FY2018 1Q Financial Results

May 11, 2018

HEALIOS K.K.
(TSE 4593)

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1. Financial Highlights

Statement of income

(Million yen)

	FY 2017 1Q	FY 2018 1Q		
			YoY change	Main reasons for increase/decrease
Sales	20	—	▲20	Compound drug business transfer
Operating income	▲490	**▲553**	▲63	Research & Development Cost increased ▲27
Ordinary income	▲525	**▲551**	▲26	-
Net income	▲526	**▲553**	▲26	

R&D	340	**367**	+27	
Amortization of goodwill	25	**-**	▲25	Compound drug business transfer
Number of employees	61	75	+14	-

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Balance sheet

(Million yen / %)

		December 31, 2017	March 31, 2018		
				Change	Main reasons for increase/decrease
	Current assets	19,288 (97.9%)	**15,950** (84.7%)	▲3,337	Cash and deposit ▲4,525 (Cash and deposit balance 14,514)
	Non-current assets	408 (2.1%)	**2,873** (15.3%)	+2,464	Investment securities +2,442
Total assets		19,696 (100.0%)	**18,824** (100.0%)	▲872	
	Current liabilities	1,300 (6.6%)	**2,953** (15.7%)	+1,652	Current portion of long-term loans payable +2,000
	Non-current liabilities	2,232 (11.3%)	**204** (1.1%)	▲2,027	Long-term loans payable ▲2,043
Total liabilities		3,532 (17.9%)	**3,157** (16.8%)	▲374	
Total equity		16,163 (82.1%)	**15,666** (83.2%)	▲497	Earned surplus ▲553
Total assets		19,696 (100.0%)	**18,824** (100.0%)	▲872	

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2. FY2018 1Q Business Overview

New Management team



NEW **Gregory Bonfiglio**
Investing in RM venture
Chairman of the Board of CCRM

Michael Alfant
Healios' outside director since 2013

Yoshinari Matsuda
Attorney-at-Law

Jun Narimatsu
Supporting various venture companies

Seigo Kashii
Ex-corporate auditor of Astellas Pharma

NEW **Richard Kincaid**
Managing hedge fund

NEW **David Smith**
Extensive experience in cell manufacturing

Ken Ishikawa
Administrative field and Director

Kouichi Tamura
Research and Manufacturing

Hardy TS Kagimoto
Chairman and CEO

Masanori Sawada
Chief Medical Officer

Michihisa Nishiyama
Domestic Development

Al Reaves
Overseas Development

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Pipeline

Field	Development Code	Indication	Market	Pre-clinical test	Phase I Trial	Phase II Trial	Phase III Trial	Apply-approve	On the Market	Progress Status
Somatic stem cell Regenerative Medicine	HLCM051	Ischemic Stroke	Japan	→	→	→	→			Phase 2/3 Trial
iPSC Regenerative Medicine	HLCR011	Wet AMD	Japan	→	⇢ Transplantation conducted under Clinical research(*1)					Start of clinical studies originally scheduled in 2017 may be delayed
	HLCL041	Metabolic Liver Disease	Japan	→						Joint research with Yokohama City University
	HLCR012	Dry AMD	US	→						Technical transfer
	HLCR012	Dry AMD	EU	→						Global Trial Under Consideration based on US Phase III Trial

* 1 “Clinical research of transplantation of induced pluripotent stem cells – derived retinal pigment epithelium (RPE) cells for exudative age-related macular degeneration (AMD)” conducted by RIKEN etc.

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Manufacturing for iPSC-derived RPE products

iPSC Regenerative medicine

RPEs in Japan



Sighregen (our joint venture with Sumitomo Dainippon Pharma) is establishing a manufacturing facility in “SMaRT”, the Manufacturing Plant for Regenerative Medicine & Cell Therapy by Sumitomo Dainippon Pharma.



Sumitomo Dainippon Pharma completed the new manufacturing plant for regenerative medicine & cell therapy “SMaRT” in Osaka in March 2018.

Sighregen rent the facility in SMaRT and begin establishing the iPSC-RPE manufacturing system.



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Strategic Investment in Athersys

Healios invested $21.1 million in Athersys and acquired 12 million shares

- Healios became its largest shareholder, acquiring 8.7% of Athersys' issued shares
- Our CEO Hardy Kagimoto will be appointed as the Athersys Board of Director in June 2018

<Potential in short-term> MultiStem may become a new cell therapy for various indications.
<Potential in long-term> MultiStem may become one of the important elements in our development of regenerative medicine.

