
Dividend per share	-	-	-	-	-	-	-	-	-	-
Book value per share	125.8	60.3	107.9	142.4	73.8	54.7	42.3	78.4	111.8	244.5
Balance sheet (JPYmn)										
Cash and cash equivalents	1,576	355	2,295	6,017	2,075	996	1,148	5,785	10,041	11,537
Total current assets	**2,635**	**1,342**	**3,305**	**7,594**	**4,243**	**3,619**	**3,434**	**7,542**	**10,992**	**14,167**
Tangible fixed assets	62	45	23	28	76	76	-	47	49	236
Investments and other assets	1,050	770	506	508	382	789	530	461	1,483	1,238
Intangible assets	142	103	70	54	51	55	-	-	-	22,714
Total assets	**3,889**	**2,260**	**3,904**	**8,184**	**4,752**	**4,539**	**3,964**	**8,051**	**12,525**	**38,355**
Accounts payable	60	67	42	207	247	389	201	113	183	514
Short-term debt	417	331	218	116	83	1	1	686	-	3,595
Total current liabilities	**601**	**507**	**345**	**423**	**482**	**631**	**318**	**292**	**443**	**5,590**
Total fixed liabilities	**17**	**15**	**15**	**26**	**49**	**39**	**24**	**25**	**26**	**85**
Total liabilities	**618**	**522**	**361**	**449**	**531**	**670**	**342**	**316**	**469**	**5,675**
Total net assets	**3,271**	**1,739**	**3,544**	**7,734**	**4,221**	**3,869**	**3,622**	**7,734**	**12,055**	**32,680**
Total interest-bearing debt	-	-	-	-	-	-	-	-	-	-
Cash flow statement (JPYmn)										
Cash flows from operating activities	-1,706	-1,631	-1,457	-2,704	-4,599	-4,984	-2,991	-2,523	-2,180	-2,961
Cash flows from investing activities	768	7	-27	-52	-69	-830	227	-123	-1,250	-6,964
Cash flows from financing activities	368	387	3,390	6,427	717	4,793	2,916	7,283	7,677	11,404
Financial ratios										
ROA (RP-based)	-	-	-	-	-	-	-	-	-	-
ROE	-	-	-	-	-	-	-	-	-	-
Equity ratio	84.1%	76.9%	90.8%	94.5%	88.8%	85.2%	91.4%	96.1%	96.3%	85.2%

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

Recent updates

Highlights

On May 24, 2021, Shared Research updated the report following interviews with AnGes, Inc.

On May 10, 2021, the company announced earnings results for Q1 FY12/21; see the results section for details.

On April 12, 2021, the company announced its progress in development of NF-κB decoy oligo DNA (AMG0103) in patients with chronic discogenic low back pain.

The company announced favorable results from a late Phase I study of AMG0103 (to be intradiscally administered once) for the treatment of chronic discogenic low back pain (DLBP), aimed at evaluating safety and efficacy through 12 months following treatment with the investigational drug via single injection into the intervertebral disc.

The trial was a multi-center, placebo-controlled, randomized, and double-blind study divided into two parts: a six-month, double-blind study (Part 1) and a further six months of continued evaluation (Part 2). The trial was conducted in 25 men and women with chronic DLBP, aged between 32 and 70 years with a mean age of 53.5 years. The results indicated that the intradiscal injection of AMG0103 was highly safe, and no serious adverse events were reported throughout the 12-month observation period of study. Regarding efficacy as well, the investigational drug significantly reduced low back pain soon after it was administered, and its effect on controlling low back pain was sustained for 12 months after administration. Patients themselves also reported high satisfaction.

Safety results

The primary endpoint of the late Phase I study was to evaluate the safety and tolerability of AMG0103 through 12 months following administration. AMG0103 (0.3mg, 3.0mg and 10.0mg) were injected directly into the intervertebral disc, and safety was evaluated for 12 months after injection. As a result, no abnormality that may become clinically problematic was noted in renal, hepatic, and hematologic functions. In addition, no decline in neurologic, sensory, or motor function was observed. Only a single episode of mild nausea was reported immediately after the administration of a low dose (0.3mg) as an adverse event, for which causal association with the investigational drug cannot be denied, but it disappeared without treatment.

Efficacy results

To evaluate efficacy of AMG0103 on impairment in activities of daily living associated with low back pain and on low back pain and leg pain, the Patient Global Impression of Change (PGI-C), the Roland-Morris Disability Questionnaire (RMDQ) and the Oswestry Disability Index were used. Administration of AMG0103 resulted in a dose-dependent improvement of low back pain evaluated at six months after administration in a 100mm VAS scale rating.

The patient group receiving a single 10mg dose reported a reduction of low back pain by almost 50% 14 days after administration. Low back pain in this group continued to decline, reaching an 84% median reduction from baseline by six months, which was more significant improvement (p=0.033) than the placebo control group that showed a 14% improvement. The 10mg group continued to show improvement in low back pain through 12 months, reaching a median reduction of 97.5% compared to baseline, which was also more significant (p=0.045) than the control group.

In the measurement of intervertebral disc height six months after administration, the placebo group used as a control showed declining disc height, while AMG0103 group showed increasing disc height, suggesting that AMG0103 may potentially suppress intervertebral disk degeneration. This result reproduced the results obtained in animal studies of AMG0103. The company will continue to make evaluation, including analysis of the 12-month evaluation.

The PGI-C score (in a rating scale from 1 to 7) that evaluates patient's subjective satisfaction levels, revealed a dose-dependent improvement from baseline at six months, and the improvement in AMG0103 10mg group was superior to that of the control group throughout the 12-month observation period. In the AMG0103 10mg group, the PGI-C score improved on average 2.83 (p=0.001) at six months after administration and 1.67 points (p=0.042) at 12 months after administration. In addition to this outcome, all three treatment arms showed a 20–50% mean improvement in RDMQ score (self-rated degree of impairments in activities of daily living) at six months while the control arm's scores declined 15% on average from baseline. At 12 months, the 10mg AMG0103 arm still showed a 38% mean improvement over baseline, while the control group's scores declined by 45%.

Patients enrolled in this study were not allowed to self-medicate with opioids at any time, but were allowed to use oral non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen for breakthrough pain. Patients were required to cease these "rescue medications" prior to follow-up visits, and their drug use diary was examined at each visit to record the frequency of use. Patients in the placebo control group used rescue medications on an average of 16 days throughout the 12-month study, with a maximal use of 98 days by one patient. By contrast, not a single patient in the 10mg AMG0103 arm ever took a rescue medication during the course of the study.

On March 25, 2021, the company announced favorable results from a Phase I clinical study investigating its co-development product AV-001 targeting COVID-19.

AnGes and Vasomune Therapeutics are co-developing AV-001 as a breakthrough first-in-class drug targeting COVID-19, and in the Phase I study this investigational medicine delivered favorable results. The data showed that AV-001 was safe and well-tolerated, suggesting a pharmacokinetic profile consistent with once-daily dosing.

> First-in-class (breakthrough) drugs are considered particularly innovative and useful among new drugs, having a chemical structure that differs fundamentally from existing drugs, with the potential to change the conventional therapeutic system.

The purpose of this Phase I study was to assess the safety, tolerability, and pharmacokinetics of both single and multiple doses of AV-001, in 48 healthy subjects aged between 20 and 63. The study confirmed that AV-001 was safe and well-tolerated when administered in a single dose or multiple doses of up to 56μg/kg/day for seven consecutive days. There were no serious adverse events or clinically significant laboratory test abnormalities, nor were there any clinically significant ECG abnormalities. Pharmacokinetic analysis moreover indicated a wide margin of safety.

AnGes and Vasomune plan to submit the data to the US Food and Drug Administration (FDA), to discuss initiation of a Phase IIa proof-of-concept study to assess efficacy in patients with severe COVID-19. They plan to conduct this trial at facilities in the US and Canada.

In March 2021, Vasomune received a subsidy in AV-001 through the National Research Council (NRC), on behalf of the Government of Canada. Prior to that, in August 2020 Vasomune received a Peer-Reviewed Medical Research Program (PRMRP) grant award for USD2.8mn from the US Department of Defense (DoD). AnGes and Vasomune plan to use this help from the US and Canadian governments to accelerate their clinical trial program evaluating AV-001.

On March 17, 2021, Shared Research updated the report following interviews with the company.

On March 10, 2021, the company announced the completion of vaccination in the Phase II/III studies of its DNA vaccine against COVID-19.

The company completed dosing all 500 participants at eight trial facilities in Kanto and Kansai on schedule in the Phase II/III studies of its DNA vaccine against COVID-19 currently under development. The studies, by inoculating 500 participants, aim to

assess the safety and immunogenicity of the study vaccine administered in a predetermined dose using predetermined methods (e.g., number of doses and dosing intervals). The company will assess the safety and immunogenicity after completing several months of observation period.

Summary of Phase II/III studies of the DNA vaccine against COVID-19

- ▷ Summary: Randomized, double-blind, and placebo-controlled trial aimed at assessing the safety and immunogenicity of the investigational vaccine (an intramuscular injection) in healthy adult volunteer trial participants
- ▷ Target number of trial participants: 500 (dose of 2.0mg; 250 participants inoculated twice at two-week intervals and 250 participants inoculated twice at four-week intervals; 50 participants in each group will receive a placebo)
- ▷ Number of trial facilities: Eight in the Kansai and Kanto regions

On March 8, 2021, the company announced the issue of the 41st share subscription rights with exercise price revision provisions through third-party allocation.

Overview of issue

Allotment date	March 24, 2021 (the share subscription rights shall be exercisable for a period of two years from the allotment date (the "exercise period"))
Total number of share subscription rights	200,000 units
Issue price	JPY491 per subscription right (total: JPY98.2mn)
Number of residual securities associated with the issue	20.0mn (100 securities per subscription right, dilution of 15.03% of shares on issue as of end-December 2020) No maximum exercise price. Even at the minimum exercise price, number of residual securities is 20.0mn.
Amount to be raised	JPY16.8bn (estimated net proceeds)
Exercise price and exercise price revision provisions	JPY841 (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 Tuesday each week ("price revision date") by 0.90 (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 JPY467 (minimum exercise price), the minimum exercise price shall be the revised price.
Subscription or allocation method (allottee)	Third-party allotment to Cantor Fitzgerald & Co.
Other	The principle matters that the company plans to agree with its counterpart Cantor Fitzgerald & Co. (the "allottee") are as follows. ➢ The company shall be able to suspend the exercise of the share subscription rights by the allottee at any time, with certain exceptions, by notifying the allottee in accordance with the procedures set out in the third-party allocation agreement. Further, after such suspension has become effective, the company shall be able to allow the resumption of the exercise of the share subscription rights at any time by notifying the allottee. ➢ The allottee intends to sell the company's common shares acquired through exercise of the share subscription rights to overseas institutional investors who have the intention of maintaining their holdings for the long-term.

