AnGes / 4563

COVERAGE INITIATED ON: 2014.08.28
LAST UPDATE: 2019.02.01

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

Executive summary

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

- Since the company's establishment in 1999, HGF gene therapy drug (a new drug candidate; regenerates blood vessels by medicating HGF—hepatocyte growth factor—genes) has been the mainstay pipeline drug for AnGes.
- The company has continued to post operating losses, with the exception of FY12/01 prior to its public listing. By February 2018, the company had not brought to market any self-developed drugs. Sales are limited to development cooperation payments and milestone payments from partner pharmaceutical companies, plus Naglazyme sales. Naglazyme, developed by US-based BioMarin Pharmaceutical, is a drug for treating MPS VI, an inherited life-threatening lysosomal storage disorder caused by a deficiency of the lysosomal enzyme arylsulfatase.
- The efficacy of HGF gene therapy drug for critical limb ischemia (CLI) was proved in a Phase III trial in Japan in 2007. In 2008, the company applied for approval to market the drug in Japan, but dropped the application in 2010, after the Pharmaceuticals and Medical Devices Agency made a request for additional clinical trial data. AnGes started investigator-initiated clinical research in October 2014 and ended the observation period of the sixth of the six target cases in August 2017. In January 2018, the company submitted an application to the Japanese Ministry of Health, Labour and Welfare for the approval to manufacture and sell a regenerative medicine product, namely its HGF gene therapy drug for the treatment of severe CLI, combining the outcome of the investigator-initiated clinical research and existing clinical data. It aims to obtain the approval of the drug in 2019 using the conditional time-limited approval system.
- The company also commenced a joint global Phase III trial, mainly in the US, for the HGF gene therapy drug for the treatment of severe CLI in October 2014. Regarding this trial, however, the company in June 2016 announced a change in its development strategy. It now aims to prevent further delays in its application process and to reduce trial-related expenses by ensuring that the timing of the company's original plan is maintained by reviewing evaluation criteria. As of February 2018, the company was compiling a clinical trial plan in the US.
- AnGes estimates the US markets for the drug at about USD5.0bn. It is possible for sales to reach a maximum of about JPY100.0bn. Shared Research assumes that the company will receive royalties equating to 30–40% of sales.

Performance

- In FY12/18, AnGes booked operating revenues of JPY610mn (+67.1% YoY), an operating loss of JPY3.1bn (operating loss of JPY3.3bn in FY12/17), recurring loss of JPY3.1bn (recurring loss of JPY3.3bn in FY12/17), and net loss attributable to parent company shareholders of JPY3.0bn (net loss attributable to parent company shareholders of JPY3.8bn in FY12/17).
- For FY12/19, the company is forecasting operating revenues of JPY335mn (operating revenues of JPY610mn in FY12/18), an operating loss of JPY2.8bn (operating loss of JPY3.1bn in FY12/18), recurring loss of JPY2.8bn (recurring loss of JPY3.1bn in FY12/18), and net loss attributable to parent company shareholders of JPY2.8bn (net loss attributable to parent company shareholders of 3.0bn in FY12/18).
- When AnGes released its FY12/18 earnings results, it also withdrew two of the objectives contained in its "2025 Vision" announced in February 2015. These objectives were to move into the black in 2019 and to achieve sales of JPY50bn or more in 2025. Clinical trials of its HGF gene therapy drug in the US have not proceeded as anticipated at the time the company formulated 2025 Vision.

Strengths and weaknesses

Strengths include the proven efficacy of the company's HGF gene therapy drug, relationships with partner pharmaceutical companies, and the potential to capitalize on the conditional time-limited approval system under the amended Pharmaceutical Affairs Law of Japan. Weaknesses include a lack of capital, the absence of a marketed self-developed drug and heavy dependence on its HGF gene therapy drug (see Strengths and weaknesses).

Key financial data

Income statement (JPYmn)	FY12/09 Cons.	FY12/10 Cons.	FY12/11 Cons.	FY12/12 Cons.	FY12/13 Cons.	FY12/14 Cons.	FY12/15 Cons.	FY12/16 Cons.	FY12/17 Cons.	FY12/18 Cons.	FY12/19 Est.
Operating revenues	**586**	**287**	**243**	**445**	**491**	**910**	**430**	**514**	**365**	**610**	**335**
YoY	-38.4%	-51.0%	-15.2%	82.6%	10.5%	85.2%	-52.7%	19.6%	-29.0%	67.1%	-45.1%
Operating profit	**-2,611**	**-2,010**	**-2,101**	**-1,785**	**-1,363**	**-2,274**	**-4,172**	**-4,763**	**-3,289**	**-3,065**	**-2,800**
YoY	-	-	-	-	-	-	-	-	-	-	-
OPM	-	-	-	-	-	-	-	-	-	-	-
Recurring profit	**-2,784**	**-1,911**	**-1,791**	**-1,716**	**-1,383**	**-2,395**	**-4,089**	**-4,847**	**-3,307**	**-3,096**	**-2,800**
YoY	-	-	-	-	-	-	-	-	-	-	-
RPM	-	-	-	-	-	-	-	-	-	-	-
Net income	**-2,921**	**-1,967**	**-1,815**	**-1,708**	**-1,410**	**-2,369**	**-4,143**	**-4,777**	**-3,765**	**-2,997**	**-2,800**
YoY	-	-	-	-	-	-	-	-	-	-	-
Net margin	-	-	-	-	-	-	-	-	-	-	-
Per share data											
Shares issued (year-end; '000)	23,598	23,646	24,467	26,226	31,268	53,544	53,544	70,631	79,724	97,981	
EPS	-124.0	-83.3	-74.6	-67.7	-46.9	-62.1	-74.5	-75.3	-49.4	-34.5	-28.6
EPS (fully diluted)	-	-	-	-	-	-	-	-	-	-	
Dividend per share	-	-	-	-	-	-	-	-	-	-	
Book value per share	271.7	175.1	125.8	60.3	107.9	142.4	73.8	54.7	42.3	78.4	
Balance sheet (JPYmn)											
Cash and cash equivalents	5,047	3,053	1,576	355	2,295	6,017	2,075	996	1,148	5,785	
Total current assets	**5,935**	**4,143**	**2,635**	**1,342**	**3,305**	**7,594**	**4,243**	**3,619**	**3,434**	**7,542**	
Tangible fixed assets	61	72	62	45	23	28	76	76	-	47	
Investments and other assets	954	633	1,050	770	506	508	382	789	530	461	
Intangible fixed assets	212	157	142	103	70	54	51	55	-	-	
Total assets	**7,162**	**5,004**	**3,889**	**2,260**	**3,904**	**8,184**	**4,752**	**4,539**	**3,964**	**8,051**	
Accounts payable	49	98	60	67	42	207	247	389	201	113	
Short-term debt	515	488	417	331	218	116	83	1	1	686	
Total current liabilities	**649**	**716**	**601**	**507**	**345**	**423**	**482**	**631**	**318**	**292**	
Total fixed liabilities	**-**	**-**	**17**	**15**	**15**	**26**	**49**	**39**	**24**	**25**	
Total liabilities	**649**	**716**	**618**	**522**	**361**	**449**	**531**	**670**	**342**	**316**	
Net assets	**6,513**	**4,288**	**3,271**	**1,739**	**3,544**	**7,734**	**4,221**	**3,869**	**3,622**	**7,734**	
Total interest-bearing debt	-	-	-	-	-	-	-	-	-	-	
Cash flow statement (JPYmn)											
Cash flows from operating activities	-2,225	-1,843	-1,706	-1,631	-1,457	-2,704	-4,599	-4,984	-2,991	-2,523	
Cash flows from investing activities	-531	952	768	7	-27	-52	-69	-830	227	-123	
Cash flows from financing activities	12	12	368	387	3,390	6,427	717	4,793	2,916	7,283	
Financial ratios											
ROA (RP-based)	-	-	-	-	-	-	-	-	-	-	
ROE	-	-	-	-	-	-	-	-	-	-	
Equity ratio	90.9%	85.7%	84.1%	76.9%	90.8%	94.5%	88.8%	85.2%	91.4%	96.1%	

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

Recent updates

Highlights

On **February 1, 2019,** AnGes, Inc. announced earnings results for full year FY12/18; see the results section for details.

On **December 25, 2018,** the company announced a change regarding the domestic sales agreement of Naglazyme®, a drug for treating mucopolysaccharidosis VI (MPS VI).

In January 2007, the company entered into an agreement with US-based BioMarin Pharmaceutical Inc. (BioMarin) for the development and sales of Naglazyme® 5mg intravenous solution in Japan, and began distributing the product from April 2008. The contract period of this agreement is now slated to end on March 31, 2019, and the company has decided to transfer its rights (approval for domestic manufacture and sales, and distribution) to this product to BioMarin Pharmaceutical Japan K.K., BioMarin's subsidiary in Japan. AnGes plans to continue selling the product after end March 2019 until its inventory is cleared.

According to AnGes, the conclusion of the subject contract period will have no impact on FY12/18 earnings. The company is in the process of formulating its forecasts for FY12/19, which it plans to disclose together with the earnings results for full-year FY12/18.

On **November 12, 2018,** Shared Research updated the report following interviews with the company.