Athersys inc.

Location	Cleveland, Ohio, U.S.
Listed	NASDAQ：ATHX
Products	**Stem cell products：MultiStem®**



（Source）Athersys

- Cell therapy product based on patented technology
- Developing for "off-the-shelf" administration: no tissue matching needed
- Long shelf life: can be kept frozen in a stable condition for years
- Consistent safety profile
- Promotes healing and tissue repair through multiple mechanisms of action
- Not a permanent transplant: cells cleared from the body over time

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Expansion of MultiStem Collaboration (In Process)

Existing License

Ischemic stroke / Japan

In case of the whole expansion: $35 million

License

- Japan
  - Trauma
  - Acute Respiratory Distress Syndrome (ARDS)
- World wide
  - Organ bud therapies using MultiStem
  - MultiStem products for ophthalmological indications
  - iPSC derived RPE products using MultiStem
- Others

Option

※Payment for exercise fee is required to start development

- China
  - Ischemic stroke
  - Acute Respiratory Distress Syndrome (ARDS)
  - Trauma

Execution of $10 million in escrow

（In Japan Only）

$25 million may be deducted from certain milestone payments

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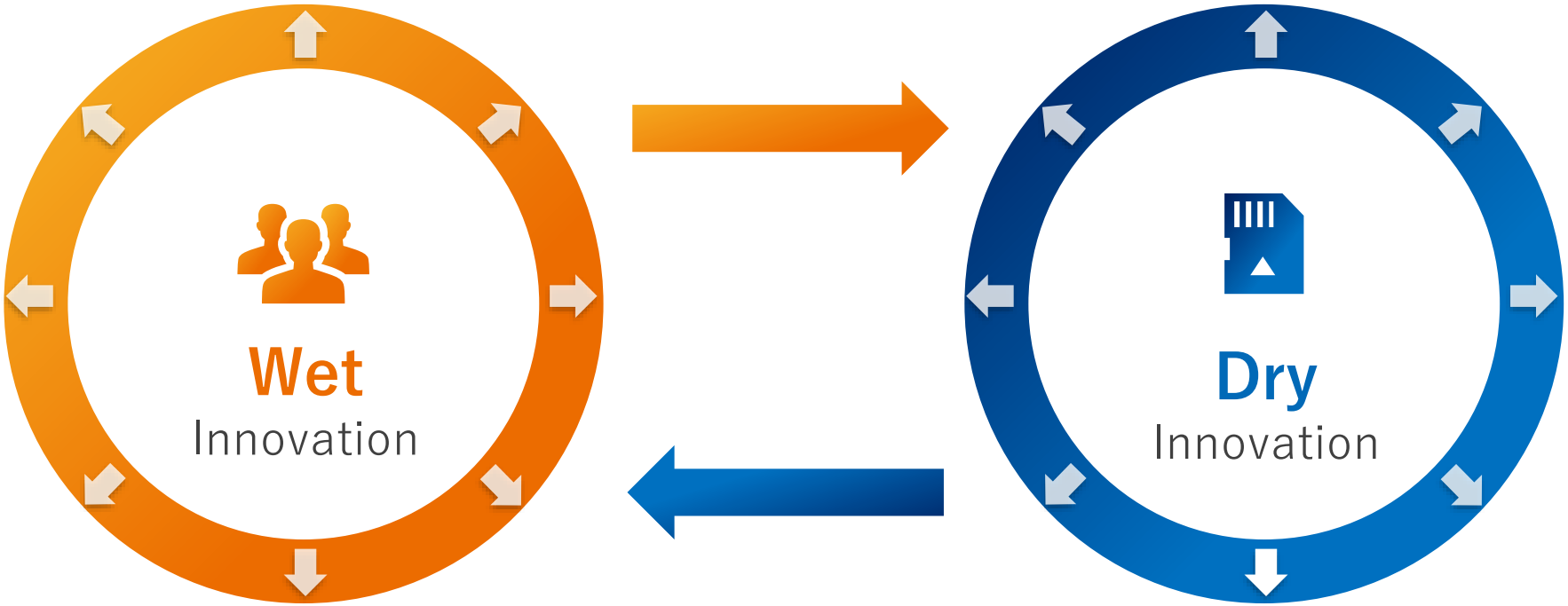
3. Growth Strategy

Wet Innovation/ Dry Innovation



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Core of wet innovation, today