	➢ On the final day of the exercise period, the company shall buy back the remaining share subscription rights at a price equal to the issue price per share subscription right. ➢ Except where the allottee's cancellation right has been triggered (for example, by the commencement of insolvency proceedings of the company), the allottee shall not be able to sell the company's common shares obtained through the exercise of the share subscription rights on financial instrument exchanges without the prior written consent of the company.

Specific uses of funds to be raised (estimated net proceeds of JPY16.8bn)

▷ Working capital for Emendo (R&D expenses, personnel expenses, and the like): JPY9.0bn, scheduled for expenditure in the period from March 2021 to December 2023.

▷ Expansion of the company's business base through the acquisition of, or capital participation in, overseas companies: JPY6.8bn, scheduled for expenditure in the period from July 2021 to June 2025.

▷ Expansion of the company's business base by other means: JPY1.0bn, scheduled for expenditure in the period from July 2021 to June 2025.

On March 1, 2021, the company announced that it entered into a committed credit line agreement.

The company entered into a committed credit line agreement with its main partner bank, Mizuho Bank, Ltd. on February 26, 2021. Funds secured through this agreement are intended to be used in pharmaceutical R&D. The agreement is for a total committed credit line of JPY1.0bn, unsecured and non-guaranteed, and is set to expire on February 26, 2022 (effective for one year).

On February 24, 2021, the company announced a reduction in the amount of its capital reserve and a disposal of surplus.

At end-December 2020, the company recorded a loss of retained earnings carried forward of JPY15.9bn. AnGes will dispose of surplus after reducing the capital reserve amount, aiming to ensure the agility and flexibility of its capital policy and to limit its tax base by offsetting the above loss, correcting its capital structure, and strengthening its financial position. The effective date is set for April 9, 2021.

This is a reduction of capital without compensation, whereby the company draws down the capital reserve without changing the total number of issued shares. Because the reserve draw down will not affect either the number of shares issued or the company's net assets, net assets per share will remain unchanged.

Capital reserve decrease, net assets after disposal of surplus

(JPYmn)	FY12/20	After the change
Shareholders' equity	29,155	29,155
Capital stock	24,612	24,612
Capital surplus	20,427	4,543
Legal capital surplus	20,427	4,543
Retained earnings	-15,884	-
Other retained earnings	-15,884	-
Retained earnings brought forward	-15,884	-
Treasury stock	0	0
Valuation and translation adjustments	59	59
Share subscription rights	143	143
Total net assets	**29,356**	**29,356**

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

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

Trends and outlook

Quarterly trends and results

Quarterly performance

Cumulative (JPYmn)	FY12/20 Q1	Q2	Q3	Q4	FY12/21 Q1	Q2	Q3	Q4
Operating revenues	6	17	28	40	12			
YoY	-92.4%	-90.2%	-91.2%	-87.8%	101.4%			
Operating expenses	980	1,783	2,886	5,639	3,640			
YoY	-1.4%	-5.3%	7.6%	56.8%	271.5%			
Operating profit	-974	-1,766	-2,858	-5,599	-3,628			
YoY	-	-	-	-	-			
OPM	-	-	-	-	-			
Recurring profit	-923	-1,896	-3,151	-6,618	-3,361			
YoY	-	-	-	-	-			
RPM	-	-	-	-	-			
Net income	-920	-1,896	-3,175	-4,210	-3,314			
YoY	-	-	-	-	-			
Net margin	-	-	-	-	-			

Quarterly (JPYmn)	FY12/20 Q1	Q2	Q3	Q4	FY12/21 Q1	Q2	Q3	Q4
Operating revenues	6	11	12	12	12			
YoY	-92.4%	-88.5%	-92.4%	318.2%	101.4%			
Operating expenses	980	803	1,103	2,753	3,640			
YoY	-1.4%	-9.6%	37.8%	201.1%	271.5%			
Operating profit	-974	-792	-1,092	-2,742	-3,628			
YoY	-	-	-	-	-			
OPM	-	-	-	-	-			
Recurring profit	-923	-973	-1,254	-3,468	-3,361			
YoY	-	-	-	-	-			
RPM	-	-	-	-	-			
Net income	-920	-976	-1,279	-1,035	-3,314			
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)

	FY12/20				FY12/21			
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Operating revenues	6	17	28	40	12			
YoY	-92.4%	-90.2%	-91.2%	-87.8%	101.4%			
Sales of merchandise	-	-	-	-	-			
YoY	-	-	-	-	-			
Sales of finished goods	6	17	28	40	12			
YoY	-	-	-	859.2%	101.4%			
R&D revenues	-	-	-	-	-			
YoY	-	-	-	-	-			
Operating expenses	980	1,783	2,886	5,639	3,640			
YoY	-1.4%	-5.3%	7.6%	56.8%	271.5%			
Cost of sales	3	9	16	23	7			
YoY	-90.4%	-89.0%	-81.0%	-73.6%	100.0%			
Cost ratio	60.3%	54.7%	56.8%	57.6%	59.8%			
R&D expenses	628	1,105	1,881	3,796	2,416			
YoY	-9.4%	-2.2%	18.5%	71.4%	284.5%			
Salaries and allowances	-	124	-	259	-			
YoY	-	8.3%	-	14.5%	-			
Outsourcing expenses	-	578	-	2,324	-			
YoY	-	18.5%	-	118.3%	-			
Commission fees	-	88	-	255	-			
YoY	-	-12.6%	-	24.2%	-			
SG&A expenses	348	669	989	1,820	1,217			
YoY	31.8%	0.1%	-2.1%	40.6%	249.5%			
Operating profit	-974	-1,766	-2,858	-5,599	-3,628			
YoY	-	-	-	-	-			

	FY12/20				FY12/21			
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Operating revenues	6	11	12	12	12			
YoY	-92.4%	-88.5%	-92.4%	318.2%	101.4%			
Sales of merchandise	-	-	-	-	-			
YoY	-	-	-	-	-			
Sales of finished goods	6	11	12	12	12			
YoY	-	-	730.1%	318.2%	101.4%			
R&D revenues	-	-	-	-	-			
YoY	-	-	-	-	-			
Operating expenses	980	803	1,103	2,753	3,640			
YoY	-1.4%	-9.6%	37.8%	201.1%	271.5%			
Cost of sales	3	6	7	7	7			
YoY	-90.4%	-88.0%	500.0%	200.0%	100.0%			
Cost ratio	60.3%	51.8%	59.8%	59.4%	59.8%			
R&D expenses	628	476	776	1,915	2,416			
YoY	-9.4%	9.2%	69.7%	205.2%	284.5%			
SG&A expenses	348	321	320	831	1,217			
YoY	31.8%	-20.6%	-6.3%	192.2%	249.5%			
Operating profit	-974	-792	-1,092	-2,742	-3,628			
YoY	-	-	-	-	-			

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

Q1 FY12/21 results

Operating revenues: JPY12mn (+101.4% YoY)

Operating revenues broke down into sales of finished goods of JPY12mn (+101.4% YoY), and no R&D revenue (none in Q1 FY12/20).

▷ 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: JPY3.6bn (loss of JPY974mn in Q1 FY12/20)

Operating expenses: JPY3.6bn (+271.5%, +JPY2.7bn YoY)

▷ Cost of sales was JPY7mn (+100.0%, +JPY3mn YoY). The company booked the cost of HGF gene therapy Collategene®.

- R&D expenses were JPY2.4bn (+284.5%, +JPY1.8bn YoY). The company moved ahead with the development of a DNA vaccine for COVID-19. As a result, outsourcing expenses grew by JPY748mn YoY, supplies expenses by JPY255mn, and research material expenses by JPY575mn. In addition, salaries increased by JPY103mn as the company added Emendo Biotherapeutics, Inc. to consolidated accounts.
- SG&A expenses were JPY1.2bn (+249.5%, +JPY869mn YoY). Commission expenses were JPY170mn higher YoY due to increases in legal, consulting, and banking fees. Goodwill amortization expense also increased by JPY567mn. The company booked JPY22.7bn, to be amortized over 10 years using the straight-line method, for having made Emendo its subsidiary in December 2020.

Recurring loss: JPY3.4bn (loss of JPY923mn in Q1 FY12/20)

- The company booked non-operating income of JPY302mn (+311.7% YoY), including a JPY281mn forex loss on revaluation of foreign currency deposits and loans to Emendo.
- Non-operating expenses were JPY35mn (-59.8% YoY). Share issuance costs associated with the issue and exercise of stock options were JPY33mn (JPY22mn in Q1 FY12/20).

Net loss attributable to owners of the parent: JPY3.3bn (net loss of JPY920mn in Q1 FY12/20)

Extraordinary gains

- The company booked a JPY32mn gain from the reversal of share subscription rights on the expiry of stock options at the end of the exercise period.

Main pipeline progress

AnGes is involved in drug discovery, focusing on gene therapy. Among its pipeline products, it has a two-pronged approach toward COVID-19 since its emergence in late 2019, comprising the development of a vaccine and treatment in Japan and overseas. In genetic therapies based on genome editing, the company has made Emendo (holder of advanced technologies) a wholly owned subsidiary, and is developing therapeutic agents for patients with diseases for which there was no previously available treatment using Emendo's genome editing technologies.

In September 2019, AnGes conducted clinical trials in Japan and overseas for its commercialized HGF gene therapy drug Collategene®, aiming at additional indications and approval in the US. It also signed an exclusive sales agreement with Turkish company Er-Kim with a view to out-licensing. The company continues to develop NF-κB decoy oligo DNA for discogenic low back pain and a DNA vaccine for high blood pressure. Further, in collaboration with overseas companies, the company is jointly developing promising drugs with a view to commercialization.

Progress of main pipeline products in Q1 FY12/21

Progress made since end-FY12/20

- In April 2021, the company announced that the late Phase I study of NF-κB decoy oligo DNA (development code: AMG0103), nucleic acid agent for the treatment of discogenic low back pain (to be intradiscally injected once), demonstrated favorable safety and efficacy results in a 12-month follow-up period.
- In March 2021, vaccination of 500 subjects was completed as scheduled in the Phase II/III clinical studies of a DNA vaccine for COVID-19.
- In March 2021, the Phase I clinical study results confirmed the safety and tolerability of AV-001 under development for the treatment of COVID-19, and showed a pharmacokinetic profile that can substantiate the development of the drug on the condition of once daily administration.