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

Trends and outlook

Quarterly trends and results

Quarterly performance

Cumulative	FY12/17				FY12/18				FY12/18	
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	% of FY	FY Est.
Operating revenues	83	169	255	365	74	176	276	610	101.7%	600
YoY	0.1%	-0.3%	-0.4%	-29.0%	-11.4%	4.0%	8.2%	67.1%		64.3%
Operating expenses	1,119	1,872	2,999	3,654	664	1,381	2,519	3,675		
YoY	-11.7%	-36.9%	-25.4%	-30.8%	-40.7%	-26.2%	-16.0%	0.6%		
Operating profit	-1,036	-1,703	-2,743	-3,289	-590	-1,205	-2,242	-3,065	-	-3,100
YoY	-	-	-	-	-	-	-	-		-
OPM	-	-	-	-	-	-	-	-		-
Recurring profit	-1,031	-1,699	-2,757	-3,307	-587	-1,206	-2,260	-3,096	-	-3,100
YoY	-	-	-	-	-	-	-	-		-
RPM	-	-	-	-	-	-	-	-		-
Net income	-1,512	-2,300	-3,359	-3,765	-537	-1,147	-2,203	-2,997	-	-3,100
YoY	-	-	-	-	-	-	-	-		-
Net margin	-	-	-	-	-	-	-	-		-

Quarterly	FY12/17				FY12/18			
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Operating revenues	83	86	86	110	74	102	100	334
YoY	0.1%	-0.8%	-0.5%	-57.4%	-11.4%	19.0%	16.5%	203.8%
Operating expenses	1,119	753	1,127	655	664	717	1,137	1,157
YoY	-11.7%	-55.7%	7.2%	-48.0%	-40.7%	-4.7%	0.9%	76.6%
Operating profit	-1,036	-667	-1,041	-545	-590	-615	-1,037	-823
YoY	-	-	-	-	-	-	-	-
OPM	-	-	-	-	-	-	-	-
Recurring profit	-1,031	-668	-1,058	-550	-587	-619	-1,053	-837
YoY	-	-	-	-	-	-	-	-
RPM	-	-	-	-	-	-	-	-
Net income	-1,512	-788	-1,060	-405	-537	-610	-1,055	-794
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 (revenue and cost breakdown)

	FY12/17				FY12/18			
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Operating revenues	83	169	255	365	74	176	276	610
YoY	0.1%	-0.3%	-0.4%	-29.0%	-11.4%	4.0%	8.2%	67.1%
Sales of goods	83	169	255	365	74	176	276	383
YoY	1.7%	1.1%	0.7%	5.3%	-11.4%	4.1%	8.3%	4.9%
R&D revenues	0	0	0	0	-	-	-	227
YoY	-97.3%	-96.1%	-96.5%	-99.9%	-	-	-	-
Operating expenses	1,119	1,872	2,999	3,654	664	1,381	2,519	3,675
YoY	-11.7%	-36.9%	-25.4%	-30.8%	-40.7%	-26.2%	-16.0%	0.6%
Cost of sales	40	82	124	178	36	86	136	188
YoY	-4.1%	-4.0%	-3.9%	2.0%	-10.7%	5.0%	9.2%	5.7%
Cost ratio	48.6%	48.6%	48.7%	48.8%	49.0%	49.0%	49.1%	49.2%
R&D expenses	875	1,392	2,182	2,600	403	804	1,650	2,540
YoY	-11.7%	-42.2%	-31.6%	-37.9%	-54.0%	-42.3%	-24.4%	-2.3%
Salaries and allowances	-	188	-	364	-	136	-	245
YoY	-	-20.8%	-	-17.4%	-	-27.7%	-	-32.7%
Outsourcing expenses	-	825	-	1,370	-	269	-	1,174
YoY	-	-50.6%	-	-50.5%	-	-67.5%	-	-14.3%
Commission fees	-	124	-	225	-	116	-	249
YoY	-	49.0%	-	12.2%	-	-6.3%	-	10.6%
SG&A expenses	203	398	692	876	225	491	733	947
YoY	-13.1%	-15.6%	-0.5%	-4.3%	10.8%	23.6%	6.0%	8.2%
Operating profit	-1,036	-1,703	-2,743	-3,289	-590	-1,205	-2,242	-3,065
YoY	-	-	-	-	-	-	-	-

	FY12/17				FY12/18			
(JPYmn)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Operating revenues	83	86	86	110	74	102	100	334
YoY	0.1%	-0.8%	-0.5%	-57.4%	-11.4%	19.0%	16.5%	203.8%
Sales of goods	83	86	86	110	74	102	100	107
YoY	1.7%	0.6%	0.0%	17.5%	-11.4%	19.1%	16.5%	-3.0%
R&D revenues	0	0	0	0	-	-	-	227
YoY	-97.3%	-94.6%	-98.8%	-100.0%	-	-	-	-
Operating expenses	1,119	753	1,127	655	664	717	1,137	1,157
YoY	-11.7%	-55.7%	7.2%	-48.0%	-40.7%	-4.7%	0.9%	76.6%
Cost of sales	40	42	42	54	36	50	49	52
YoY	-4.1%	-3.8%	-3.9%	19.2%	-10.7%	20.1%	17.6%	-2.5%
Cost ratio	48.6%	48.6%	48.8%	49.0%	49.0%	49.1%	49.2%	49.2%
R&D expenses	875	517	791	418	403	401	846	890
YoY	-11.7%	-63.6%	1.0%	-58.1%	-54.0%	-22.4%	7.0%	113.1%
SG&A expenses	203	195	294	184	225	266	242	214
YoY	-13.1%	-18.2%	31.2%	-16.1%	10.8%	36.9%	-17.8%	16.6%
Operating profit	-1,036	-667	-1,041	-545	-590	-615	-1,037	-823
YoY	-	-	-	-	-	-	-	-

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

Full-year FY12/18 results

Operating revenues rose 67.1% YoY to JPY610mn.

▷ Operating revenues included JPY383mn in product sales (+4.9% YoY) and JPY227mn in R&D revenue (JPY0mn in FY12/17). The company booked upfront payments and development support fees from partner companies as R&D revenue. It also booked sales of Naglazyme, a drug for mucopolysaccharidosis VI (MPS VI).

Operating loss was JPY3.1bn (operating loss of JPY3.3bn in FY12/17).

▷ Operating expenses were JPY3.7bn (+0.6% YoY). The breakdown is as follows: CoGS of JPY188mn (+5.7% YoY), R&D expenses of JPY2.5bn (-2.3% YoY), and SG&A expenses of JPY947mn (+8.2% YoY).

▷ CoGS increased to JPY188mn (+5.7% YoY) due to an increase in product sales.

▷ R&D expenses fell to JPY2.5bn (-2.3% YoY), owing to a decrease in expenses for global joint Phase III trials for its HGF gene therapy drug, which lowered outsourcing expenses by JPY196mn. Salaries and other allowances also decreased by JPY119mn, primarily due to job cuts at a subsidiary. In FY12/17, the company booked stock-based compensation expenses worth JPY168mn due to granting share subscription rights to employees, but none in FY12/18. Research material costs increased by JPY403mn as the company reassessed the value of, and disposed of, raw materials.

▷ SG&A expenses were up 8.2% YoY at JPY947mn. Commissions paid increased to JPY53mn due to increases in consulting expenses, and consumables expenses rose JPY26mn with the purchase of fixtures and fittings on relocation of the Tokyo branch office. Taxes and dues increased by JPY50mn on an increase in the portion of corporate tax determined based on the company's capital. In FY12/17, the company booked stock-based compensation expenses of JPY98mn due to granting share subscription rights to employees, while it booked stock-based compensation expenses of JPY18mn due to granting share subscription rights to directors.

Recurring loss was JPY3.1bn (recurring loss of JPY3.3bn in FY12/17).

▷ The operating loss narrowed and there was subsidy revenue of JPY3mn, with the receipt of a grant from the Osaka Foundation for Trade & Industry. There were share issuance expenses of JPY42mn (JPY25mn in FY12/17) as shares were issued on the exercise of share subscription rights.

Net loss attributable to parent company shareholders was JPY3.0bn (net loss attributable to parent company shareholders of JPY3.8bn in FY12/17).

▷ The company booked a JPY31mn gain on sale of investment securities due to selling some of its shareholdings. It also posted a JPY62mn gain on reversal of share subscription rights as some stock options had been lapsed due to right holders leaving the company.

▷ There were no extraordinary losses in FY12/18, whereas the company booked an impairment loss of JPY112mn and a valuation loss on investment securities of JPY476mn in FY12/17.

▷ The company booked an JPY11mn refund of income taxes due to tax credits for R&D expenditure at its US subsidiary.

Main pipeline progress

HGF gene therapy drug to treat CLI

▷ Regarding the development of its HGF gene therapy drug for CLI, in January 2018 the company filed an application with the Ministry of Health, Labour and Welfare for approval for the manufacture and marketing of a regenerative medicine product, utilizing the conditional time-limited approval system (a new approval system aiming for the early commercialization of regenerative medicines and other drugs included under the Pharmaceuticals and Medical Devices Law, which went into force in November 2014).

▷ Based on the change of its overseas development schedule decided in June 2016 for its HFG gene therapy drug for treating CLI, AnGes is developing plans for clinical trials in the US aimed at acquiring application approval data more quickly.

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

▷ The company is progressing with the development of NF-κB decoy oligonucleotide to treat lumbar disc disorders and back pain. The company's Investigational New Drug application (IND) with the FDA was approved in April 2017. The company began Phase Ib clinical trials in February 2018 and is currently enrolling patients.

DNA vaccine to treat high blood pressure

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

Strategic alliance with Vical

▷ In December 2016, AnGes concluded a strategic business alliance with Vical, Inc. for co-development. As the first project, the two companies signed an agreement to co-develop a gene therapy drug that completely cures chronic hepatitis B in April 2017. Under the terms of the agreement, AnGes has first refusal rights on development and sales in Japan.