Small molecule



Large molecule



Cell

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Cell innovation, today

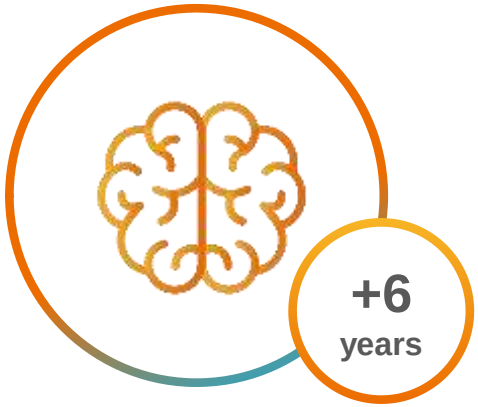
Short term pipelines would be able to fund future pipelines
Reach fastest approval/POC in Japan and fuel global development



MSC somatic stem



iPS/ES single



iPS/ES organ

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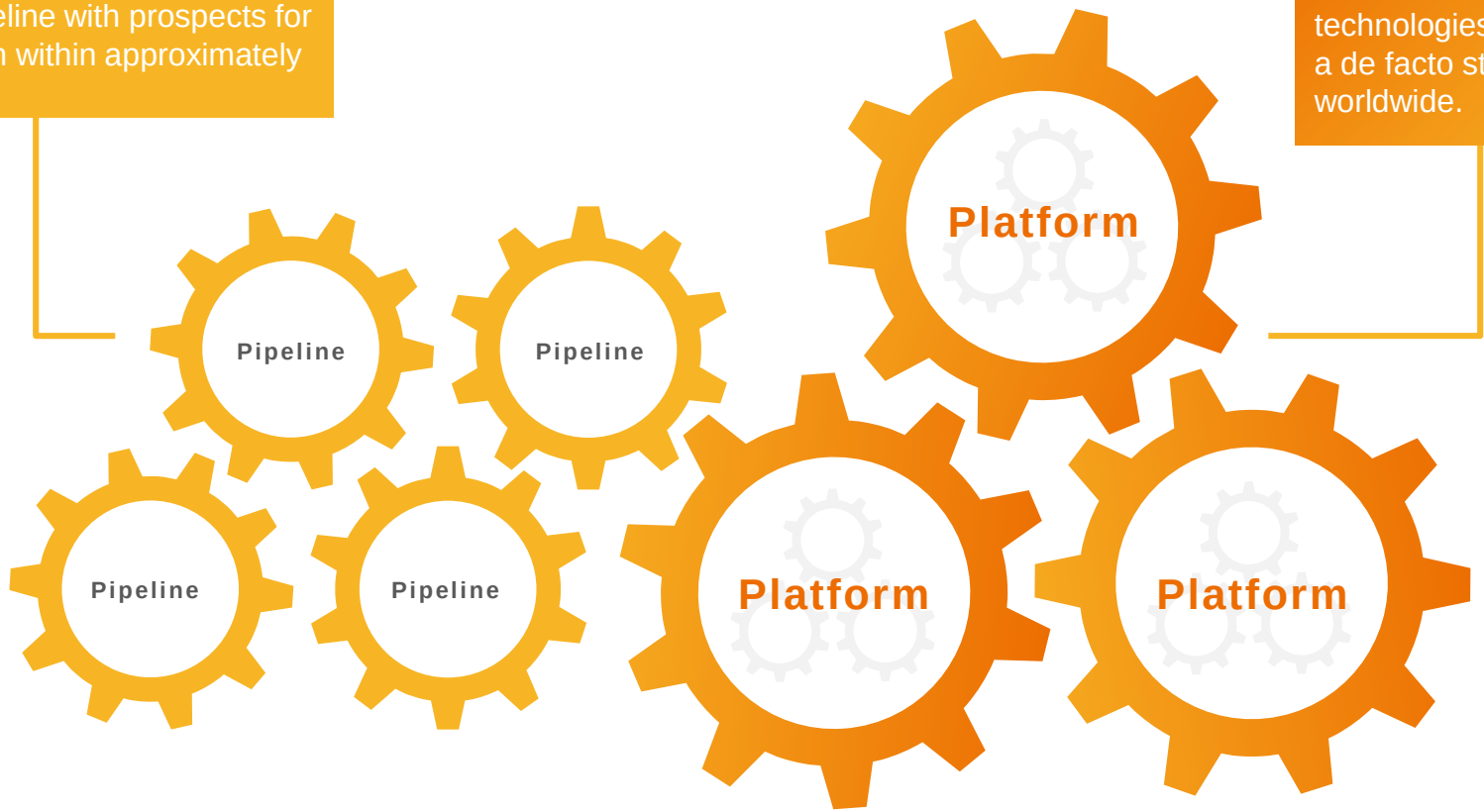
Short-term

(a) The development of products that contribute to strengthening the company's business position, through a development pipeline with prospects for approval in Japan within approximately 3 years.