DNA vaccine for COVID-19 (own development)

Since March 2020, AnGes and Osaka University have been jointly developing a DNA vaccine for COVID-19 using plasmid DNA technology. In the Phase II/III clinical trials currently under way, the two parties completed vaccinating 500 subjects in March 2021. Following a several months of follow-up, safety and immunogenicity will be evaluated.

COVID-19 treatment (joint development)

AnGes entered an agreement with Canadian biomedical company Vasomune Therapeutics to jointly develop a treatment targeting diseases caused by vascular dysfunction and destabilization such as acute respiratory failure. Phase I clinical trials in healthy adults for investigational new drug (IND) AV-001 as a treatment for COVID-19 infections began in the US in December 2020, delivering favorable results confirming that AV-001 is both safe and well tolerated. Preparations are now under way to conduct Phase II studies in the US and Canada.

HGF gene therapy drug (own development)

Indication: Chronic arterial occlusion

- Regarding the development of its HGF gene therapy drug for chronic arterial occlusion, in March 2019 AnGes 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, 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 Act, which went into force in November 2014). The company launched the product 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 complete post-marketing evaluation and obtain full manufacture and marketing approval by 2024.
- Overseas, the company began a Phase IIb clinical trial in the US in January 2020 targeting chronic arterial occlusion with lower limb ischemic ulcers.

Indication: Pain at rest in patients with chronic arterial occlusion

- In October 2019, the company began a Japan-based Phase III study 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 study to take about two years with around 40 patients enrolled.

NF-κB decoy oligo DNA (own development)

Indication: Discogenic low back pain

- AnGes is progressing with the development of NF-κB decoy oligo DNA to treat low back pain including discognic low back pain. The company began Phase Ib clinical trials targeting discogenic low back pain in February 2018, the results of which indicated that at both six and 12 months following treatment, the injection was well-tolerated, and no patients experienced serious adverse events, validating drug safety. In NF-κB decoy oligo DNA group, low back pain of the patients was significantly reduced compared with the control group, and the drug's sustained effects and efficacy were confirmed. AnGes will continue to analyze the data with a view to moving onto Phase II studies.
- In nucleic acid medicines, AnGes has been conducting research on next-generation decoy oligonucleotide to follow NF-κB decoy oligo DNA. The company is making progress on the development of the basic technology for Chimera decoy, which acts to simultaneously suppress NF-κB and STAT6, two of the key transcription factors. Compared with decoys that only target NF-kB, the company expects this decoy to suppress many inflammation-associated factors and have a broad range of effects.

DNA vaccine to treat high blood pressure (own development)

▷ 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. The company evaluated the initial results of the Australia-based Phase I/IIa studies after completing the post-vaccination observation period. No serious adverse effects were found, there were no safety issues, and the investigational vaccine was confirmed to induce the production of antibodies against angiotensin II. AnGes will continue trials to evaluate its safety, immunogenicity, and efficacy.

Gene therapy drug development using genome editing technology

In December 2020, the company invested additional funds in Emendo, making it a wholly owned subsidiary. Emendo has advanced genome editing technologies and a development pipeline leveraging them. The aim is to develop gene therapies for genetic disorders using genome editing technology.

Using microbiomes for disease prevention and health maintenance

In July 2018, AnGes entered into a capital alliance with Israeli biotechnology company MyBiotics Pharma, which is engaged in research into treatments for disease and supplements to maintain health that use intestinal flora. It aims to identify intestinal bacteria that suit individuals' health conditions and constitutions and develop drugs and supplements containing such bacteria.

Foray into the diagnostic business

To broaden its business portfolio, in February 2020 the company entered a joint research agreement with the Japanese Foundation for Cancer Research with the aim of commercializing diagnostic technology developed by Israeli biotech company Barcode Diagnostics Ltd. The technology is to be used as a decision-making tool to quickly select the most effective anticancer drugs for individual patients.

Strategic development tie-up with Brickell Biotech (formerly Vical)

In December 2016, AnGes concluded a strategic business alliance with Vical, which merged with US-based Brickell Biotech in August 2019. In September 2020, AnGes and Brickell Biotech entered a joint development agreement for clinical trials of an investigational DNA vaccine for COVID-19 in the US.

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 end-March 2021, cash and deposits totaled JPY14.2bn (JPY11.5bn at end-FY12/20).

Progressing own existing projects and expanding business base

The company is progressing three development projects: HGF gene therapy drug for chronic arterial occlusion, the nucleic acid drug NF-κB decoy oligo DNA 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. 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.

In addition to these ongoing projects, the company embarked on joint development of a COVID-19 vaccine with Osaka University in March 2020. In December 2020, it made Emendo (which owns advanced new genome editing technology) a wholly owned subsidiary to step up its efforts in genomic drug discovery, and will be more heavily involved in genome editing to develop gene therapies. It aims to continue 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 nucleic acid medicine (NF-κB decoy oligo 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 24, 2021, AnGes issued the 41st share subscription rights with exercise price revision provisions through third-party allocation to Cantor Fitzgerald & Co. As of May 10, 2021, JPY15.2bn had been raised through the partial exercise of these share subscription rights (and proceeds from the original issuance).

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

Full-year company forecast

As of May 2021, AnGes had not disclosed its FY12/21 forecast. The company is developing a DNA vaccine for COVID-19. The scope and methodology of clinical trials are yet to be determined, and it is unclear what sort of government subsidies would be provided at future development stages and what form calls for participants may take. Thus, the company commented that it was difficult to make a reasonable earnings estimate at the start of the fiscal year, and said it would disclose its full-year forecast when possible based on business progress.

- Operating revenues: Shared Research understands that sales revenue from HGF gene therapy drug Collategene® 4mg Intramuscular Injection (Collategene®) will be booked as sales of finished goods. Sales of finished goods totaled JPY40mn in FY12/20.
- Operating expenses comprise cost of HGF gene therapy drug Collategene® (JPY23mn in FY12/20), R&D expenses (JPY3.8bn), and SG&A expenses (JPY1.8bn).
- AnGes made Emendo a subsidiary in December 2020. In FY12/21, Emendo's operating expenses will be incorporated into consolidated accounts. Emendo posted operating revenues of JPY0mn and an operating loss of JPY567mn in FY12/19.

- AnGes was selected to receive the following subsidies for development of a DNA vaccine against COVID-19, of which it recorded JPY3.6bn in advances received. Future subsidies are unknown.
  - The company's joint development project with Osaka University for a DNA vaccine against COVID-19 was selected for the Japan Agency for Medical Research and Development (AMED)'s FY2020 COVID-19 Vaccine Development Program, which called for applications in May 2020. The R&D grant totals JPY2.0bn and the project duration is May 2020–March 2021.
  - In August 2020, the company's joint development project with Osaka University for a DNA vaccine against COVID-19 was selected for the Japan Agency for Medical Research and Development (AMED)'s FY2020 COVID-19 Vaccine Development Program (second round).
  - Also in August 2020, the company was selected for MHLW's Emergency Project for the Establishment of Vaccine Manufacturing Systems for FY2020. It will receive a grant totaling JPY9.4bn and the project duration is August 2020–March 2022.

- The main pipeline products undergoing clinical trials as of FY12/21 are as follows. R&D expenses will vary according to the state of progress of clinical trials. Shared Research understands that R&D expenses will increase sharply if the company were to conduct large-scale Phase III clinical trial for the development of a DNA vaccine against COVID-19.
  - Domestic Phase III clinical trial of HGF gene therapy drug Collategene® for the treatment of pain at rest in patients with chronic arterial occlusion
  - Phase II clinical trial in the US of HGF gene therapy drug Collategene® for the treatment of lower limb ischemic ulcers in patients with chronic arterial occlusion
  - Domestic Phase II/III clinical trial of DNA vaccine against COVID-19
  - Phase I clinical trial in the US of treatment for COVID-19

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. As of February 2021, the company is also developing a DNA vaccine against COVID-19. Shared Research understands that the scale of clinical trials going forward, government and other subsidies, and earnings contribution of the vaccine if it goes on sale will have a substantial impact on the company's earnings in the medium term.

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 pain at rest
- ▷ 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 in 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.

The company commented that it would complete the post-marketing surveillance by 2024 to obtain manufacturing and marketing approval, and as of December 2020, around 80 of 120 patients in the Collategene® group had received treatment.

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 pain at rest

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.

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

Approval for the additional indication of treatment for patients with pain at rest 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 late Phase II clinical trial of the HGF gene therapy drug in patients with arteriosclerosis obliterans with lower limb ischemic ulcers (assess effectiveness in alleviating lower limb ulcers, target enrollment of 60 patients, post-administration 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), in Israel to Kamada, and in Turkey to Er-Kim. As of February 2021, no marketing agreements had been concluded for other markets. In the medium term, the company aims to out-license rights to other markets.

Expanded indications 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 2021, development of pipeline candidates other than the HGF gene therapy drug include a Phase Ib clinical trial of NF-κB decoy oligo DNA for discogenic low back pain and a Phase I/II clinical trial 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.

Vaccine and treatment for COVID-19

AnGes is developing a vaccine and treatment for COVID-19 in Japan and overseas. As of February 2021, the DNA vaccine for COVID-19 is undergoing a Phase II/III clinical trial and may progress to a Phase III placebo-controlled comparative trial. Shared Research understands that the scale of clinical trials going forward, government and other subsidies, and earnings contribution of the vaccine if it goes on sale will have a substantial impact on the company's earnings in the medium term.

DNA vaccine for COVID-19

Using plasmid DNA technology, AnGes began development its joint development project with Osaka University for a DNA vaccine against COVID-19 in March 2020. The project is at the stage of Phase II/III clinical trial with a target of 500 cases. Having established dose and dosage regimen in the trial, the company plans to conduct a large-scale, placebo-controlled Phase III comparative clinical trial to evaluate the vaccine's efficacy in preventing symptomatic COVID-19 infection.

Treatment for COVID-19

In December 2020, the company began a Phase I clinical trial of AV-001, an investigational drug for the treatment of COVID-19, with healthy adults in the US with Canadian biomedical company Vasomune Therapeutics.

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) in 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.

Risk diversification 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 2021, 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 company was awarded conditional and time-limited approval in Japan for its HGF gene therapy drug to treat critical limb ischemia and licensee Mitsubishi Tanabe Pharma began commercialization in 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 drugs (new drug candidates)

The main pipeline drugs (new drug candidates) are HGF gene therapy drug Collategene® for critical limb ischemia (CLI), NF-κB decoy oligo DNA for the treatment of discogenic low back pain, and DNA vaccine for high blood pressure. The company is also developing a vaccine and treatment for COVID-19.