Alliance with Vasomune

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

Capital status

▷ At the end of FY12/18, cash and deposits totaled JPY5.8bn (JPY1.1bn at end-FY12/17). Given the shortage of capital to progress all projects, significant doubt has arisen as to the company's ability to continue as a going concern. For this reason, AnGes aims to secure partners for some projects and reduce its development spending by obtaining development cooperation payments. The company is selling Naglazyme®, a drug for treating MPS VI, but the earnings are not yet adequate to recover the full development investment.

Progressing own existing projects and expanding business base

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

▷ For the first, the company has filed for Ministry of Health, Labour and Welfare's (MHLW) approval to manufacture and sell the drug and plans to build an earnings base after obtaining approval.

▷ AnGes has started clinical trials for the second and third drugs, and plans to license-out to pharmaceutical companies at an early stage to earn upfront/milestone payments and reduce R&D spending if results are favorable.

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

Financing

The company issued the 31st share subscription rights through a third-party allocation. As of August 2018, 100% of these share subscription rights had been exercised, from which the company raised JPY5.1bn. Further, the company resolved at a board of directors meeting in September 2018 to issue its 33rd share subscription rights through a third-party allocation with Mita Securities as the allottee. The total issue price of JPY64mn had been paid in as of October 11, 2018, and the company raised JPY2.8bn from the exercise of rights as of the end of FY12/18.

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

Full-year company forecasts

(JPYmn)	FY12/17 FY Act.	FY12/18 FY Act.	FY12/19 FY Est.
Operating revenues	**365**	**610**	**335**
Operating expenses	3,654	3,675	
Cost of sales	178	188	
R&D expenses	2,600	2,540	
SG&A expenses	876	947	
Operating profit	**-3,289**	**-3,065**	**-2,800**
OPM	-	-	-
Recurring profit	**-3,307**	**-3,096**	**-2,800**
RPM	-	-	-
Net income	**-3,765**	**-2,997**	**-2,800**
Net margin	-	-	-

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

For FY12/19, AnGes is forecasting operating revenues of JPY335mn (operating revenues of JPY610mn in FY12/18), an operating loss of JPY2.8bn (operating loss of JPY3.1bn in FY12/18), recurring loss of JPY2.8bn (recurring loss of JPY3.1bn in FY12/18), and net loss attributable to parent company shareholders of JPY2.8bn (net loss attributable to parent company shareholders of 3.0bn in FY12/18).

In regard to operating revenues, the company expects contributions from sales of Naglazyme®, a drug for treating MPS VI, and milestone and royalty payments from Mitsubishi Tanabe Pharma Corporation, a partner in the development on HGF gene therapy drugs in Japan.

The company expects the operating loss, recurring loss, and net loss attributable to parent company shareholders to narrow. Although it expects an increase in SG&A expenses, including expenses related to post-marketing surveillance of HGF gene therapy drugs in Japan, it also expects a decrease in R&D expenses, as there should be no reassessment of raw materials as in FY12/18.

Medium-term outlook

When AnGes released its FY12/18 earnings results, it also withdrew two of the objectives contained in its "2025 Vision" announced in February 2015. These objectives were to move into the black in 2019 and to achieve sales of JPY50bn or more in 2025. Clinical trials of its HGF gene therapy drug in the US have not proceeded as anticipated at the time the company formulated 2025 Vision.

The following explanation is based on information prior to withdrawal of the two objectives. Shared Research plans to update this explanation following interviews with the company.

Hoping to be profitable by getting approval for HGF gene therapy drug

In February 2015, the company unveiled its "2025 Vision," which targets sales of JPY50bn or more in 2025. The first stage of this plan is to move into the black by 2019.

Pipeline drugs to boost sales

Shared Research believes that the main sources of revenue for the medium term includes milestone payments and royalty payments associated with HGF gene therapy drug for treating critical limb ischemia (CLI) overseas and in Japan.

The status of the pipeline is as follows. The main changes since the company unveiled its "2025 Vision" in February 2015 are as follows.

- For the HGF gene therapy drug for treating CLI in Japan, the company initially aimed to apply for approval during FY12/16, but delayed the application to January 2018. It aims to obtain the approval of the drug in 2019 using the conditional time-limited approval system.
- For the HGF gene therapy drug for treating CLI in the US and Europe, AnGes aimed to end Global Phase III clinical trials during FY12/18 and apply for approval in the US in FY12/18–FY12/19. However, the Global Phase III clinical trials ended in June 2016. As of February 2018, the company was wrapping up a plan for the new clinical trials in the US with a shorter period and less expenses than in the previous trials.
- Although AnGes conducted phase I/II clinical trials of the HGF gene therapy drug for lymphedema starting in October 2013, the company decided against progressing to the next stage, because data analysis did not show a significant reduction in edema volume.
- NF-κB decoy oligonucleotide for treating atopic dermatitis: AnGes announced in July 2016 that the drug did not show a statistically significant difference of efficacy in Phase III clinical trials. It plans to determine the direction it will take going forward based on a detailed data analysis of the results (stratified analysis).
- In December 2016, AnGes decided to abandon development of a PTA balloon catheter coated with NF-κB decoy oligonucleotides.
- NF-κB decoy oligonucleotide for lumbar disc disorders and back pain: the company planned to launch Phase I/II clinical trials in the US in FY12/17. The US Food and Drug Administration (FDA) approved an Investigational New Drug application (IND) in April 2017, marking the end of the preparation phase for initiating the clinical trials. AnGes started Phase Ib clinical trials for the drug in February 2018.
- Also in December 2016, the company signed an agreement to exclusively reassign all rights it possesses for the CIN therapeutic vaccine it has been developing to Morishita Jintan.
- DNA vaccine for high blood pressure: the company announced that it would move into the therapeutic DNA vaccine business in July 2016 and started Phase I/II clinical trials in Australia in April 2018.

Main pipeline development schedule

Main pipeline development schedule	FY12/16	FY12/17	FY12/18	FY12/19
HGF gene therapy drug for CLI (Japan)			Apply for conditional time-limited approval	Receive conditional time-limited approval, begin sales
HGF gene therapy drug for CLI (US)	Joint global Phase III trial Discontinued. Change in development strategy		Set up a new trial	Apply for approval in US (2019)
HGF gene therapy drug for lymphedema (Japan)	Domestic Phase I/II trials completed	Decision not to progress to the next stage		
NF-κB decoy oligonucleotide ointment for atopic dermatitis (Japan)	Domestic Phase III trial. Efficacy not proven	Decision to be based on results of stratified analysis		
Balloon catheter coated with NF-κB decoy oligonucleotide for vascular restenosis (Japan)	Decision to abandon development			
NF-κB decoy oligonucleotide for lumbar disc disorders (US)			Begin Phase Ib clinical trial	
CIN therapeutic vaccine for cervical precancerous lesions (Japan)	Reassigned development, manufacturing and marketing rights to Morishita Jintan Co., Ltd., and transferred development			
DNA vaccine for high blood pressure			Launch Phase I/II clinical trials (Australia)	

Source: Shared Research based on company data

The company entered into an agreement with Mitsubishi Tanabe Pharma Corporation (TSE1: 4508) granting the pharmaceutical giant exclusive domestic and US marketing rights for its HGF gene therapy drug for CLI.
Under this agreement, AnGes is set to receive development milestone payments, and a percentage of sales from Mitsubishi Tanabe Pharma. Shared Research believes that milestone payments will increase incrementally during the phase that runs up until the start of sales.

Shared Research thinks the company is likely to see a significant boost to revenues from royalty payments if HGF gene therapy drug for CLI is brought to market in the US. AnGes estimates the US market at USD5.0bn, and maximum sales have a potential of about JPY100.0bn. Shared Research assumes that the royalties from Mitsubishi Tanabe Pharma will amount to 30–40% of sales.

AnGes's NF-κB decoy oligonucleotide for treating lumbar disc disorders and DNA vaccine for high blood pressure have not made it to Phase III trials, and the company is unlikely to obtain approval by FY12/19, and may have to forego the revenue boost it may have gotten by bringing those drugs to market. That said, Shared Research believes it may be able to receive upfront payments and milestone payments from partner companies, depending on the results of the trials.

Business

Business description

Established to develop gene-based medicines

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

Gene medicines for intractable and rare diseases

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

Reducing risk through partnerships

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

Ordinary process and periods of developing new drugs

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

Source: Shared Research based on company data

CMR International 2013 Pharmaceutical R&D Factbook: In 2006-2008 the success rate by phase of pharmaceutical companies globally was 67% for preclinical, 46% for Phase I, 19% for Phase II, 77% for Phase III and 90% for regulatory review. Pharmaceutical companies quit Phase II trials as early as possible to avoid potential failure of high-cost Phase III trials.

Key revenues—milestone payments

The company has posted operating losses every year except for FY12/01, before it began full-scale trials and research. As of February 2018, it has no self-developed drug on the market. Operating revenues accrue from upfront payments, development cooperation payments and milestone payments from partner companies. Separately it posts revenues of JPY300mn-400mn per year relating to Naglazyme, a drug for mucopolysaccharidosis VI (MPS VI).

▷ Upfront payment: conclusion of agreement.

▷ Development cooperation payment: financial help for R&D.

▷ Milestone payment: R&D progress at agreed stages.

▷ Royalty: percentage of sales post product launch.

Key pipeline drug—HGF gene therapy drug

The prime pipeline drug is an HGF gene therapy drug for critical limb ischemia (CLI). In January 2018, the company submitted an application to the Japanese Ministry of Health, Labour and Welfare for the approval to manufacture and sell its HGF gene therapy drug for the treatment of severe CLI as a regenerative medicine product.