Long-term

(b) The development of innovative foundational technologies that build a de facto standard worldwide.



Using the know-how and earnings we acquire through (a), we will invest strategically in (b) in order to achieve sustained, explosive growth.

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4. Details of Somatic Stem Cell Regenerative Medicine

Outline of ischemic stroke in Japan

Ischemic stroke

Ischemic stroke, which represents the most common form of stroke (70–75% of cases in Japan), is caused by a blockage of blood flow in the brain that cuts off the supply of oxygen and nutrients, resulting in tissue loss.

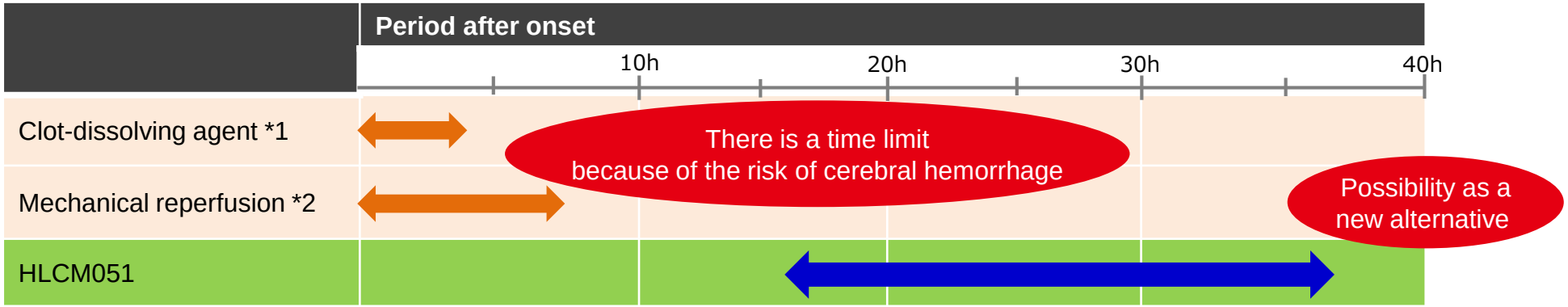
It is estimated that 37.9% of bedridden patients and 21.7% of persons who were in need of care were affected by ischemic stroke.



（Source）Athersys

Treatment in accordance with the period after onset

■ Expected development of a new therapy that can be applied in a longer treatment widow period following the onset of ischemic stroke (ability to help more patients)



*1: Dissolves blood clots in the brain vessels. *2: Insertion of the catheter into a blood vessel and recovery of the thrombus directly with a wire

(Note) This material was prepared to explicitly describe the major therapeutic options for ischemic stroke and their treatment window periods after onset. Appropriate treatments are conducted according to patients' conditions and classification of their symptoms. Experimental or investigational treatments not included in the above are also performed.

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Annual number of new patients with ischemic stroke in Japan

Target population

	Japan	Note
Number of patients (yearly)	**230,000 – 330,000**	Annual medical costs for ischemic stroke estimated at 1,070.7 billion yen（2009）
Severe patients（atherothrombotic and cardiogenic cerebral infarction)	**130,000**	
patients within 36 h after onset	**62,000**	

(Source) Healios estimated the annual number of new patients with ischemic stroke in Japan according to materials issued by the Fire and Disaster Management Agency, the Ministry of Internal Affairs and Communication, and the Ministry of Health, Labour and Welfare – DATAMONITOR epidemiological estimates also shown as upper end of range.
(Source) Healios estimated the percentage of patients who reach the hospital within 36 hours after onset at 47% according to the results of its market research.

(Note) Calculated using 2013 and 2014 fiscal year-end exchange rates.