Main pipeline products

The internal development pipeline includes an HGF gene therapy drug, NF-κB decoy oligo DNA, and DNA vaccine for high blood pressure. The company is also developing a vaccine and treatment for COVID-19. Although in pre-clinical and basic research stages of development, the company is 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

Product/Project	Indications	Area	Development stage	Partner
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 pain at rest in chronic arterial occlusion	Japan	Phase III clinical trial under way	
	Improvement of lower limb ulcers in chronic arterial occlusion	US	Late Phase II clinical trial under way	Mitsubishi Tanabe Pharma (licensing marketing rights)
NF-κB decoy oligo DNA	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 (observation period)	TBD
DNA vaccine for high blood pressure	High blood pressure	Australia	Phase I/II clinical trial completed	TBD
DNA vaccine against COVID-19	COVID-19	Japan and overseas	Phase II/III clinical trial under way	Internal development
Treatment for COVID-19	COVID-19	US	Phase I clinical trial under way	Vasomune (Canada)

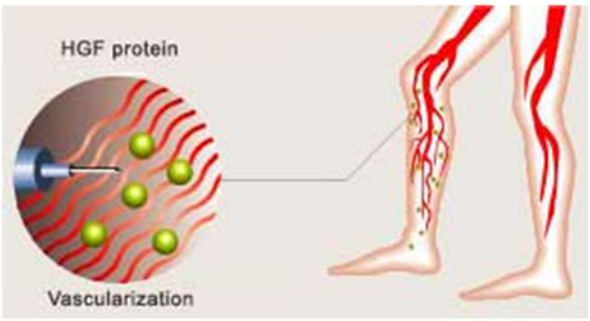
Source: Shared Research based on company data
Note: In July 2016, AnGes announced that data analysis had not shown a statistically significant difference between the treatment group for this drug and the placebo group in terms of its main efficacy evaluation criterion. The company plans to determine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

Gene drugs

HGF gene therapy drug

HGF discovered in Japan (1984)

Hepatocyte growth factor (HGF) 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

In 2003, AnGes launched a Phase III study of its HGF gene therapy drug for peripheral vascular diseases, targeting arteriosclerosis obliterans with CLI and Buerger's disease as indications. In this trial, in which a total of 120 cases were initially planned, interim analysis of 40 cases in June 2007 showed efficacy.

In the Phase III study, the study drug was intramuscularly injected twice at an interval of four weeks into the ischemic parts of the limbs of patients with severe ischemic limbs at stage III (pain at rest) and stage IV (ischemic ulcers or gangrene) according to the Fontaine classification (see below), and their clinical courses were observed for eight weeks. The primary endpoint for efficacy validation was an improvement of pain at rest or the size of ischemic ulcers at 12 weeks after administration of the study drug.

The rate of improvement for pain at rest or the size of ischemic ulcers after 12 weeks was 70.4% (19/27 cases) with patients in the HGF gene therapy group, and 30.8% (4/13 cases) for those in placebo group. 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-pain at rest, 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.

HGF gene therapy drug to treat chronic arterial occlusion received conditional and time-limited approval in Japan

Since it had shelved the application for the HGF gene therapy drug for CLI in September 2010, AnGes 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 in September 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).

AnGes aims to complete post-marketing evaluation (target: 120 cases for Collategene® group and 80 cases for placebo group) and obtain full manufacture and marketing approval by 2024. As of December 2020, around 80 of the 120 patients in the Collategene® group had received the drug.

HGF gene therapy drug to treat pain at rest in patients with chronic arterial occlusion in Phase III clinical trial in Japan

To further expand the approved indications, AnGes started a Phase III clinical trial in Japan for improvement of pain at rest in October 2019 (target: 40 cases).

HGF gene therapy drug to treat chronic arterial occlusion in Phase IIb clinical trial in the US

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

As noted above, 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. In October 2014, the company began a global Phase III clinical trial targeting CLI and commenced administration of the drug in November 2014.

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. The company was aiming to apply for approval in the US in 2018, and then in Europe.

However, AnGes in June 2016 decided to discontinue 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 Phase II study in the US in February 2020

AnGes 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-based late Phase II clinical trial was started in January 2020 to evaluate HGF gene therapy drug in 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).

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.

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 oligo DNA

AnGes has designed NF-κB decoy oligo DNA 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 oligo DNA 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 oligo DNA injection for treating discogenic low back pain

In February 2018, AnGes began a Phase Ib clinical trial for NF-κB decoy oligo DNA for the treatment of discogenic low back pain in the US and administration was completed in February 2020. In February 2021, the company announced preliminary results. In the Phase Ib clinical trial, NF-κB decoy oligo DNA was intradiscally injected once to 25 men and women (aged 32–70; mean age of 53.5 years) with discogenic low back pain in a double-blind, randomized study (observation period of six months). The dose was well tolerated, and no patients had serious adverse events, validating the safety of NF-κB decoy oligo DNA. An exploratory evaluation of the data also confirmed the efficacy of the treatment, with patients experiencing a notable and sustained reduction in low back pain.

Administration of NF-κB decoy oligo DNA resulted in a dose-dependent reduction in low back pain measured on a 100mm visual analogue scale (VAS) throughout the six-month study period (Part 1). All doses of NF-κB decoy oligo DNA showed improvement compared to the placebo control group, but the treatment group receiving a high 10mg dose of NF-κB decoy oligo DNA saw a

reduction of low back pain of almost 50% 14 days after treatment. Low back pain in this group continued to decline, reaching a 71% reduction from baseline at six months, which was significantly better (p=0.033) than the placebo control group that showed just a 15% improvement.

As for improvements in low back pain-related impairment in activities of daily living, psychological burden, and QOL, the PGI-C score (measured from 1 to 7 on an ordinal scale based on self-evaluations of patients) revealed a dose-dependent improvement from baseline at six months, and was numerically superior to the placebo control group for all NF-κB decoy oligo DNA treatment groups. In the 10mg NF-κB decoy oligo DNA arm, the improvement was almost three points better than that observed in the control group, and was also statistically significant (p=0.001). The PGI-C instrument quantifies how patients regard their improvement from baseline. Using the seven-point scale, a three-point difference between any two groups is clinically meaningful. In addition to this outcome, all three NF-κB decoy oligo DNA treatment arms showed a 20–50% improvement in RDMQ score (an index that measures low back pain-related disability in everyday life) at six months, while the control group declined more than 15% from baseline.

The company stated that it would report on additional test results (12-month efficacy findings) going forward before moving on to the Phase II trial.

As of March 2021, AnGes has yet to conclude a development and marketing agreement for NF-κB decoy oligo DNA with a pharmaceutical company.

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 oligo DNA. 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 disease (COVID-19).

DNA vaccine for high blood pressure

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

In April 2018, AnGes began a Phase I/II clinical trial of a DNA vaccine for high blood pressure in Australia. Twenty-four patients with mild to moderate high blood pressure are enrolled for the double-blind, placebo-controlled comparative study, of whom 18 were assigned to the treatment group and six to the placebo group. The study will confirm safety and efficacy over a 12-month follow-up period after administration. In February 2021, the company analyzed the early-stage results of the study. No

adverse events were observed, there were no issues with safety, and the production of antibodies against angiotensin II was confirmed. The company will continue to evaluate safety, immunogenicity, and efficacy of the treatment.

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 in 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 2021, AnGes has yet to conclude a development and marketing agreement for the DNA vaccine for high blood pressure with a pharmaceutical company.

Vaccine against COVID-19

In March 2020, AnGes and Osaka University embarked on joint development of a preventive DNA vaccine against the novel coronavirus disease (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).

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.

How DNA vaccine against COVID-19 works

- ▷ When the spike protein of the novel coronavirus (SARS-CoV-2), which plays a key role in infection, binds to a receptor in the body, it allows the virus to enter cells and cause infection.
- ▷ The DNA vaccine creates a harmless spike with the same virus layout as the novel coronavirus. The vaccine only produces spikes in the body that will not be directly infected by the virus. Body cells produce antibodies against the harmless spike, providing resistance against infection.
- ▷ After inoculation, antibodies produced in the body capture the novel coronavirus before it enters cells. This stops the virus from binding to the cell receptor and prevents infection.

Overview of project for development and manufacture of preventive DNA vaccine against 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.
- AnGes and 3-D Matrix, Ltd. (JASDAQ Growth: 7777) are exploring the potential for domestic clinical use of an antibody test kit.
- AGC Biologics, Inc., Shionogi Pharma Co., Ltd., and Kaneka Eurogentec S.A. as joint intermediate manufacturers and Cytiva as a priority supplier of refining materials will participate as collaboration partners in Takara Bio's vaccine production structure.

Progress of development of vaccine against COVID-19

In September 2020, AnGes began administration of the DNA vaccine against COVID-19 in Phase I/II clinical trial at Osaka University Hospital, and completed the administration of all vaccines in the following month. The clinical trial evaluated the optimal interval between doses and dosage frequency with 30 cases.

In December 2020, the company began administration of the DNA vaccine against COVID-19 in Phase II/III clinical trial. This trial will evaluate safety and immunogenicity of the vaccine at the dose and dosage regimen determined in the Phase I/II trial with a target of 500 cases. The company plans to publish the results of this trial around summer 2021. Having established the optimal dose and dosage regimen in the trial, the company plans to conduct a large-scale, placebo-controlled comparative Phase III trial to verify efficacy in preventing COVID-19 infection.

Summary of Phase II/III clinical trial of the DNA vaccine against COVID-19

- Target number of trial participants: 500 (dose of 2.0mg: 250 participants inoculated twice at two-week intervals and 250 participants inoculated twice at four-week intervals; 50 participants in each group will receive a placebo)
- Trial period: December 2020–March 2022 (inoculations are scheduled to be completed by sometime in March 2021. The trial period includes a follow-up span of 52-weeks after the inoculations are performed)

Financial support for development of vaccine against COVID-19

- The company's joint development project with Osaka University for a DNA vaccine against COVID-19 was selected for the Japan Agency for Medical Research and Development (AMED)'s COVID-19 Vaccine Development Program, which called for applications in May 2020. The R&D grant totals JPY2.0bn and the project duration is May 2020–March 2021.

- In August 2020, the company's joint development project with Osaka University for a vaccine against COVID-19 was selected for the Japan Agency for Medical Research and Development (AMED)'s COVID-19 Vaccine Development Program (second round).
- Also, in August 2020, the company was selected for MHLW's Emergency Project for the Establishment of Vaccine Manufacturing Systems for FY2020. It will receive a grant totaling JPY9.4bn and the project duration is August 2020–March 2022.