AnGes also began a global Phase III trial in the US in October 2014. AnGes in June 2016 announced that it has discontinued the joint global Phase III clinical trial, to be replaced by another clinical trial. The company is angling to complete the clinical study within a shorter period of time through revising evaluation criteria and selecting study sites exclusively in the US. Through these

measures it is hoping to avoid delays in application for approval and to reduce trial expenses. As of February 2018, the company was compiling a plan on clinical trial plan in the US.

It aims to obtain approval of the HGF gene therapy drug to treat severe CLI during 2018 in Japan and later in the US. Shared Research thinks that the company may receive peak royalties of JPY30bn-JPY40bn per year after sales begin.

HGF gene therapy drug approval application—previous shelving in 2010 hit fund raising

The HGF gene therapy drug showed substance efficacy during the interim analysis of its Phase III trial in Japan in 2007. As a result in 2008 the company applied for approval. Yet following consultation with the Japanese certification body (the Pharmaceuticals and Medical Devices Agency, or PMDA), the company decided that more clinical data would be necessary to get approval for the indications as applied by the company. AnGes shelved the application in September 2010, impacting sales estimates. This, together with the aftermath of the 2008 global financial crisis, hit fund raising during FY12/11 and FY12/12.

Resumed HGF gene therapy drug development after FY12/13

The company made an agreement with Mitsubishi Tanabe Pharma in October 2012 on licensing the exclusive right to sell its HGF gene therapy drug in the US. The company announced a revised plan for the drug in Japan in August 2013, and announced plans for launching a global phase III trial in February 2014.

Main pipeline products

The internal development pipeline includes an HGF gene therapy drug, NF-κB decoy oligonucleotide, and DNA vaccine for high blood pressure. The company also imports and sells Naglazyme. Although in non-clinical development stages, the company is also making progress in developing a gene therapy drug for the treatment of chronic hepatitis B in collaboration with Vical Inc., and a compound (Tie2 agonist peptide Vasculotide) targeting diseases caused by vascular dysfunction and destabilization such as acute respiratory failure jointly with Vasomune Therapeutics Inc.

Internal development pipeline

Type	Product/Project	Indications	Area	Development stage	Partner
Medications	HGF gene therapy drug	Critical limb ischemia (Arteriosclerosis obliterans & Buerger's disease)	Japan	Physician-led clinical trials*1	Mitsubishi Tanabe Pharma (licensing marketing rights)
			US	Planning Phase III clinical trials	Mitsubishi Tanabe Pharma (licensing marketing rights)
	NF-κB decoy oligonucleotide	Atopic dermatitis	Japan	(Ointment) Phase III clinical trials completed*2	Shionogi & Company (worldwide licensing marketing rights)
		Lumbar disc disorders	US	Phase Ib clinical trial under way	TBD
	DNA vaccine for high blood pressure	High blood pressure	Australia	Phase I/II clinical trials under way	TBD

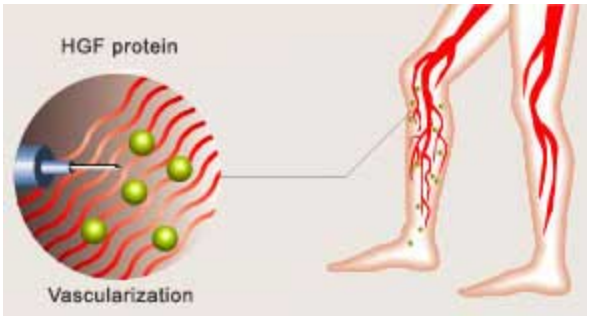
Source: Shared Research based on company data
*1 Domestic Phase III clinical trials have been completed. The company is carrying out physician-led clinical trials in order to obtain approval under the conditional approval system.
*2 In July 2016, AnGes announced that data analysis had not shown a statistically 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 genetic medication (critical limb ischemia)

HGF discovered in Japan (1984)

HGF (Hepatocyte Growth Factor) was discovered in Japan in 1984 as a factor that increases liver cells, the human organ with the highest regenerative capacity. In 1995, a research group led by Dr. Ryuichi Morishita found a method that regenerates blood vessels by medicating HGF genes. HGF genetic medication can be used to treat ischemic diseases, where blood flow is impeded, by regenerating blood vessels.



Source: Company materials

Severe cases of ischemic diseases—no completely effective treatment

Ischemic diseases include 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 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 genetic medication can help via an approach that regenerates vessels. AnGes has been developing such HGF gene therapy drug that targets treatment of critical limb ischemia (CLI).

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

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

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

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

Fontaine classification: Used to clinically classify arteriosclerosis obliterans. Stage I-asymptomatic, stage II-intermittent claudication, stage III-rest pain, and stage IV-ischemic ulcers or gangrene. Patients at stages III and IV are seriously ill.

P-value： A measure of the probability of a discrepancy from a group or relationship happening randomly, with a p-value of 0.01 suggesting that the probability of a test result occurring randomly is 1 in 100.

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

Upon receiving the results of interim analysis of the Phase III trial in June 2007, AnGes in March 2008 applied for approval of the manufacture and marketing of its HGF gene therapy drug for arteriosclerosis obliterans and Buerger's disease with CLI as indications. However, following consultations with the Pharmaceuticals and Medical Devices Agency (PMDA), it concluded that further clinical data were necessary for approval. The company shelved the application in September 2010, intending to make an application again after conducting additional tests.

US Phase II trial—safety demonstrated

In the US in May 2003 the company started Phase II trial of its HGF gene therapy drug. In June 2006 the results were announced. The trial did not show a statistically significant difference of efficacy. However, patients who had been given more than a certain amount of the drug showed a statistically significant improvement in comparison with patients tested with a placebo in stratified analysis of transcutaneous partial pressure of oxygen (TcPO2), the main way to measure hemodynamic improvements. For ischemic ulcers, the trial did not show a significant difference, but it showed a tendency for patients given the HGF gene therapy drug to show improvements, compared with those given a placebo. Between the two groups there was no difference in safety, demonstrating the high degree of safety that the drug offers.

The Phase II trial in the US did not show efficacy. According to the company, unlike the Phase III trial in Japan, in which the places of injections changed according to the patient's affected parts, in the US Phase II trial the injections were administered to a fixed part (the same part for all patients). The company plans to adopt the method used in Japan for global Phase III trials.

In 2007-2010 AnGes prioritized applying for approval of its HGF gene therapy drug in Japan. Following the completion of the Phase II trial in the US in 2006, in November 2009 it got only a special protocol assessment (SPA) from the FDA.

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

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

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

In July 2012, AnGes made an agreement with Mitsubishi Tanabe Pharma regarding licensing the exclusive right to market its HGF gene therapy drug for peripheral vascular diseases in the US. In October 2014, the company launched global Phase III clinical trials of the drug for CLI and began enrolling patients in the US, and in November 2014 began administering the drug under trial protocols. During the same month, the company began its application to begin trials in six key European countries, including the UK and Germany.

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

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

As of February 2018, the company was creating a new plan for clinical trials in the US involving HGF gene therapy drug for CLI. Aiming to complete the clinical study more quickly, the company has adopted a new development strategy: 1) revision of primary endpoint to ulcer and pain (pain-at-rest) healings 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. It is hoping to avoid delays in application for approval and to reduce trial expenses through these measures.

Aiming for approval in Japan, utilizing the conditional and time-limited approval system

Since it had shelved the application for the HGF gene therapy drug for CLI in September 2010, it refrained from testing the drug. However, Osaka University Hospital began conducting investigator-initiated clinical studies for an HGF gene therapy drug to treat CLI in October 2014. In these studies, six new cases of clinical trials utilizing the Japanese Advanced Medical Care B program were conducted. CLI patients enrolled in the study receive the HGF gene therapy drug two or three times with a four-week interval between the first and second dose. A third dose is not given if the first two doses achieve a sufficient treatment effect. After treatment, the patient is followed up over three months to assess ulcer reduction and pain improvement.

As of August 2017, the observation period for the sixth of the six target cases has ended. 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 CLI in Japan as a regenerative medicine.

With the November 2014 enforcement of the Pharmaceutical and Medical Devices Law, Japan introduced an early approval system for regenerative medicines and other products, so the company aims to obtain the approval of the HGF gene therapy drug to treat CLI in 2019 using this conditional and time-limited approval system.

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."

US market for the HGF gene therapy drug estimated at USD5.0bn

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. The company sees potential US sales of USD5.0bn.

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.

Shared Research thinks that annual sales have the potential to reach peak levels of about JPY100.0bn in the US.

Competitor drugs

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.

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 2018, the company did not have any sales partners in Europe or Asia.

Under this agreement, 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 once the HGF gene therapy drug is brought to the market.

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 HFG gene therapy drug for peripheral vascular diseases.
The agreement with Daiichi Sankyo for exclusive marketing rights in Japan for AnGes's 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 HFG gene therapy drug for peripheral vascular diseases.

Nucleic acid medicines

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

NF-κ(kappa)B decoy oligonucleotide

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

NF-κB decoy oligonucleotide injection for treating lumbar disc disorders

In February 2018, AnGes began Phase Ib clinical trials for NF-κB decoy oligonucleotide targeting treatment of lumbar disc disorders in the US. Twenty-four patients are enrolled in the study, which will confirm safety and efficacy over a 12-month follow-up period after administration. The planned length of the study is approximately two years.

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

As of May 2018, AnGes has yet to conclude a development and marketing agreement for NF-κB decoy oligonucleotide with a pharmaceutical company.