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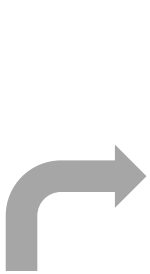
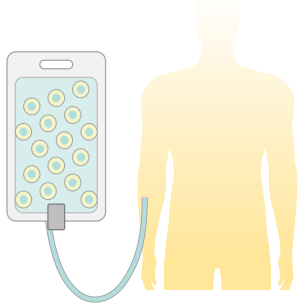
Mechanism of HLCM051 treatment

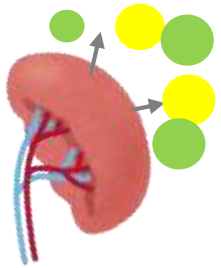
- Following intravenous administration after acute neurological injury, HLCM051 distributes to spleen, downregulating hyperinflammatory response.
- HLCM051 promotes the neuroprotective effect by releasing various cytokines and growth factors.



Stroke-induced neuronal damage (Primary)

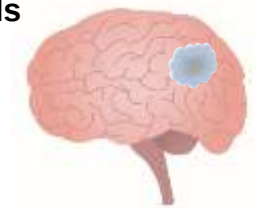
With HLCM051



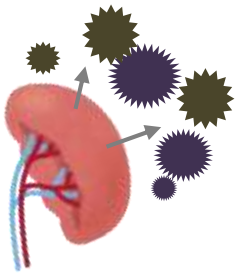


HLCM051
- **Suppress the mobilization/ release of inflammatory cells (lymphocytes, cytokines)**
- **Activate the mobilization/ release of anti-inflammatory cells**

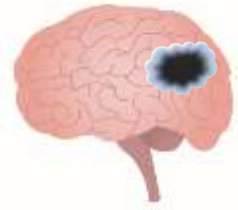
Attenuate neuronal damage in the acute phase of stroke caused by inflammatory cells



Without HLCM051



Mobilization / release of inflammatory cells (lymphocytes, cytokines) in the spleen is activated



Exacerbate neuronal damage caused by inflammatory chemokines/ cytokines (Secondary)

Inflammatory cells are released from the spleen and exacerbate the neuronal damage of the ischemic site.

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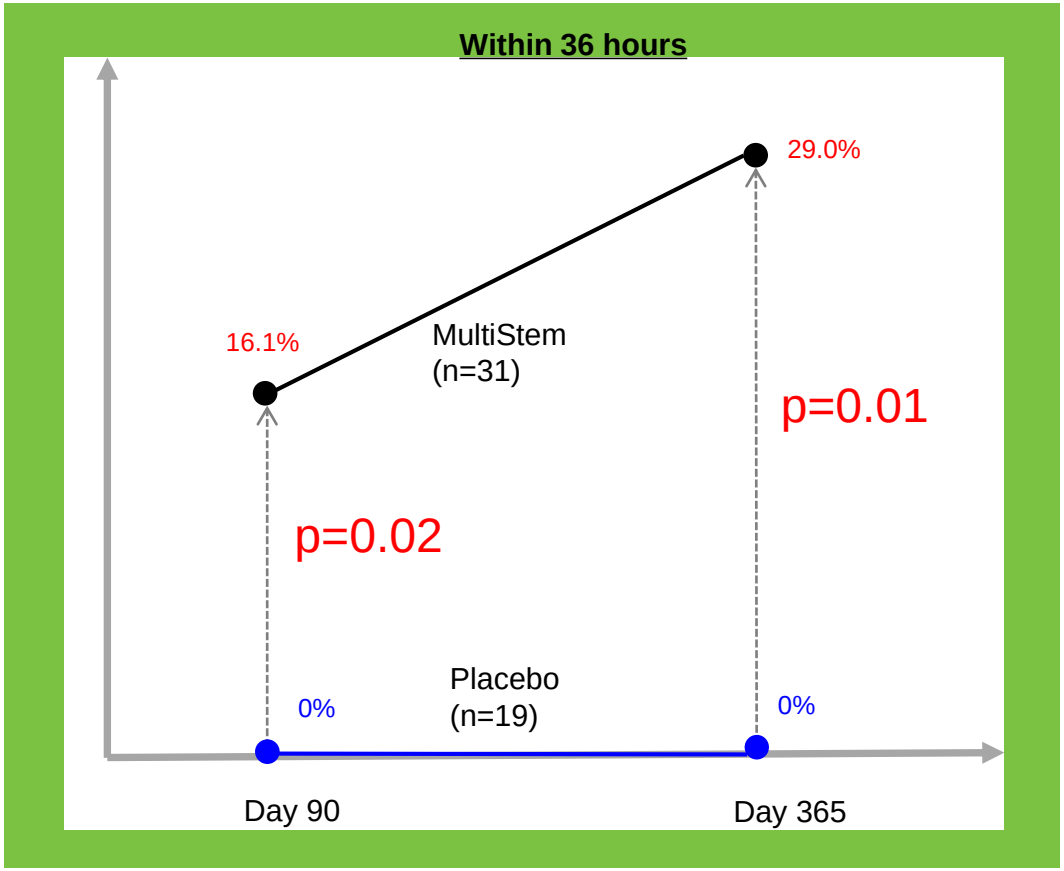
The proportion of patients who achieved Excellent Outcome was statistically significant (compared with the placebo group) both at Day 90 and Day 365 in the group of patients who received MultiStem within 36 hours of the onset of cerebral infarction.