COVID-19 treatment targeting Tie2 receptor

AV-001, an investigational drug for the treatment of COVID-19

AV-001 is a novel investigational drug that targets the Tie2 receptor, a transmembrane protein mostly expressed on the surface of vascular endothelial cells. AnGes is developing AV-001 with Canadian biomedical company Vasomune Therapeutics as a treatment for moderate to severe symptoms of COVID-19 and acute respiratory distress syndrome (ARDS).

AV-001 restores normal vascular function and endothelial stability through activation of the Tie2 angiopoietin pathway. Vascular dysfunction contributes to the underlying disease pathophysiology in patients with COVID-19 and acute respiratory distress syndrome (ARDS), especially in patients with preexisting vascular comorbidities such as hypertension, diabetes, and obesity. Recent findings suggest that SARS-CoV-2 infects pulmonary endothelial cells and causes microvascular leaks, contributing to the initiation and propagation of respiratory distress and ARDS in COVID-19 patients by altering blood vessel barrier integrity and promoting a coagulated state, inducing vascular inflammation and mediating inflammatory cell migration.

In preclinical studies involving a lethal RNA virus infection animal model of influenza/ARDS, AV-001 has been shown to stabilize the vasculature by enhancing endothelial cell stability, restoring normal barrier defense, and blocking vascular leak. AV-001 monotherapy also significantly improved survival and lung function compared to the untreated control group and showed enhanced efficacy in combination with antiviral therapy.

Development status of AV-001, an investigational drug for the treatment of COVID-19

In December 2020, AnGes and Vasomune Therapeutics began a Phase I clinical trial of AV-001 in the US.

The Phase I clinical trial is a double-blind, placebo-controlled study in healthy adult participants. The study will evaluate the safety, tolerability, and pharmacokinetics of single-dose and continuous administration of AV-001. If the company obtains favorable results from the Phase I trial as well as from subsequent phases of clinical trials, it will consider applying for the Emergency Use Authorization (EUA) to the U.S. Food and Drug Administration.

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
DNA vaccines, other	Brickell Biotech	December 2016

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.

AnGes commented that the market size of genetic disorders treatable using Emendo's genome editing technology (allele-specific gene editing) is JPY1.1tn.

Additional investment in Emendo

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

In December 2020, AnGes acquired 100% of Emendo's outstanding shares (previous stake: 40.04%; acquired the remaining 59.96% for roughly JPY20.2bn) through a share issue and third-party allocation of shares to Emendo shareholders, and made it a subsidiary. As a result, the company booked JPY22.7bn in goodwill in FY12/20.

Microbiome: formulation of indigenous bacteria

In July 2018, AnGes entered into a capital alliance with Israeli biotechnology company MyBiotics Pharma Ltd. (MyBiotics). 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.

In February 2020, the company concluded a joint research agreement with the Japanese Foundation for Cancer Research to achieve early practical application of diagnostics technology developed by Barcode to identify anticancer drugs most suited to individual patients in a short period of time.

Strategic development alliance with Brickell Biotech (formerly Vical)

In December 2016, AnGes concluded a strategic business alliance with US company Vical Incorporated. Vical signed a merger agreement with another US company Brickell Biotech in August 2019 and changed its name to Brickell Biotech. In September 2020, AnGes and Brickell Biotech entered a joint development agreement for clinical development of an investigational DNA vaccine against COVID-19 in the US.

Earnings structure

Earnings structure

(JPYmn)	FY12/11	FY12/12	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20
Operating revenue	243	445	491	910	430	514	365	610	327	40
Sales of merchandise	181	242	271	309	350	347	365	383	170	-
Sales of finished goods	-	15	8	-	-	-	-	-	4	40
R&D revenues	63	187	212	601	80	167	0	227	153	-
Operating expenses	2,344	2,230	1,854	3,184	4,602	5,278	3,654	3,675	3,597	5,639
Cost of sales	81	129	131	151	180	175	178	188	87	23
% of sales of goods	44.9%	50.3%	47.1%	48.9%	51.3%	50.3%	48.8%	49.2%	50.0%	57.6%
R&D expenses	1,444	1,200	1,025	2,339	3,533	4,189	2,600	2,540	2,215	3,796
Salaries and allowances	348	312	247	309	456	441	364	245	226	259
Outsourcing expenses	348	374	274	1,194	2,145	2,769	1,370	1,174	1,065	2,324
SG&A expenses	819	901	699	694	890	915	876	947	1,294	1,820
Directors' compensations	123	121	72	74	83	78	91	90	76	96
Salaries and allowances	230	224	139	125	155	148	140	127	147	161
Commission fee	145	197	197	163	240	265	179	232	373	839
Operating profit	-2,101	-1,785	-1,363	-2,274	-4,172	-4,763	-3,289	-3,065	-3,270	-5,599

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)	FY12/11	FY12/12	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17	FY12/18	FY12/19	FY12/20
Mitsubishi Tanabe Pharma	-	-	-	500	50	-	-	-	154	40
Daiichi Sankyo	42	159	35	92	-	-	-	-	-	-
TS Alfresa (former Seiwa Sangyo)	90	132	151	148	160	176	179	196	91	-
Alfresa	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 (0% of the FY12/20 total), sales of finished goods (100%), and research and development revenues (0%).

Sales of merchandise

Under sales of merchandise, AnGes booked sales of Naglazyme through FY12/19. The company procured Naglazyme from BioMarin Pharmaceuticals Inc., and sold 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 oligo DNA 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 are booked in 2H and beyond.

AnGes procures the HGF gene therapy drug from Boehringer Ingelheim and sells it to Mitsubishi Tanabe Pharma. The cost ratio exceeding 80% in 2H FY12/19 is attributable to small lot production, but the cost ratio fell to 57.6% in FY12/20. The company expects the cost ratio to go down over the medium term as production lot volumes increase.

R&D expenses

Mainly salaries, allowances, and outsourcing expenses. 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 expenses

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 expenses increased to roughly JPY900mn from FY12/15 to FY12/18 due to higher commissions paid, owing mainly to higher business compensation.
- Commissions paid increased in FY12/19 and FY12/20. In FY12/19, expenses for sales of HGF gene therapy drug Collategene® and a consulting agreement for new businesses resulted in higher commissions paid. In FY12/20, the company recorded consulting expenses and legal fees related to making Emendo a subsidiary.

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 Corporation began marketing it in 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, granting the latter exclusive rights to sell the HGF gene therapy drug in Japan and the US. As of February 2021, 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, sales have been limited. Shared Research believes that as of February 2021 there is still a lack of visibility over the timing of a medium-term transition to profitability as well as its sustainability.

Historical performance

Full-year FY12/20 results

Operating revenues: JPY40mn (-87.8% YoY)

Operating revenues broke down into zero sales of merchandise (JPY170mn in FY12/19), sales of finished goods of JPY40mn (JPY4mn in FY12/19), and zero R&D revenue (JPY153mn in 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: JPY5.6bn (loss of JPY3.3bn in FY12/19)

Operating expenses: JPY5.6bn (+56.8%, +JPY2.0bn YoY)

- Cost of sales was JPY23mn (-73.6%, -JPY64mn YoY). The company booked the cost of HGF gene therapy drug Collategene®. Cost of sales was down YoY due to sales of Naglazyme® (a drug for mucopolysaccharidosis VI) being completed.
- R&D expenses were JPY3.8bn (+71.4%, +JPY1.6bn 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, incurring clinical trial expenses. The company also moved ahead with the development of a COVID-19 vaccine. As a result, outsourcing expenses grew by JPY1.3bn YoY, supplies expenses by JPY241mn, and research material expenses by JPY94mn.
- SG&A expenses were JPY1.8bn (+40.6%, +JPY526mn YoY). Commission expenses increased by JPY465mn as the company made Emendo and its subsidiary Emendo Bio Research and Development Ltd. (collectively "Emendo") wholly owned subsidiaries and booked associated consulting and legal fees. In addition, taxes and dues increased by JPY139mn on an increase in the portion of corporate tax determined based on the company's capital. On the other hand, travel and transportation expenses declined by JPY47mn as the company refrained from business travel due to the spread of COVID-19. In FY12/19, the company booked share-based payment expenses of JPY88mn following the issue of stock options to directors and employees; in FY12/20, the company recorded share-based payment expenses of JPY48mn.

Recurring loss: JPY6.6bn (loss of JPY3.3bn in FY12/19)

- The company booked non-operating income of JPY25mn (+13.2% YoY), as interest income, commission income, and insurance claim income increased.
- Non-operating expenses were JPY1.0bn (roughly 23x the FY12/19 figure). Share issuance costs associated with the issue and exercise of stock options were JPY117mn (JPY42mn in FY12/19). The company also recorded equity-method investment losses of JPY909mn (zero in FY12/19) as Emendo became an equity-method affiliate in Q1.

Net loss attributable to owners of the parent: JPY4.2bn (net loss of JPY3.8bn in FY12/19)

Extraordinary gains

- The company booked a gain of JPY2.4bn on the step acquisition of shares after making Emendo a consolidated subsidiary. Gains associated with the step acquisition of shares arose when Emendo changed from an equity-method affiliate to consolidated subsidiary in December 2020.
- 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.

Extraordinary losses

- The company recorded JPY468mn in loss on valuation of investment securities in FY12/19, but none in FY12/20.
- The company recorded a JPY20mn loss from a change in equity stake in Emendo (none in FY12/19).

Main pipeline progress

AnGes is involved in drug discovery, focusing on gene therapy. Among its pipeline products, it has a two-pronged approach toward COVID-19 since its emergence in late 2019, comprising the development of a vaccine and treatment in Japan and overseas. In genetic therapies based on genome editing, the company has made Emendo (holder of advanced technologies) a wholly owned subsidiary, and is developing therapeutic agents for patients with diseases for which there was no previously available treatment using Emendo's genome editing technologies.

In September 2019, AnGes conducted clinical trials in Japan and overseas for its commercialized HGF gene therapy drug Collategene®, aiming at additional indications and approval in the US. It also signed an exclusive sales agreement with Turkish company Er-Kim with a view to out-licensing. The company continues to develop NF-κB decoy oligo DNA for treating discogenic low back pain and a DNA vaccine for high blood pressure. Further, in collaboration with overseas companies, the company is jointly developing promising drugs with a view to commercialization.

Main pipeline progress in FY12/20

Main pipeline progress since end-FY12/19 is as follows.