NF-κB decoy oligonucleotide ointment for atopic dermatitis

In March 2015, the company launched domestic Phase III clinical trials. The company aimed to confirm the safety and efficacy of the drug in this trial, which covers about 200 patients with at least medium facial atopic dermatitis. Subsequently, however, it announced in July 2016 that results of the trials did not yield a statistically significant difference versus the placebo group. While the company continues a detailed analysis of the trials, it states that it is not in a position to apply for approval to market the product targeting patients with atopic dermatitis. As of February 2018, the company was conducting a detailed analysis of the results of the trials, and examining the direction of future drug development.

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

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

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

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

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

Therapeutic vaccines

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

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

DNA vaccine for high blood pressure

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

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

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

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.

As of May 2018, AnGes has yet to conclude a development and marketing agreement for the DNA vaccine for high blood pressure with a pharmaceutical company.

Orphan drugs (Naglazyme)

As of February 2018, the company was selling Naglazyme to treat mucopolysaccharidosis VI (MPS VI).

Orphan drugs are aimed at rare diseases with few patients but a serious need for treatment. To promote orphan drug R&D, the Ministry of Health, Labour and Welfare provides orphan drug applicants with such preferential measures as subsidies and priority review for marketing authorization.

Naglazyme

Naglazyme, developed by BioMarin Pharmaceutical Inc. of the US, is a drug for the treatment of MPS VI, an inherited life-threatening lysosomal storage disorder caused by a deficiency of the lysosomal enzyme arylsulfatase B. Naglazyme provides a recombinant version of this enzyme to individuals diagnosed with MPS VI.

MPS VI is a rare disease with a rate of incidence of around one to 300,000 in the US and Europe. In Japan, there are only about 10 patients diagnosed with MPS VI so far. A human body without sufficient arylsulfatase B cannot break down dermatan sulfate and chondroitin sulfate, which accumulates in the body. With the progressive type, patients develop various symptoms affecting body tissues and internal organs including delayed growth from childhood, skeletal deformities, distinctive facial features, upper airway obstruction, corneal opacity, recurrent respiratory and ear infections, and joint contracture.

It applied for approval of Naglazyme in August 2007, got approval to manufacture and sell the drug in March 2008 and started selling it in April 2008.

Pipeline drugs in non-clinical development stage

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

Gene therapy drug targeting chronic hepatitis B

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

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

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

Tie2 agonist peptide, Vasculotide

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

an upfront payment (on concluding the agreement) and milestone payments in accordance with development progress to Vasomune.

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

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

Tie2 agonist peptide, Vasculotide

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

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

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

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

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

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

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

Earnings structure

Earnings structure

(JPYmn)	FY12/09	FY12/10	FY12/11	FY12/12	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17
Operating revenue	586	287	243	445	491	910	430	514	365
Sales of goods	142	181	181	242	271	309	350	347	365
Sales of finished goods	-	-	-	15	8	-	-	-	-
R&D revenues	444	106	63	187	212	601	80	167	0
Operating expenses	3,197	2,297	2,344	2,230	1,854	3,184	4,602	5,278	3,654
Cost of sales	68	83	81	129	131	151	180	175	178
% of sales of goods	48.0%	45.8%	44.9%	53.5%	48.4%	48.9%	51.3%	50.3%	48.8%
R&D expenses	2,350	1,440	1,444	1,200	1,025	2,339	3,533	4,189	2,600
Salaries and allowances	503	420	348	312	247	309	456	441	364
Outsourcing expenses	1,062	315	348	374	274	1,194	2,145	2,769	1,370
SG&A expenses	779	775	819	901	699	694	890	915	876
Directors' compensations	104	123	123	121	72	74	83	78	91
Salaries and allowances	218	217	230	224	139	125	155	148	140
Commission fee	183	135	145	197	197	163	240	265	179
Operating profit	-2,611	-2,010	-2,101	-1,785	-1,363	-2,274	-4,172	-4,763	-3,289

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)	FY12/09	FY12/10	FY12/11	FY12/12	FY12/13	FY12/14	FY12/15	FY12/16	FY12/17
Mitsubishi Tanabe Pharma	-	-	-	-	-	500	50	-	-
Daiichi Sankyo	289	102	42	159	35	92	-	-	-
TS Alfresa (former Seiwa Sangyo)	89	97	90	132	151	148	160	176	179
Alfresa	53	83	91	110	120	161	190	171	186
Shionogi	-	-	-	26	113	8	-	-	-
Ishihara Sangyo	-	-	-	2	50	-	-	-	-
Morishita Jintan	-	-	-	-	-	-	-	155	-

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 net sales of goods (100.0% of the FY12/17 total) and research and development revenues (0% of the FY12/17 total).

Net sales of goods

Naglazyme sales are reported as net sales of goods. The company procures Naglazyme from BioMarin Pharmaceuticals Inc., and sells to TS Alfresa Corporation (formerly SEIWA SANGYO CO., LTD.), and Alfresa Corporation. Sales are gradually rising as dosage increases as patients grow and put on weight.

R&D

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

- In FY12/13, AnGes received milestone payment from Shionogi for NF-κB decoy oligonucleotide ointment for atopic dermatitis and an upfront payment from Nippon Zoki Pharmaceutical Co., Ltd.
- In FY12/14, AnGes recorded an upfront payment from Mitsubishi Tanabe Pharma for use of its HGF gene therapy drug to treat peripheral vascular disease in the US.
- In FY12/15, the company booked a milestone payment following the conclusion of an exclusive licensing agreement with Mitsubishi Tanabe Pharma for use of its HGF gene therapy drug in Japan for patients afflicted with peripheral vascular diseases.
- In FY12/16, the company signed an agreement that reassigned exclusive development, manufacturing, use and marketing rights for its CIN therapeutic vaccine in Japan, the US, UK and China to Morishita Jintan. In exchange, AnGes received upfront payments.

Operating expenses

Cost of goods sold, research and development expenses, and SG&A expenses.

CoGS

Costs relating to Naglazyme. Shared Research estimates Naglazyme's gross profit margin at around 50%.

R&D

Mainly salaries, allowances and subcontract expenses. Salaries and allowances rose to JPY615mn in FY12/07 on more personnel but decreased from FY12/08 onward, due partly to the departure of employees via an early retirement program in January 2013, reaching JPY247mn in FY12/2013. Salaries and allowances have remained in the JPY300mn to JPY500mn range since FY12/14.

Subcontract expenses concern clinical trials entrusted to contract research organizations (CROs). The amount totaled JPY1.9bn in FY12/06 due to the Phase III clinical trial of its HGF gene therapy drug in Japan. After completion, expenses trended south from FY12/07 onward, nudging JPY274mn in FY12/13. With the launch of the HGF gene therapy drug's global Phase III clinical trial in Q3 FY12/14, and Phase III clinical trials of NF-κB decoy oligonucleotide for atopic dermatitis in Q1 FY12/15, the company's subcontract expenses have been increasing since FY12/14.

According to the company, subcontract expenses rose in FY12/14–FY12/16 as the company started a joint global Phase III trial for the HGF gene therapy drug in Q3 FY12/14 and a Phase III clinical trial for NF-κB decoy oligonucleotide for treating atopic dermatitis in Q1 FY12/15. The subcontract expenses decreased as the joint global Phase III trial for the HGF gene therapy drug ended in June 2016, lessening the related expenses in FY12/17.,

SG&A

Mainly directors' compensation, salaries and allowances—and fixed. Due to cost rationalization, such as a reduction in rewards to directors, in Q3 FY12/12 and beyond, SG&A expenses fell from JPY901mn in FY12/12 to JPY693mn in FY12/14. Expenses were also down as a result of a reduction in employee count from an early retirement program implemented in January 2013. SG&A increased to roughly JPY900mn from FY12/15 due to higher commissions paid, owing mainly to higher business compensation.

Strengths and weaknesses

Strengths

- **Proven efficacy of HGF gene therapy drug**: The drug's efficacy was demonstrated in the Phase III trial in Japan in 2007. Phase II clinical trials conducted in the US in June 2006 have also shown that there is no statistical variation between safety of the HGF gene therapy drug and the placebo.
- **Partnerships with pharmaceutical companies**: AnGes has entered partnerships with major domestic pharmaceutical companies—Daiichi Sankyo, Mitsubishi Tanabe Pharma and Shionogi—highlighting high development capabilities. The company has reduced development risk by getting development cooperation payments, milestone payments and royalties from partners.
- **Utilization of Japan's conditional and time-limited approval system:** The conditional and time-limited approval system, introduced along with the November 2014 enforcement of the Pharmaceutical and Medical Devices Law, applies to the firm's HGF gene therapy drug. As such the company aims to get approval to sell the drug in Japan by the end of 2019.

Weaknesses

- **Insufficient funding**: Cash and deposits at end FY12/17 totaled JPY1.1bn (JPY1.0bn a year ago). The company faces a situation that may cause material doubt about the going concern assumption as it lacks sufficient funds to keep proceeding with all of its projects. In September 2017, AnGes issued its 31st share subscription rights through a third-party allocation with JPY8.1bn in estimated net proceeds. As of January 2018, the company had raised JPY977mn from the exercise of some of these share subscription rights.
- **No track record marketing self-developed product**: It typically takes five to six years for a company to market a drug it created. But the company, 17 years after formation and 10 years after listing, has not marketed a single self-developed drug. As of February 2018, Japan has not approved a gene therapy drug and there are few such drugs in the US and Europe.
- **Dependent on its HGF gene therapy drug**: As of February 2018, aside from introduction of orphan drugs, only AnGes's HGF gene therapy drug is lined up for application for approval or Phase III trial and thus may contribute to sales over the medium term. Considering its limited war chest, business continuity may hinge on the drug's successful approval or Phase III trial in Japan and the US.