(Source) Prepared by Healios based on the data provided by Athersys.

(Note) Excellent outcome = All of the following: mRS ≤ 1, NIHSS ≤ 1, and BI ≥ 95)

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HLCM051: Clinical trial status

"Placebo-Controlled, Double-Blind, Phase 2/3 Efficacy and Safety Trial of HLCM051 (MultiStem®) in Patients With Ischemic Stroke" (**TREASURE study)**

▲Problems at the manufacturing contractor in the United States
▲Patient enrollment had been temporarily suspended due to the deviation of placebo

The first patient was enrolled on November 15, 2017.
Enrollment continues to make good progress.
It will take about 2 years for the inclusion of subjects as originally estimated.



First Patients enrolled
Nov 2017

TREASURE study completion: within FY2020
Note: This includes 1 year follow up, but primary endpoint assessment will occur at 3 months after last subject enrolled

The approval period may be shortened from 12 months to 6 months by the SAKIGAKE Designation System

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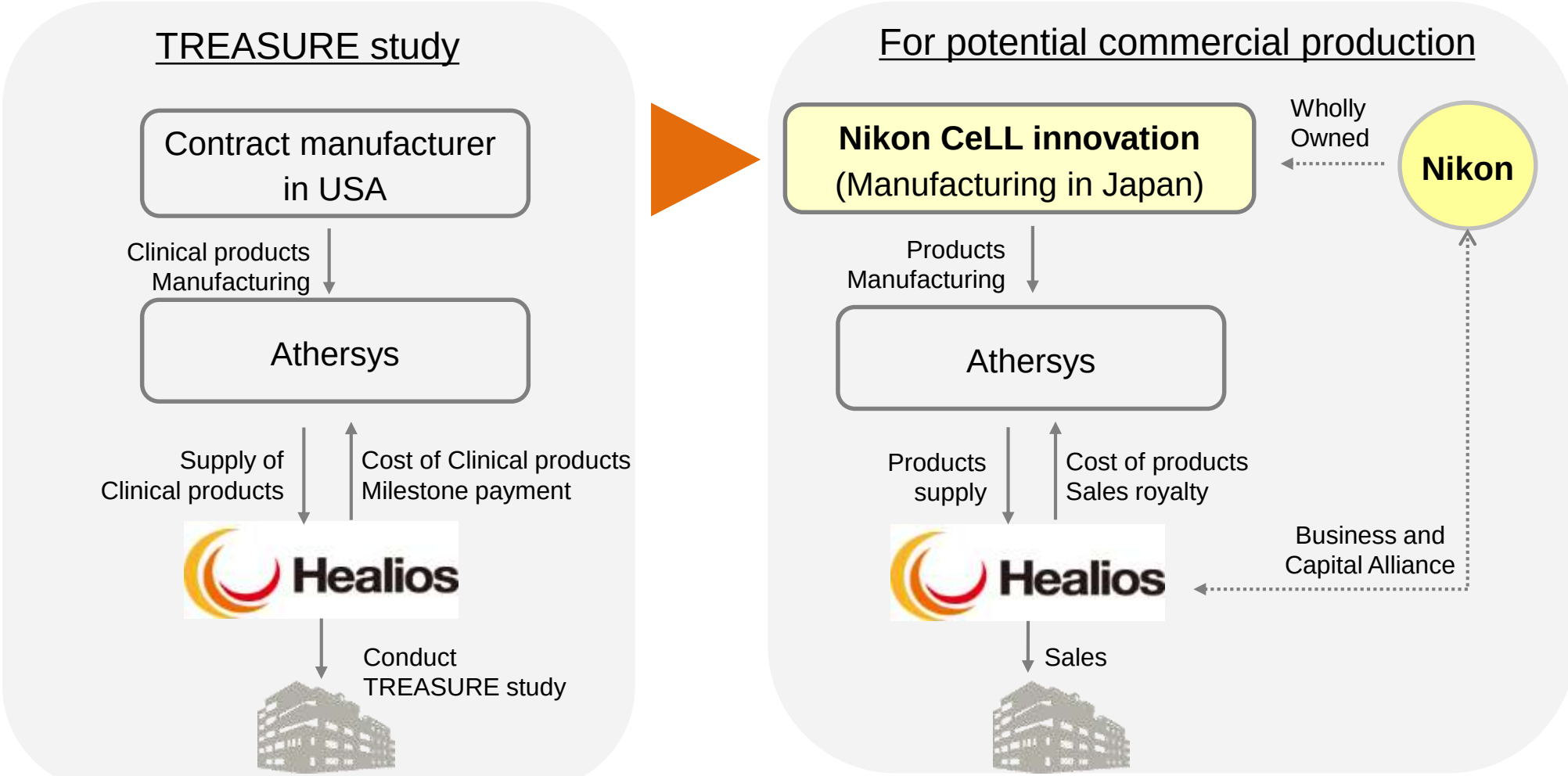
HLCM051: Business Partners