- In December 2020, AnGes and Vasomune Therapeutics began a Phase I clinical trial in the US of AV-001, an investigational drug for the treatment of novel coronavirus disease (COVID-19).
- In December 2020, AnGes began administration of a DNA vaccine against COVID-19 in Phase II/III clinical trial to evaluate safety and immunogenicity at the dose and dosage regimen determined in Phase I/II clinical trial with a target of 500 cases. The company plans to announce results of the trial around summer 2021.
- In October 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. Prior to approval being granted, AnGes and Er-Kim will begin supplying Collategene® in Turkey via the Named Patient Program.
- In August 2020, 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 announced that administration of a DNA vaccine for hypertension was completed for 24 patients in a Phase I/IIa clinical trial in Australia. The company evaluated the early-stage results of the trial in February 2021, finding no severe adverse events and no issues with safety, as well as confirming the production of antibodies against angiotensin II.
- In February 2020, enrollment of 25 patients was completed in a Phase Ib clinical trial in the US of NF-κB decoy oligo DNA for discogenic low back pain. The company announced preliminary results in February 2021.The drug was well tolerated by patients, no severe adverse events were reported, and safety of NF-κB decoy oligo DNA was confirmed. Exploratory data analysis found that patients experienced significant relief of low back pain, which was sustained, and efficacy was confirmed.
- In January 2020, the company initiated a US-based late Phase II clinical trial for 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).

DNA vaccine to prevent COVID-19 infection (own development)

Since March 2020, AnGes and Osaka University have been jointly developing a DNA vaccine for COVID-19 using plasmid DNA technology, and are conducting a Phase II/III clinical trial to evaluate safety and immunogenicity at the dose and dosage regimen

determined in Phase I/II clinical trial with a target of 500 cases. The company plans to announce results of the trial around summer 2021. After confirming the dose and dosage regimen, the company plans to conduct a large-scale, placebo-controlled comparative Phase III trial to evaluate the vaccine's efficacy in preventing COVID-19.

COVID-19 treatment (joint development)

AnGes entered an agreement with Canadian biomedical company Vasomune Therapeutics to jointly develop a treatment targeting diseases caused by vascular dysfunction and destabilization such as acute respiratory failure. Phase I clinical trial using healthy adults for investigational new drug (IND) AV-001 as a treatment for COVID-19 infections began in the US in December 2020.

HGF gene therapy drug (own development)

Indication: Chronic arterial occlusion

- Regarding the development of its HGF gene therapy drug for chronic arterial occlusion, in March 2019 AnGes 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, 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). The company began sales of the product 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 complete post-marketing evaluation (target: 120 cases for Collategene® group and 80 cases for placebo group) and obtain full manufacture and marketing approval by 2024. As of December 2020, around 80 of the 120 patients in the Collategene® group had received the drug.
- Overseas, the company began a Phase IIb clinical trial in the US in 2020 targeting chronic arterial occlusion with lower limb ischemic ulcers.

Indication: Pain at rest in patients with chronic arterial occlusion

- In October 2019, the company began a Japan-based 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.

NF-κB decoy oligo DNA (own development)

Indication: Discogenic low back pain

- AnGes is progressing with the development of NF-κB decoy oligo DNA to treat low back pain including discogenic low back pain. The company began a Phase Ib clinical trial targeting discogenic low back pain in February 2018 and completed administration of the drug to 25 patients as scheduled in February 2020, and is currently conducting follow-up monitoring. The company evaluated the early-stage results of the trial in February 2021. The vaccine was well tolerated by patients, no severe adverse events were reported, and safety of NF-κB decoy oligo DNA was confirmed. Exploratory data evaluation found that patients experienced significant relief of low back pain, which was sustained, and efficacy was confirmed. The company plans to progress to a Phase II clinical trial based on additional results when the 12-month efficacy data are available.
- In nucleic acid medicines, AnGes has been conducting research on next-generation decoy oligonucleotide to follow NF-κB decoy oligo DNA. The company is making progress on the development of the basic technology for Chimera decoy, which acts to simultaneously suppress NF-κB and STAT6, two of the key transcription factors. Compared with decoys that only target NF-kB, the company expects this decoy to suppress many inflammation-associated factors and have a broad range of effects.

DNA vaccine to treat high blood pressure (own development)

▷ 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. The company evaluated the initial results of the Australia-based Phase I/IIa clinical trial after completing the post-vaccination observation period. No serious adverse effects were found, there were no safety issues, and the investigational vaccine was confirmed to induce the production of antibodies against angiotensin II. AnGes will continue trials to evaluate its safety, immunogenicity, and efficacy.

Gene therapy drug development using genome editing technology

In December 2020, the company invested additional funds in Emendo, making it a wholly owned subsidiary. Emendo has advanced genome editing technologies and a development pipeline leveraging them. The aim is to develop gene therapies for genetic disorders using genome editing technology.

Using microbiomes for disease prevention and health maintenance

In July 2018, AnGes entered into a capital alliance with Israeli biotechnology company MyBiotics Pharma, which is engaged in research into treatments for disease and supplements to maintain health that use intestinal flora. It aims to identify intestinal bacteria that suit individuals' health conditions and constitutions and develop drugs and supplements containing such bacteria.

Foray into the diagnostic business

To broaden its business portfolio, in February 2020 the company entered a joint research agreement with the Japanese Foundation for Cancer Research with the aim of commercializing diagnostic technology developed by Israeli biotech company Barcode Diagnostics Ltd. The technology is to be used as a decision-making tool to quickly select the most effective anticancer drugs for individual patients.

Strategic development tie-up with Brickell Biotech (formerly Vical)

In December 2016, AnGes concluded a strategic business alliance with Vical, which merged with US-based Brickell Biotech in August 2019. In September 2020, AnGes and Brickell Biotech entered a joint development agreement for clinical trials of an investigational DNA vaccine for COVID-19 in the US.

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 end-December 2020, cash and deposits totaled JPY11.5bn (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 oligo DNA 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. 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.

In addition to these ongoing projects, the company embarked on joint development of a COVID-19 vaccine with Osaka University in March 2020. In December 2020, it made Emendo (which owns advanced new genome editing technology) a wholly owned subsidiary to step up its efforts in genomic drug discovery, and will be more heavily involved in genome editing to develop gene therapies. It aims to continue 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 nucleic acid medicine (NF-κB decoy oligo 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.

Balance sheet

- At end-FY12/20, current assets stood at JPY14.2bn (up JPY3.2bn from end-FY12/19).
- Cash and deposits increased to JPY11.5bn (up JPY1.5bn from end-FY12/19) due to an inflow of JPY11.5bn from the issue and exercise of stock options and consolidation of Emendo, offset against the cost of acquisition of Emendo shares and operating expenses.

- Fixed assets came to JPY24.2bn (up JPY22.7bn from end-FY12/19).
  - Under intangible fixed assets, the company booked goodwill of JPY22.7bn after making Emendo a wholly owned subsidiary, which will be amortized over 10 years by the straight-line method.

- Liabilities totaled JPY5.7bn (up JPY5.2bn from end-FY12/19).
  - The company recorded JPY3.6bn in advances received. The company received subsidies from Japan Agency for Medical Research and Development (AMED)'s COVID-19 Vaccine Development Program and from MHLW Emergency Project for the Establishment of Vaccine Manufacturing Systems for FY2020.
  - Accounts payable–other rose JPY1.1bn from end-FY12/19 to JPY1.2bn due to expenses associated with making Emendo a wholly owned subsidiary.

- Net assets stood at JPY32.7bn (up JPY20.6bn from end-FY12/19).
  - Capital increased by JPY11.3bn as a result of a third-party allotment of shares and issue and exercise of stock options. Capital surplus rose by JPY13.6bn due to the consolidation of Emendo.

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), as the company booked cost of sales for Collategene®. Cost of sales was down YoY due to sales of Naglazyme® (a drug for mucopolysaccharidosis VI) being discontinued.
- R&D expenses were JPY1.9bn (+18.5%, +JPY293mn YoY). R&D expenses trended lower YoY during 1H on smaller losses from reassessment of research materials, but increased in Q3 (July–September 2020). 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 expenses.
- 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 in Cumulative Q3 FY12/20

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

- In October 2020, AnGes announced that it had completed vaccinating all 30 subjects in the Phase I/II clinical trials of its investigational DNA vaccine targeting the novel coronavirus disease (COVID-19) conducted at Osaka University Hospital. The purpose of the trial was 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 trials conducted at Osaka City University Hospital and Osaka University Hospital in Q4 FY12/20. Based on these results, the company plans to conduct larger-scale clinical trials.

- In October 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. Prior to approval being granted, AnGes and Er-Kim will begin supplying Collategene® in Turkey via the Named Patient Program.
- In August 2020, the company announced that it had completed vaccinating all subjects in the Phase I/II clinical trials of its investigational DNA vaccine targeting COVID-19 conducted at Osaka City University Hospital.
- 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 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 around Q4 FY12/20.
- In February 2020, enrollment of 25 patients was completed in a Phase Ib clinical trial in the US of NF-κB decoy oligo DNA for discogenic low 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 around Q4 FY12/20.
- In January 2020, a US-based late Phase II 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.
- 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.

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.

NF-κB decoy oligo DNA indicated for discogenic low back pain

- The company is progressing with the development of NF-κB decoy oligo DNA to treat low back pain including discogenic low 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 oligo DNA. 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.

- In June 2020, the company started Phase I/II clinical trials at Osaka City University Hospital with 30 subjects (of the target enrollment of 30 subjects, 15 were assigned to the low-dose group, and another 15 to the high-dose group. All subjects received two doses of the vaccine at a two-week interval).
- The company also started Phase I/II clinical trials at Osaka University Hospital with 30 subjects to confirm the interval and number of vaccinations required (2.0mg in a single dose of the vaccine; two doses were administered at a two-week interval in 10 subjects, two doses at a four-week interval in another 10 subjects, and three doses at a two-week interval in the remaining 10 subjects).
- The company plans to release preliminary results that comprehensively evaluate the outcomes of the Phase I/II trials conducted at Osaka City University Hospital and Osaka University Hospital in Q4 FY12/20. Based on these results, it plans to conduct larger clinical studies.

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).

The company is taking following steps to rectify the situation:

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 oligo DNA 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. 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 oligo DNA 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 nucleic acid medicine (NF-κB decoy oligo 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.

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 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 around Q4 FY12/20.
- In February 2020, enrollment of 25 patients was completed in a Phase Ib clinical trial in the US of NF-κB decoy oligo DNA for discogenic low 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 around Q4 FY12/20.

▷ In January 2020, a US-based late Phase II 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 oligo DNA indicated for discogenic low back pain

▷ The company is progressing with the development of NF-κB decoy oligo DNA to treat low back pain including discogenic low 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 oligo DNA. 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 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 Osaka University Hospital to determine optimal vaccination intervals and frequency. Preliminary results of the Phase I/II clinical trials at Osaka University Hospital and Osaka City University Hospital are scheduled to be released in Q4 FY12/20.