Historical performance

Q3 FY12/18 results

Operating revenues rose 8.2% YoY to JPY276mn. The company booked upfront payments and development support fees from partner companies as R&D revenue. It also booked sales of Naglazyme®, a drug for mucopolysaccharidosis VI (MPS VI). In accordance with the full-year FY12/18 earnings forecasts announced in August 2018, the company expects to book revenue from transferring its non-clinical study data in Q4 (October–December 2018).

Operating expenses were JPY2.5bn (-16.0% YoY).

- ▷ CoGS increased to JPY136mn (+9.2% YoY) due to an increase in product sales.
- ▷ R&D expenses fell to JPY1.7bn (-24.4% YoY), owing to a decrease in expenses for global joint Phase III trials for its HGF gene therapy drug, which lowered outsourcing expenses by JPY368mn. Salaries and other allowances also decreased by JPY92mn, primarily due to job cuts at a subsidiary. In Q3 FY12/17, the company booked stock-based compensation expenses worth JPY168mn due to granting share subscription rights to employees, but none in Q3 FY12/18. Research material costs increased by JPY83mn as the company reassessed the value of, and disposed of, raw materials. Further, the company made a lump-sum payment to Vasomune in Q3 (July–September 2018).
- ▷ SG&A expenses were up 6.0% YoY at JPY733mn. Commissions paid increased to JPY48mn due to increases in consulting expenses, and consumables expenses rose JPY25mn with the purchase of fixtures and fittings on relocation of the Tokyo branch office. Taxes and dues increased by JPY28mn on an increase in the portion of corporate tax determined based on the company's capital. In Q3 FY12/17, the company booked stock-based compensation expenses of JPY98mn due to granting share subscription rights to employees, while it booked stock-based compensation expenses of JPY11mn due to granting share subscription rights to directors.

As a result of the above, the company booked an operating loss of JPY2.2bn (operating loss of JPY2.7bn in Q3 FY12/17). Recurring loss was JPY2.3bn (recurring loss of JPY2.8bn in Q3 FY12/17). There was subsidy revenue of JPY3mn, with the receipt of a grant from the Osaka Foundation for Trade & Industry. The company booked zero foreign exchange gains in Q3 FY12/18 (forex gains of JPY6mn in Q3 FY12/17). There were share issuance expenses of JPY23mn as shares were issued on the exercise of share subscription rights.

Net loss attributable to parent company shareholders was JPY2.2bn (net loss attributable to parent company shareholders of JPY3.4bn in Q3 FY12/18). The company booked a JPY31mn gain on sale of investment securities due to selling some of its shareholdings. It also posted a JPY33mn gain on reversal of share subscription rights as some stock options had been lapsed due to right holders leaving the company. There were no extraordinary losses in Q3 FY12/18, whereas the company booked an impairment loss of JPY112mn and a valuation loss on investment securities of JPY476mn in Q3 FY12/17.

Main pipeline progress

The company's priority pipeline projects are an HGF gene therapy drug for critical limb ischemia (CLI), NF-κB decoy oligonucleotide to treat lumbar disc disorders and back pain, and a DNA vaccine to treat high blood pressure.

Development progress in Q3 FY12/18 was as follows. In January 2018, the company submitted an application to the Japanese Ministry of Health, Labour and Welfare for the approval to manufacture and sell a regenerative medicine product, namely its HGF gene therapy drug for the treatment of CLI. Further, the company started Phase Ib clinical trials in February 2018 for NF-κB decoy oligonucleotide to treat lumbar disc disorders and back pain. Phase I/II clinical trials began in April 2018 for the DNA vaccine to treat blood pressure.

HGF gene therapy drug to treat CLI

Regarding the development of its HGF gene therapy drug for CLI, in January 2018 the company filed an application with the Ministry of Health, Labour and Welfare for approval for the manufacture and marketing of a regenerative medicine product, utilizing the conditional time-limited approval system (a new approval system aiming for the early commercialization of regenerative medicines and other drugs included under the Pharmaceuticals and Medical Devices Law, which went into force in November 2014).

Based on the change of its overseas development schedule decided in June 2016 for its HFG gene therapy drug for treating CLI, AnGes is developing plans for clinical trials in the US aimed at acquiring application approval data more quickly.

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

The company is progressing with the development of NF-κB decoy oligonucleotide to treat lumbar disc disorders and back pain. The company's Investigational New Drug application (IND) with the FDA was approved in April 2017. The company began Phase Ib clinical trials in February 2018.

DNA vaccine to treat high blood pressure

AnGes plans to focus on the development of DNA vaccines as the third pillar of gene medicines in addition to gene therapy drugs and nucleic acid medicines. 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.

Strategic alliance with Vical

In December 2016, AnGes concluded a strategic business alliance with Vical, Inc. for co-development. As the first project, the two companies signed an agreement to co-develop a gene therapy drug that completely cures chronic hepatitis B in April 2017. Under the terms of the agreement, AnGes has first refusal rights on development and sales in Japan.

Alliance with Vasomune

In July 2018, the company and a Canada-based biomedical company Vasomune Therapeutics signed a global co-development agreement of therapeutics (Tie2 agonist peptide Vasculotide) 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.

> Tie2 is a receptor expressed on the surface of vascular endothelial cells that when activated, stabilizes the structure of blood and lymph vessels. Receptors are proteins found in cells and cell membranes. When receptors are bound to hormones or chemical substances, they propagate a reaction in the cell.
> An agonist is a substance that binds to a receptor and induces a physiological reaction.

Raising capital

At the end of Q3 FY12/18, cash and deposits totaled JPY3.5bn (JPY1.1bn at end-FY12/17). Given the shortage of capital to progress all projects, significant doubt has arisen as to the company's ability to continue as a going concern. The company is taking following actions to address this problem:

Progressing own existing projects and expanding business base

The company is progressing three development projects: HGF gene therapy drug for critical limb ischemia (CLI), the NF-κB decoy oligonucleotide for treating lumbar disc disorders, and the DNA vaccine for high blood pressure. For the first, the company has filed for Ministry of Health, Labour and Welfare's (MHLW) approval to manufacture and sell the drug and plans to build an earnings base after obtaining approval. 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 to ensure growth in the longer term.

Financing

The company believes that it can resolve or improve the situation of significant doubt over its ability to continue as a going concern by implementing the actions outlined above. The company issued the 31st share subscription rights through a third-party allocation. As of August 2018, 100% of these share subscription rights had been exercised, from which the company raised JPY5.1bn. Further, the company resolved at a board of directors meeting in September 2018 to issue its 33rd share subscription rights through a third-party allocation with Mita Securities as the allottee (the number of dilutive shares from the issuance accounted for 17.6% of the total number of issued shares, and net proceeds totaled JPY9.5bn). The total issue price of JPY64mn had been paid in as of October 11, 2018, and the company raised JPY346mn from the exercise of rights as of October 24, 2018.

1H FY12/18 results

Operating revenues rose 4.0% YoY to JPY176mn. The company booked upfront payments and development support fees from partner companies as R&D revenue. It also booked sales of Naglazyme®, a drug for mucopolysaccharidosis VI (MPS VI).

Operating expenses were JPY1.4bn (-26.2% YoY). CoGS increased to JPY86mn (+5.0% YoY) due to an increase in product sales. R&D expenses fell to JPY804mn (-42.3% YoY), owing to a decrease in expenses for global joint Phase III trials for its HGF gene therapy drug, which lowered outsourcing expenses by JPY556mn. Salaries and other allowances also decreased by JPY52mn, primarily due to job cuts at a subsidiary. Meanwhile, research material costs increased by JPY25mn as the company reassessed the value of, and disposed of, raw materials; SG&A expenses were up 23.6% YoY at JPY491mn. Commissions paid increased to JPY34mn due to increases to consulting expenses, and consumables expenses rose to JPY26mn with the purchase of fixtures and fittings on relocation of the Tokyo branch office. Taxes and dues increased by JPY20mn on an increase in the portion of corporate tax determined based on the company's capital.

As a result of the above, the company booked an operating loss of JPY1.2bn (operating loss of JPY1.7bn in 1H FY12/17). Recurring loss was JPY1.2bn (recurring loss of JPY1.7bn in 1H FY12/17). There was subsidy revenue of JPY3mn, with the receipt of a grant from the Osaka Foundation for Trade & Industry. The company booked foreign exchange gains of JPY3mn in 1H FY12/18 (forex gains of JPY11mn in 1H FY12/17). There were share issuance expenses of JPY10mn as shares were issued on the exercise of share subscription rights.

Net loss attributable to parent company shareholders was JPY1.1bn (net loss attributable to parent company shareholders of JPY2.3bn in 1H FY12/17). The company booked a JPY31mn gain on sale of investment securities due to selling some of its shareholdings. It also posted a JPY33mn gain on reversal of share subscription rights as some stock options had been lapsed due to right holders leaving the company.

Main pipeline progress

The company's priority pipeline projects are an HGF gene therapy drug for critical limb ischemia (CLI), NF-κB decoy oligonucleotide to treat lumbar disc disorders and back pain, and a DNA vaccine to treat high blood pressure.

Development progress in 1H FY12/18 was as follows. In January 2018, the company submitted an application to the Japanese Ministry of Health, Labour and Welfare for the approval to manufacture and sell a regenerative medicine product, namely its HGF gene therapy drug for the treatment of CLI. Further, the company started Phase Ib clinical trials in February 2018 for NF-κB decoy oligonucleotide to treat lumbar disc disorders and back pain. Phase I/II clinical trials began in April 2018 for the DNA vaccine to treat blood pressure.