Nikon CeLL innovation executed a manufacturing service agreement with Athersys in preparation for the commercialization of HLCM051



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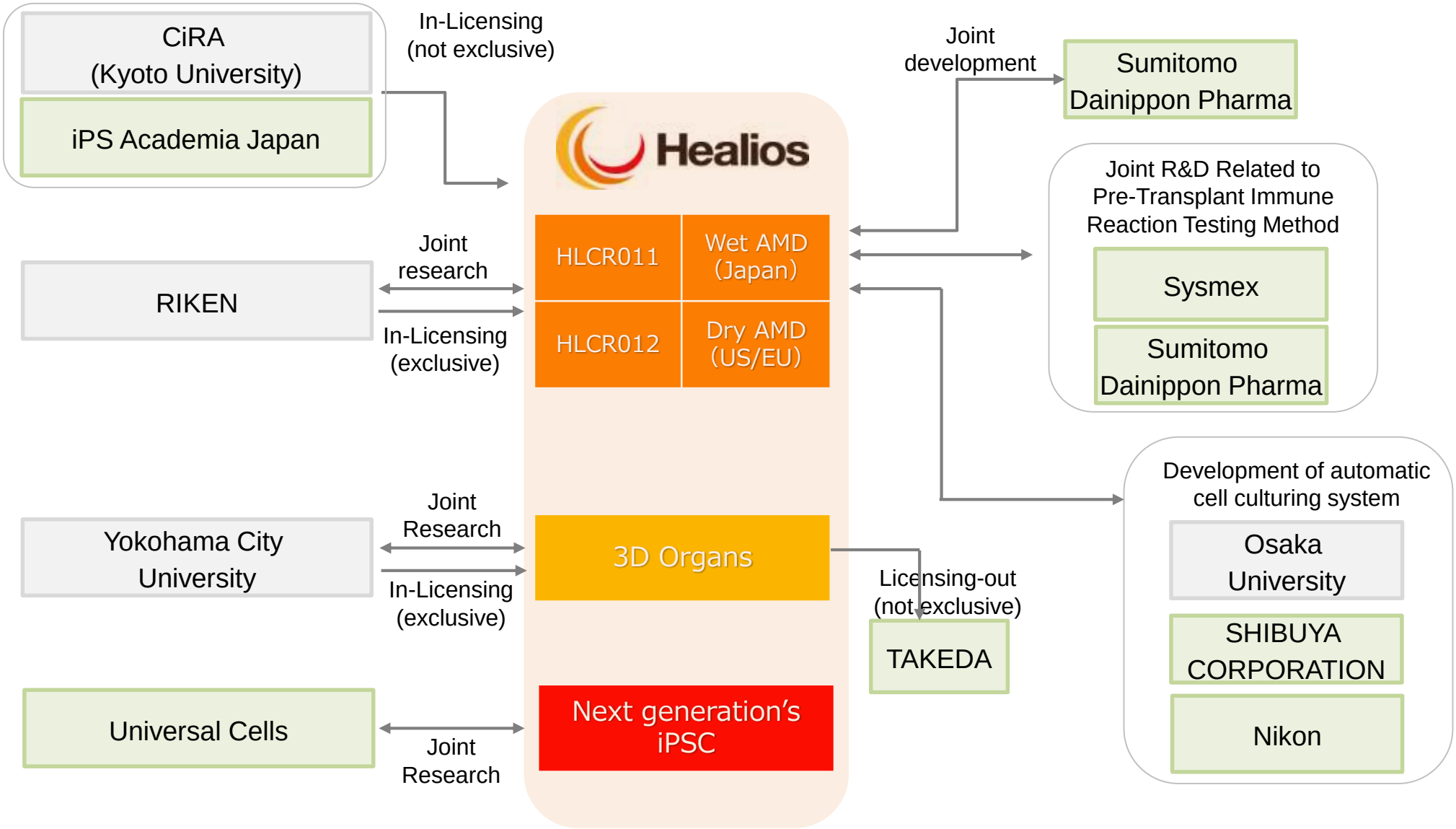
5. Details of iPSC Regenerative Medicine