- Phase I/II clinical trials at 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 oligo DNA 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. 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 oligo DNA 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 nucleic acid medicine (NF-κB decoy oligo 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 around Q4 FY12/20.

▷ In February 2020, enrollment of 25 patients was completed in a Phase Ib clinical trial in the US of NF-κB decoy oligo DNA for discogenic low 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 around Q4 FY12/20.

▷ In January 2020, a US-based late Phase II 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 oligo DNA indicated for discogenic low back pain

- The company is progressing with the development of NF-κB decoy oligo DNA to treat low back pain including discogenic low 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 around Q4 FY12/20.
- AnGes has been conducting research on next-generation decoys to follow NF-κB decoy oligo DNA. 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 around Q4 FY12/20.

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 oligo DNA 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. 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 nucleic acid medicine (NF-κB decoy oligo 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.

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
December 2020	Made Emendo a subsidiary

News and topics

February 2021

On February 17, 2021, the company announced its progress with the development of NF-κB decoy oligo DNA for patients with chronic discogenic low back pain.

The company released the (preliminary) results of its late Phase I clinical trial for NF-κB decoy oligo DNA targeting discogenic low back pain (development code: AMG0103). The results were favorable, and the company plans to advance to the Phase II clinical trial.

AMG0103 was intradiscally injected once to 25 men and women (aged 32–70; mean age of 53.5 years) with discogenic low back pain in a double-blind, randomized study (observation period of six months). The dose was well-tolerated, and no patients had serious adverse events, validating the safety of the treatment. An exploratory evaluation of the data also confirmed the efficacy of the treatment, with patients experiencing a notable and sustained reduction in low back pain. Based on the results of the 12-month study, the company intends to advance to the Phase II study.

Safety-related results

The primary endpoint of the late Phase I clinical trial was to assess the safety and tolerability of AMG0103 in adults with discogenic low back pain through 12 months following treatment. In the study, patients with discogenic low back pain received an injection of AMG0103 (increasing doses of 0.3mg, 3.0mg, and 10.0mg) or a placebo directly into the intervertebral disc in an outpatient setting, and the safety of the treatment was examined. Based on the data through six months (Part 1 of the study), there was no evidence of clinically relevant renal, hepatic, or hematologic dysfunction. Some patients experienced a transient adverse event in the immediate post-injection period, but there were no adverse events that were severe or caused patients to withdraw from the study. The company plans to report additional results when the 12-month efficacy data are available.

Efficacy-related results

Efficacy was assessed through measurements of low back pain, leg pain, and several instruments to measure low back pain-related disability in everyday life, psychological burden, and quality of life (QOL) such as the Patient Global Impression of Change (PGI-C), the Roland-Morris Disability Questionnaire (RMDQ), and the Oswestry Disability Index.

Administration of AMG0103 resulted in a dose-dependent reduction in low back pain measured on a 100mm visual analogue scale (VAS) throughout the six-month study period (Part 1). All doses showed improvement compared to the placebo control group, but the treatment group receiving a high 10mg dose saw a reduction of low back pain of almost 50% 14 days after treatment. Low back pain in this group continued to decline, reaching a 71% reduction from baseline at six months, which was significantly better (p=0.033) than the placebo control group that showed just a 15% improvement. The company plans to complete its analysis when the 12-month data becomes available, and report on those results.

As for improvements in low back pain-related disability in everyday life, psychological burden, and QOL, the PGI-C score (measured from 1 to 7 on an ordinal scale based on self-evaluations of patients) revealed a dose-dependent improvement from baseline at six months, and was numerically superior to the placebo control group for all treatment groups. In the 10mg arm, the improvement was almost three points better than that observed in the control group, and was also statistically significant (p=0.001). The PGI-C instrument quantifies how patients regard their improvement from baseline. Using the seven-point scale, a three-point difference between any two groups is clinically meaningful. In addition to this outcome, all three treatment arms showed a 20–50% improvement in RDMQ score (an index that measures low back pain-related disability in everyday life) at six months, while the control group declined more than 15% from baseline.

About AMG0103

AMG0103 is a synthetic NF-kB oligonucleotide decoy that binds the NF-kB transcription factor to suppress the release of inflammatory cytokines (physiologically active substances that are secreted by cells). It has the potential to become an effective therapeutic agent for the treatment of various disorders caused by excessive inflammatory reactions and immune responses. At present, the only pharmaceutical therapy approved by the US FDA for chronic discogenic low back pain is symptomatic treatment by anti-inflammatory analgesics. AMG0103 differs from existing analgesics because it exerts its effect by inhibiting the presumptive causative agent. The results of basic scientific research suggest that local injection of AMG0103 is also effective in suppressing the progression of intervertebral disc degeneration, which cannot be treated with existing therapeutic agents.

On February 15, 2021, the company announced the booking of goodwill, non-operating expenses, and an extraordinary gain.

In FY12/20, the company booked goodwill, non-operating expenses, and an extraordinary gain as outlined below.

Goodwill

As disclosed on December 15, 2020, the company made former equity-method affiliate Emendo Biotherapeutics Inc. a consolidated subsidiary on the same day. Accordingly, it booked goodwill of JPY22.7bn in FY12/20.

Non-operating expenses

Based on an earnings report by former equity-method affiliate Emendo, AnGes booked equity-method investment losses of JPY645mn in Q4 (October–December 2020) and JPY909mn in FY12/20.

Additionally, the company incurred share issue expenses of JPY50mn in Q4 and JPY118mn in FY12/20 due to license tax registration and brokerage commissions associated with the exercise of share subscription rights.

Extraordinary gain

By making equity-method affiliate Emendo a consolidated subsidiary, the company booked a gain of JPY2.4bn on the step acquisition of shares in FY12/20.

On February 4, 2021, the company announced the results of the Phase I/IIa clinical trial of a DNA vaccine for hypertension being conducted in Australia.

The company evaluated the initial results of the Phase I/IIa clinical trial of its DNA vaccine for hypertension being conducted in Australia, after completing the post-vaccination observation period. No serious adverse effects were found, and there were no safety issues. Further, the results confirmed that the investigational vaccine induced the production of antibodies against angiotensin II. AnGes intends to continue conducting trials to evaluate the safety, immunogenicity, and efficacy of the investigational vaccine.

Australia-based Phase I/IIa clinical trial of a DNA vaccine for hypertension

- ▷ Study overview: A double-blind, placebo-controlled, comparative study conducted in patients with hypertension whose blood pressure needs to be controlled using high doses of angiotensin II receptor blocker, with the aim of evaluating the safety, immunogenicity, and efficacy of the investigational vaccine.
- ▷ Number of patients enrolled: 24 (18 were inoculated with the DNA vaccine for hypertension, and six received placebo injections)
- ▷ Observation period: 12 months

December 2020

On December 18, 2020, the company announced that the first patient has been dosed in the Phase I clinical trial of AV-001, an investigational drug for the of COVID-19.

AnGes commenced the Phase I clinical trial of AV-001, an investigational COVID-19 drug under joint development with Vasomune Therapeutics Inc., in healthy adult participants in the US. AV-001 is a first-in-class drug targeting the Tie2 tyrosine kinase receptor, an important regulatory protein in maintaining normal vascular functions. The company said that from the results of preclinical studies, it expects AV-001 to have the potential to improve the survival rate of hospitalized COVID-19 patients and shorten their lengths of hospital stays.

First-in-class (breakthrough) drugs are new drugs that are especially unique and highly effective, and have chemical structures that are distinctive from those of existing drugs from the backbone; these innovative drugs are expected to change existing treatment regimens.

The Phase I clinical trial is a double-blind, placebo-controlled study in healthy adult participants. The study will evaluate the safety, tolerability, and pharmacokinetics of single-dose and continuous administration of AV-001. If the company obtains favorable results from the Phase I trial as well as from subsequent phases of clinical trials, it will consider applying for the Emergency Use Authorization (EUA) to the U.S. Food and Drug Administration.

AV-001: AV-001 is a novel investigational drug that targets the Tie2 receptor, a transmembrane protein mostly expressed on the surface of vascular endothelial cells. AV-001 restores normal vascular function and endothelial stability through activation of the Tie2 angiopoietin pathway. Vascular dysfunction contributes to the underlying disease pathophysiology in patients with COVID-19 and acute respiratory distress syndrome (ARDS),

especially in patients with preexisting vascular comorbidities such as hypertension, diabetes, and obesity. Recent findings suggest that SARS-CoV-2 infects pulmonary endothelial cells and causes microvascular leaks, contributing to the initiation and propagation of respiratory distress and ARDS in COVID-19 patients by altering blood vessel barrier integrity and promoting a coagulated state, inducing vascular inflammation and mediating inflammatory cell migration.

In preclinical studies involving a lethal RNA virus infection animal model of influenza/ARDS, AV-001 has been shown to stabilize the vasculature by enhancing endothelial cell stability, restoring normal barrier defense, and blocking vascular leak. AV-001 monotherapy also significantly improved survival and lung function compared to the untreated control group and showed enhanced efficacy in combination with antiviral therapy. AV-001 is being developed as a treatment for moderate-to-severe COVID-19 and ARDS.

On December 8, 2020, the company announced that the first participant has been dosed in the Phase II/III clinical trial of its DNA vaccine against COVID-19.

As disclosed in the November 2020 release, the Phase II/III clinical trial of the DNA vaccine against COVID-19 the company is currently developing has been reviewed and approved by the Institutional Review Boards (IRBs) of the clinical trial facilities, and today the company announced that the first participant has been dosed. In the trial, the company will vaccinate 500 participants to evaluate the safety and immunogenicity of the vaccine administered in a predetermine dose and dosing regimen.

Summary of Phase II/III clinical trial of the DNA vaccine against COVID-19

- ▷ Summary: Randomized, double-blind, and placebo-controlled trial aimed at assessing the safety and immunogenicity of the investigational vaccine (an intramuscular injection) in healthy adult volunteer trial participants
- ▷ Target number of trial participants: 500 (dose of 2.0mg; 250 participants inoculated twice at two-week intervals and 250 participants inoculated twice at four-week intervals; 50 participants in each group will receive a placebo)
- ▷ Number of trial facilities: Eight in the Kansai and Kanto regions
- ▷ Vaccination period: From dosing of the first participant to around March 2021 (the trial is scheduled to last till March 2022)

November 2020

On November 20, 2020, the company announced a Phase II/III clinical trial for a DNA vaccine against COVID-19.