In addition, in July 2018 the company concluded a joint development agreement with a Canada-based biomedical company Vasomune Therapeutics Inc. regarding a compound (Tie2 agonist peptide Vasculotide) targeting diseases caused by vascular dysfunction and destabilization such as acute respiratory failure.

Tie2 is a receptor expressed on the surface of vascular endothelial cells that when activated, stabilizes the structure of blood and lymph vessels.
Receptors are proteins found in cells and cell membranes. When receptors are bound to hormones or chemical substances, they propagate a reaction in the cell.
An agonist is a substance that binds to a receptor and induces a physiological reaction.

HGF gene therapy drug to treat CLI

Regarding the development of its HGF gene therapy drug for CLI, in January 2018 the company filed an application with the Ministry of Health, Labour and Welfare for approval for the manufacture and marketing of a regenerative medicine product, utilizing the conditional time-limited approval system (a new approval system aiming for the early commercialization of regenerative medicines and other drugs included under the Pharmaceuticals and Medical Devices Law, which went into force in November 2014).

Based on the change of its overseas development schedule decided in June 2016 for its HFG gene therapy drug for treating CLI, AnGes is developing plans for clinical trials in the US aimed at acquiring application approval data more quickly.

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

The company is progressing with the development of NF-κB decoy oligonucleotide to treat lumbar disc disorders and back pain. The company's Investigational New Drug application (IND) with the FDA was approved in April 2017. The company began Phase Ib clinical trials in February 2018.

DNA vaccine to treat high blood pressure

AnGes plans to focus on the development of DNA vaccines as the third pillar of gene medicines in addition to gene therapy drugs and nucleic acid medicines. 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.

Raising capital

At the end of 1H FY12/18, cash and deposits totaled JPY2.5bn (JPY1.1bn at end-FY12/17). Given the shortage of capital to progress all projects, significant doubt has arisen as to the company's ability to continue as a going concern. The company is concentrating on raising capital and taking a more selective approach to drugs for development to address this problem.

Focusing on selected drugs for development

The company plans to be more selective in development projects, focusing on projects at the final stage of development as well as licensing-out pipeline drugs to pharmaceutical companies at an early stage to earn upfront/milestone payments and reduce R&D spending.

Financing

The company is raising capital by forming new partnerships with a view to receiving upfront payments in addition to equity financing.

It believes these measures will resolve or improve the situation of significant doubt over its ability to continue as a going concern. The company issued its 31st share subscription rights through a third-party allocation. 51.7% of these share subscription rights had been exercised as of end-1H FY12/18, from which the company raised JPY3.0bn.

Q1 FY12/18 results

Operating revenues declined 11.4% YoY to JPY74mn, breaking down into upfront payments and development support fees from partner companies booked as R&D revenue, and sales of Naglazyme®, a drug for mucopolysaccharidosis VI (MPS VI). Product sales declined 11.4% YoY to JPY74mn, with no other operating revenues in Q1. Product sales were down YoY, because sales were higher in Q4 FY12/17 than in the three previous quarters.

Operating expenses were JPY664mn (-40.7% YoY). CoGS decreased to JPY36mn (-10.7% YoY) due to a drop in product sales. R&D expenses fell to JPY403mn (-54.0% YoY), owing to a decrease in expenses for global joint Phase III trials for its HGF gene therapy drug, which lowered outsourcing expenses by JPY436mn. Salaries and other allowances also decreased by JPY20mn, primarily due to job cuts at a subsidiary. Meanwhile, research material costs increased by JPY41mn as the company reassessed the value of raw materials; SG&A expenses were up 10.8% YoY at JPY225mn. Taxes and dues increased by JPY20mn on an increase in the portion of corporate tax determined based on the company's capital.

As a result of the above, the company booked an operating loss of JPY590mn (operating loss of JPY1.0bn in Q1 FY12/17). Recurring loss was JPY587mn (recurring loss of JPY1.0bn in Q1 FY12/17). Further, while the company booked foreign exchange losses of JPY6mn in Q1 FY12/17, it booked foreign exchange gains of JPY2mn in Q1 FY12/18.

Net loss attributable to parent company shareholders was JPY537mn (net loss attributable to parent company shareholders of JPY1.5bn in Q1 FY12/17). The company booked a JPY31mn gain on sale of investment securities due to selling some of its shareholdings. It also posted a JPY21mn gain on reversal of share subscription rights as some stock options had been lapsed due to right holders leaving the company.

Main pipeline progress

The company's priority pipeline projects are an HGF gene therapy drug for critical limb ischemia (CLI), NF-κB decoy oligonucleotide to treat lumbar disc disorders and back pain, and a DNA vaccine to treat high blood pressure.

As of Q1 FY12/18, the company started Phase Ib clinical trials in February 2018 for NF-κB decoy oligonucleotide to treat lumbar disc disorders. In Q2, Phase I/II clinical trials began in April 2018 for the DNA vaccine to treat blood pressure.

HGF gene therapy drug to treat CLI

In Japan, a physician-led clinical study has been conducted at Osaka University Hospital since October 2014 for the development of an HGF gene therapy drug for CLI. After obtaining study results making it possible to file for approval, the company applied for approval from the Ministry of Health, Labor and Welfare in January 2018 by utilizing the conditional time-limited approval system in Japan (a new approval system aiming for the early commercialization of regenerative medicines and other drugs included under the Pharmaceutical and Medical Devices Law, which went into force in November 2014), including the results of this clinical study in addition to existing clinical data.

Based on the change of its overseas development schedule decided in June 2016 for its HFG gene therapy drug for treating CLI, AnGes is developing plans for clinical trials in the US aimed at acquiring application approval data more quickly.

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

In April 2017, the company's Investigational New Drug application (IND) with the FDA was approved for the development of NF-κB decoy oligonucleotide to treat lumbar disc disorders and back pain. The company began Phase Ib clinical trials in February 2018.

DNA vaccine to treat high blood pressure

AnGes plans to focus on the development of DNA vaccines as the third pillar of gene medicines in addition to gene therapy drugs and nucleic acid medicines. 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.

Raising capital

At the end of Q1 FY12/18, cash and deposits totaled JPY1.5bn (JPY1.1bn at end-FY12/17). Given the shortage of capital to progress all projects, significant doubt has arisen as to the company's ability to continue as a going concern. The company is concentrating on raising capital and taking a more selective approach to drugs for development to address this problem.

Focusing on selected drugs for development

The company plans to be more selective in development projects, focusing on projects at the final stage of development as well as licensing-out pipeline drugs to pharmaceutical companies at an early stage to earn upfront/milestone payments and reduce R&D spending.

Financing

The company is raising capital by forming new partnerships with a view to receiving upfront payments in addition to equity financing.

It believes these measures will resolve or improve the situation of significant doubt over its ability to continue as a going concern. The company issued its 31st share subscription rights through a third-party allocation. 22.6% of these share subscription rights had been exercised as of end-Q1 FY12/18, from which the company raised JPY1.5bn.

FY12/17 results

Operating revenues declined 29.0% YoY to JPY365mn. The company booked a certain portion of research reagents and development support fees from partner companies as royalties in the R&D revenue. It also booked sales of Naglazyme®, a drug for mucopolysaccharidosis VI (MPS VI).

Operating expenses were JPY3.7bn (-30.8% YoY). CoGS decreased to JPY178mn (+2.0% YoY) due to an increase in product sales. R&D expenses fell to JPY2.6bn (-37.9% YoY), owing to a decrease in expenses for global joint Phase III trials for its HGF gene therapy drug, which lowered research material costs by JPY200mn and outsourcing expenses by JPY1.4bn. Salaries and other allowances also decreased by JPY76mn, primarily due to job cuts at a subsidiary. Meanwhile, there were stock-based compensation expenses worth JPY168mn due to granting subscription rights to employees. SG&A expenses fell to JPY875mn (-4.3% YoY). Taxes and dues decreased by JPY95mn owing to a reduction of the portion of capital subject to corporate tax. Commissions paid fell by JPY85mn due to a decrease in consulting expenses. Granting subscription rights to employees led to stock-based compensation expenses worth JPY98mn.

As a result of the above, the company booked an operating loss of JPY3.3bn (operating loss of JPY4.8bn in FY12/16). Recurring loss was JPY3.3bn (recurring loss of JPY4.8bn in FY12/16). Further, while the company booked foreign exchange losses of JPY4mn in FY12/16, it booked foreign exchange gains of JPY2mn in FY12/17.

Net loss was JPY3.8bn (net loss of JPY4.8bn in FY12/16). The company booked a JPY130mn loss on the sale of investment securities due to selling some of its shareholdings, and a loss of JPY476mn on the re-evaluation of investment securities due to falling prices of shareholdings and a JPY112mn loss on impairment of business assets as an extraordinary loss.

Main pipeline progress

The company's key pipeline projects are an HGF gene therapy drug for the treatment of severe critical limb ischemia (CLI), NF-κB decoy oligonucleotide for lumbar disc disorders and back pain, and a DNA vaccine to treat high blood pressure

Looking at progress with main projects in FY12/17, the observation period of the sixth of the six target cases ended in August 2017 in the investigator-initiated clinical study of an HGF gene therapy drug for the treatment of CLI. In January 2018, the company submitted an application to the Japanese Ministry of Health, Labour and Welfare for the approval to manufacture and sell its HGF gene therapy drug for the treatment of severe CLI as a regenerative medicine product. It aims to obtain the approval of the drug in 2019 using the conditional time-limited approval system.

Conditional time-limited approval system: A new approval system aiming for the early commercialization of regenerative medicines and other drugs introduced under the Pharmaceutical and Medical Devices Law, which went into force in November 2014.