The company will begin a Phase II/III clinical trial for the DNA vaccine against COVID-19 it is currently developing once the study protocol and other related materials are reviewed and approved by the Institutional Review Boards (IRBs) of the clinical trial facilities. The clinical trial will further evaluate the safety and immunogenicity of the vaccine at the dosage and regimen applied in Phase I/II clinical trials by increasing the sample size of trial participants. After a final decision is made regarding the dosage and regimen, the company will conduct a large-scale Phase III placebo-controlled clinical trial to verify the level of effectiveness at which the vaccine can prevent COVID-19.

Summary of Phase II/III clinical trial of the DNA vaccine against COVID-19

- ▷ Summary: Randomized, double-blind, and placebo-controlled trial aimed at assessing the safety and immunogenicity of the investigational vaccine (an intramuscular injection) in healthy adult volunteer trial participants
- ▷ Target number of trial participants: 500 (dose of 2.0mg; 250 participants inoculated twice at two-week intervals and 250 participants inoculated twice at four-week intervals; 50 participants in each group will receive a placebo)
- ▷ Number of trial facilities: Eight in the Kansai and Kanto regions
- ▷ Trial period: November 2020–March 2022 (inoculations are scheduled to be complete by sometime in March 2021. The trial period includes a follow-up span of 52 weeks after the inoculations are performed)

On November 13, 2020, the company announced the start of US clinical trials for AV-001, a treatment for COVID-19 infections under joint development with Vasomune Therapeutics Inc.

AV-001 is a Tie2 tyrosine kinase receptor agonist under joint development with Canada-based biomedical company Vasomune Therapeutics. The FDA approved the start of US clinical trials for investigational new drug (IND) AV-001 as a treatment for patients diagnosed with pneumonia stemming from moderate-to-severe COVID-19 infections.

AV-001

AV-001 is a novel investigational drug that targets the Tie2 receptor, a transmembrane protein mostly expressed on the surface of vascular endothelial cells. AV-001 restores normal vascular function and endothelial stability through activation of the Tie2 angiopoietin pathway. Vascular dysfunction contributes to the underlying disease pathophysiology in patients with COVID-19 and acute respiratory distress syndrome (ARDS), especially in patients with preexisting vascular comorbidities such as hypertension, diabetes, and obesity. Recent findings suggest that SARS-CoV-2 infects pulmonary endothelial cells and causes microvascular leaks, contributing to the initiation and propagation of respiratory distress and ARDS in COVID-19 patients by altering blood vessel barrier integrity and promoting a coagulated state, inducing vascular inflammation and mediating inflammatory cell migration.

In preclinical studies involving a lethal RNA virus infection animal model of influenza/ARDS, AV-001 has been shown to stabilize the vasculature by enhancing endothelial cell stability, restoring normal barrier defense, and blocking vascular leak. AV-001 monotherapy also significantly improved survival and lung function compared to the untreated control group and showed enhanced efficacy in combination with antiviral therapy. AV-001 is being developed as a treatment for moderate-to-severe COVID-19 and ARDS.

On November 9, 2020, the company announced the acquisition of Emendo Biotherapeutics Inc. and issue of new shares via third-party allocation.

At a meeting of the Board of Directors held on the same day, the company decided to acquire a maximum of 100% of the issued shares in equity-method affiliate Emendo Biotherapeutics Inc. and make it a subsidiary. Emendo is developing genome editing technology that can repair and remove genetic abnormalities in cells that cause serious diseases and disorders.

The company also decided to issue new shares via third-party allocation to provide some of the consideration for a merger between the company's subsidiary and Emendo as part of the purchase.

Emendo was established in December 2015 by scientists from the Weizmann Institute of Science, a leading Israeli multidisciplinary research organization. While Emendo is headquartered in the US, most of its research and development occurs in Israel. Since its inception, Emendo has been developing genome editing technology that uses a CRISPR-Cas9 system. It is conducting R&D into next-generation genome editing technology that will help resolve issues in existing technology in that field and enable safer applications in healthcare.

> Known nucleases that cut a specific DNA sequence include zinc-finger nucleases (ZFN), transcription activator-like effector nuclease (TALEN), and clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9. Emendo Biotherapeutics uses CRISPR-Cas9 genome editing technology. CRISPR-Cas9 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.

Overview of company to be acquired (Emendo)

- Establishment: December 2015
- Capital and capital reserve: USD68mn (as of June 2020)
- Business: Development of genome editing technology to repair and remove genetic abnormalities in cells that cause serious diseases and disorders
- AnGes shareholding: 40.04%

Key financial statistics in latest three years

Fiscal year	FY12/17	FY12/18	FY12/19
Net assets	USD1.5mn (Approx. JPY159mn)	USD272,000 (Approx. JPY29mn)	-USD6.2mn (Approx. -JPY653mn)
Total assets	USD1.9mn (Approx. JPY194mn)	USD753,000 (Approx. JPY79mn)	USD5.7mn (Approx. JPY598mn)
Sales	-	-	-
Operating loss	USD3.0mn (Approx. JPY319mn)	USD3.2mn (Approx. JPY337mn)	USD5.4mn (Approx. JPY567mn)
Net loss attributable to owners of parent	USD3.1mn (Approx. JPY325mn)	USD3.3mn (Approx. JPY345mn)	USD6.8mn (Approx. JPY718mn)

The acquisition will take place using a subsidiary newly established in the US by the company for that purpose. AnGes will issue common stock to the subsidiary which will become the absorbed company in a merger with Emendo, which will be the surviving company. As consideration for the merger, some investors in Emendo will receive common stock in AnGes, and remaining investors in Emendo will receive cash owned by Emendo.

Shares in Emendo were valued at roughly USD295mn (approx. JPY31.0bn) for the acquisition. Excluding the value of shares held by AnGes worth about USD103mn (approx. JPY10.8bn), Emendo investors in shares and other financial instruments (common stock, class shares, exercisable warrants, and options) will receive merger consideration for the remainder of roughly USD192mn (approx. JPY20.2bn).

The number of common stock planned to be issued to the allottee as consideration for the merger will be calculated by dividing USD129mn (approx. JPY13.6bn) by the volume weighted average price of the company's common stock in ordinary trading on the Tokyo Stock Exchange over 60 trading days ending three trading days before the scheduled acquisition date (planned for December 15, 2020).

Number of shares to be acquired, acquisition price, and shareholdings before and after acquisition

Share ownership before acquisition	Series B-1 preferred stock: 3,761,000 Series B-3 preferred stock: 342,000 (No. of voting rights: 4,102,000, approx. 40.04% of total voting rights)
Shares to be acquired	Common stock: Maximum of 100 shares (No. of voting rights: Maximum of 100; maximum 100% of total voting rights) All Series B-1 and Series B-3 preferred stock outstanding before the acquisition to be extinguished
Acquisition price	Common stock: Approx. USD129mn (JPY13.6bn) equivalent Advisory expenses (estimate): JPY650mn Total (estimate): Approx. JPY14.2bn Some investors in Emendo will receive cash totaling approx. USD59mn (JPY6.2bn) from Emendo in consideration for the merger
Shareholding after acquisition	Common stock: Maximum of 100 shares (No. of voting rights: Maximum of 100; maximum 100% of total voting rights)

October 2020

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.

September 2020

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 consideration, 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

August 2020

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 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 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 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.

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 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 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

Major shareholders

Top shareholders	Shares held	Shareholding ratio
MLPFS CUSTODY ACCOUNT	6,610,215	4.96%
MORGAN STANLEY SMITH BARNEY LLC CLIENTS FULLY PAID SEG ACCOUNT	2,738,938	2.05%
Shionogi & Co., Ltd.	1,186,800	0.89%
J.P. MORGAN BANK LUXEMBOURG S.A.381572	752,100	0.56%
Ryuichi Morishita	691,600	0.51%
Custody Bank of Japan, Ltd. (Trust 7)	483,600	0.36%
Nomura Securities Co., Ltd.	467,719	0.35%
SBI Securities Co., Ltd.	376,510	0.28%
Naoki Magaribuchi	330,000	0.24%
J.P. Morgan Securities plc Director Andrew J. Cox	290,179	0.21%
SUM	13,927,661	10.46%

Source: Shared Research based on company data
(As of December 31, 2020. 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
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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
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COMSYS Holdings Corporation
COTA CO.,LTD.
CRE, Inc.
CREEK & RIVER Co., Ltd.
Daiichi Kigenso Kagaku Kogyo Co., Ltd.
Daiki Axis Co.,Ltd.
Daiseki Co., Ltd.
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DIC Corporation
Digital Arts Inc.
Digital Garage Inc.
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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.
Gamecard-Joyco Holdings, Inc.
GameWith, Inc.
GCA Corporation
Good Com Asset Co., Ltd.
Grandy House Corporation
GiG Works Inc.
Hakuto Co., Ltd.
Hamee Corp.
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HENNGE K.K.
Hosokawa Micron Corporation
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i-mobile Co.,Ltd.
Inabata & Co., Ltd.
Infocom Corporation
Infomart Corporation
Intelligent Wave, Inc.
ipet Insurance CO., Ltd.
Itochu Enex Co., Ltd.
ItoKuro Inc.
JAFCO Co.,Ltd.
JMDC Inc.
JSB Co., Ltd.
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J Trust Co., Ltd
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LUCKLAND CO., LTD.
Marumae Co., Ltd.
MATSUI SECURITIES CO., LTD.
Media Do Co., Ltd.
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MedPeer,Inc.
Mercuria Investment Co., Ltd.
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Monex Goup Inc.
MORINAGA MILK INDUSTRY CO., LTD.
Mortgage Service Japan Limited.
MRT Inc.
NAGASE & CO., LTD
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NanoCarrier Co., Ltd.
Net Marketing Co., Ltd.
Net One Systems Co.,Ltd.
Nichi-Iko Pharmaceutical Co., Ltd.
Nihon Denkei Co., Ltd.
Nippon Commercial Development Co., Ltd.
Nippon Koei Co., Ltd.
NIPPON PARKING DEVELOPMENT Co., Ltd.
NIPRO CORPORATION
Nisshinbo Holdings Inc.
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ONWARD HOLDINGS CO.,LTD.
Pan Pacific International Holdings Corporation
PARIS MIKI HOLDINGS Inc.
PCA CORPORATION
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P3, inc.
QB Net Holdings Co., Ltd.
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Raysum Co., Ltd.
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TAIYO HOLDINGS CO., LTD.
Takashimaya Company, Limited
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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
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TOYOBO CO., LTD.
Toyo Ink SC Holdings Co., Ltd
Toyo Tanso Co., Ltd.
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TSURUHA Holdings
VISION INC.
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