The company filed an Investigational New Drug application (IND) with the US Food and Drug Administration (FDA) in March 2017 for NF-κB decoy oligonucleotide for lumbar disc disorders and back pain, which was approved in April 2017. In July 2017, AnGes submitted a Clinical Trials Notification (CTN) to the Therapeutic Goods Administration (TGA), the regulatory authority in Australia, for its DNA vaccine for high blood pressure.

HGF gene therapy drug to treat CLI

In Japan, a physician-led clinical study has been conducted at Osaka University Hospital since October 2014 for the development of an HGF gene therapy drug for CLI. After obtaining study results making it possible to file for approval, the company applied for approval from the Ministry of Health, Labor and Welfare in January 2018 by utilizing the conditional time-limited approval system in Japan (a new approval system aiming for the early commercialization of regenerative medicines and other drugs included under the Pharmaceutical and Medical Devices Law, which went into force in November 2014), including the results of this clinical study in addition to existing clinical data.
Based on the change of its overseas development schedule decided in June 2016 for its HFG gene therapy drug for treating CLI, AnGes is developing plans for clinical trials in the US aimed at acquiring application approval data more quickly.

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

In April 2017, the company's Investigational New Drug application (IND) with the FDA was approved for the development of NF-κB decoy oligonucleotide to treat lumbar disc disorders and back pain and the company completed preparations to start the trials. The company plans to begin phase 1b clinical trials after enrolling patients.

DNA vaccine to treat high blood pressure

AnGes plans to focus on the development of DNA vaccines as the third pillar of gene medicines in addition to gene therapy drugs and nucleic acid medicines. 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, which it plans to begin once preparations are complete.

Raising capital

At the end of FY12/17, cash and deposits totaled JPY1.1bn (JPY996mn at end FY12/16). Given the shortage of capital to progress all projects, significant doubt has arisen as to the company's ability to continue as a going concern. The company is concentrating on raising capital and taking a more selective approach to drugs for development to address this problem.

Focusing on selected drugs for development

The company plans to be more selective in development projects, focusing on projects at the final stage of development as well as licensing-out pipeline drugs to pharmaceutical companies at an early stage to earn upfront/milestone payments and reduce R&D spending.

Financing

The company is raising capital by forming new partnerships with a view to receiving upfront payments in addition to equity financing.

It believes these measures will resolve or improve the situation of significant doubt over its ability to continue as a going concern. The company issued its 29th share subscription rights through a third-party allocation and raised JPY2.4bn as a result of all share subscription rights being exercised as of June 13, 2017. On September 13, 2017, the company issued its 31st share subscription rights through a third-party allocation. As of January 2018, the company had raised JPY977mn from the exercise of some of these share subscription rights.

Other information

History

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
August 2016	Acquires additional stake in Vical Inc. to become top shareholder
December 2016	Concludes strategic business alliance agreement with Vical Inc. for DNA vaccines

News and topics

September 2018

On **September 25, 2018**, the company announced its 33rd issuance of share subscription rights (via third-party allotment) with provisions for exercise price adjustment.

Details

- ▷ Allotment date: October 11, 2018
- ▷ Number of share subscription rights issued: 160,000 units
- ▷ Total issue price: JPY64.8mn (JPY405 per unit)
- ▷ Number of resulting dilutive shares: 16,000,000 (100 shares per share subscription right; 17.6% of total shares issued)

▷ Funds to be raised: JPY9,454mn (net of cost)

▷ Allottee (planned): Mita Securities Co., Ltd. (via third-party allotment)

▷ Exercise price, and terms and conditions for exercise price adjustment: Initial exercise price is JPY590

In the event the value defined as "revision date price," which is the amount equivalent to 92% of the TSE closing price of the company's common stock (fraction less than JPY1 rounded up) on the day immediately preceding the revision date (when the subscription rights become effective), either exceeds or falls short of the valid exercise price immediately before the revision date by JPY1 or more, the exercise price will be adjusted to the revision date price from the revision date onward.

Use of proceeds

Specific Use	Amount (JPYmn)	Timing of Expenditure
Expansion of development pipeline	5,304	October 2018–October 2022
Implementation of post-commercialization study in Japan for HGF gene therapy drug	1,150	October 2018–October 2023
Working capital	3,000	October 2018–October 2020

August 2018

On **August 27, 2018,** the company announced revisions to its earnings forecasts for full-year FY12/18.

Revised full-year earnings forecasts for FY12/18

▷ Operating revenues: JPY600mn (previous forecast: JPY365mn)

▷ Operating loss: JPY3.1bn (previous forecast: JPY2.5bn)

▷ Recurring loss: JPY3.1bn (previous forecast: JPY2.5bn)

▷ Net loss attributable to parent company shareholders: JPY3.1bn (previous forecast: JPY2.5bn)

▷ Net loss per share: JPY36.06 (previous forecast: JPY29.08)

Reasons for the revision

The company revised up its previous forecast for operating revenues (JPY365mn) by JPY235mn to JPY600mn. The upward revision was due to agreeing to the data transfer request from an overseas pharmaceutical company regarding the company's non-clinical study data. The company decided to incorporate earnings from the data transfer into its operating revenues forecast as the conditions and specific dates of the transfer, which remained undetermined up until this point, became clear.
In addition, the forecast for operating loss (JPY2.5bn) widened versus the previous forecast by JPY600mn to JPY3.1bn. The downward revision was mainly attributable to an expected increase in operating expenses stemming from an upfront payment to Vasomune Therapeutics Inc.—its partner for the joint development of therapeutic agent for acute respiratory failure, which was announced in July 2018—and expenses involved in obtaining approval for HGF gene therapy drug in Japan.

July 2018

On **July 30, 2018,** the company announced it had resolved to develop a treatment for acute respiratory failure in collaboration with Canadian company Vasomune Therapeutics Inc.

At the Board of Directors meeting held on the same day, the company resolved to develop a drug targeting diseases caused by vascular deficiency such as acute respiratory failure in collaboration with Canadian biotechnology company Vasomune Therapeutics Inc. (henceforth Vasomune), and entered into an agreement accordingly. Going forward under this contract, both companies will collaborate in developing a compound discovered by Vasomune for global use, sharing development costs and future profit.

Under the terms of the agreement, the company is to make an upfront payment to Vasomune, as well as milestone payments according to development progress. As the first step of the collaboration, the company plans to begin non-clinical trials targeting Acute Respiratory Distress Syndrome (ARDS), a more severe diagnosis of respiratory failure, with a view to initiate clinical trials after two years. Thereafter, once proof of concept (POC—evidence of certain degree of effectiveness shown in patients) has been obtained in clinical trials, the plan is to out-license development and marketing rights to pharmaceutical companies.

Major shareholders

Top shareholders	Shares held	Shareholding ratio
Shionogi & Co., Ltd.	1,186,800	1.48%
Japan Securities Finance Co., Ltd.	980,800	1.23%
Ryuichi Morishita	691,600	0.86%
Hirota Securities Co., Ltd.	682,096	0.85%
Nomura Securities Co., Ltd.	678,200	0.85%
Daiwa Securities Co. Ltd.	625,800	0.78%
SBI Securities Co., Ltd.	476,300	0.59%
Shinya Otono	472,600	0.59%
Toshikazu Nakamura	412,400	0.51%
Teruo Isohata	377,000	0.47%
Total	6,583,596	8.26%

Source: Shared Research based on company data
(As of December 31, 2017)

Company profile

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

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Emergency Assistance Japan Co., Ltd.
en-Japan Inc.
euglena Co., Ltd.
Evolable Asia Corp.
FaithNetwork Co., Ltd.
Ferrotec Holdings Corporation
FIELDS CORPORATION
Financial Products Group Co., Ltd.
FreeBit Co., Ltd.
FRONTEO, Inc.
Fujita Kanko Inc.
Gamecard-Joyco Holdings, Inc.
GCA Corporation
Grandy House Corporation
Hakuto Co., Ltd.
Happinet Corporation
Harmonic Drive Systems Inc.
HOUSEDO Co., Ltd.
IDOM Inc.
IGNIS LTD.
Inabata & Co., Ltd.
Infocom Corporation
Infomart Corporation
Intelligent Wave, Inc.
istyle Inc.
Itochu Enex Co., Ltd.
JSB Co., Ltd.
JTEC Corporation
J Trust Co., Ltd
Japan Best Rescue System Co., Ltd.
JINS Inc.
JP-HOLDINGS, INC.
KAMEDA SEIKA CO., LTD.
Kenedix, Inc.
KFC Holdings Japan, Ltd.
KI-Star Real Estate Co., Ltd.
Kumiai Chemical Industry Co., Ltd.
Lasertec Corporation
LUCKLAND CO., LTD.
MATSUI SECURITIES CO., LTD.
Medical System Network Co., Ltd.
MEDINET Co., Ltd.
Mercuria Investment Co., Ltd.
Milbon Co., Ltd.
MIRAIT Holdings Corporation
Monex Goup Inc.
NAGASE & CO., LTD
NAIGAI TRANS LINE LTD.
NanoCarrier Co., Ltd.
Net One Systems Co.,Ltd.
Nichi-Iko Pharmaceutical Co., Ltd.
Nihon Denkei Co., Ltd.
Nippon Koei Co., Ltd.
NIPPON PARKING DEVELOPMENT Co., Ltd.
Nisshinbo Holdings Inc.
NS TOOL CO., LTD.
NTT URBAN DEVELOPMENT CORPORATION
Oki Electric Industry Co., Ltd
ONO SOKKI Co., Ltd.
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YUMESHIN HOLDINGS CO., LTD.
Yume no Machi Souzou Iinkai Co., Ltd.
Yushiro Chemical Industry Co., Ltd.
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