iPSC Regenerative Medicine field: Business Partners



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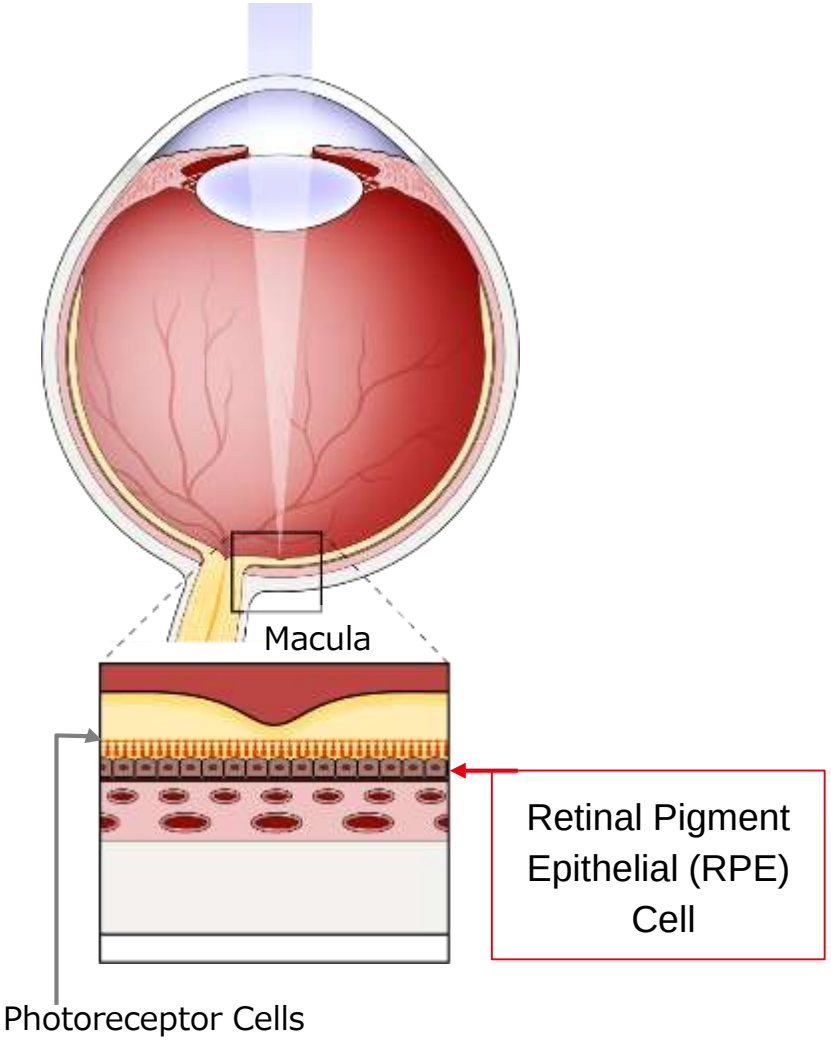
Explanation of AMD pathological condition

AMD causes RPE Cells to degenerate, which damages function.



Regular Macular Part

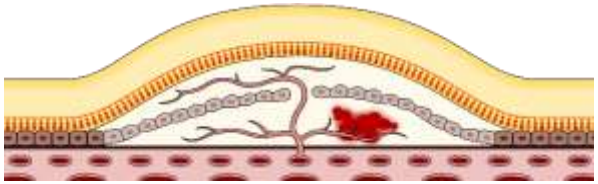
Developed Dry AMD

Immunity Barrier Maintained
→ Degeneration of photoreceptor→ Dry AMD



Wet AMD

Destruction of Immunity Barrier → Invasion of Immune Cells
→ Inflammation → Wet AMD



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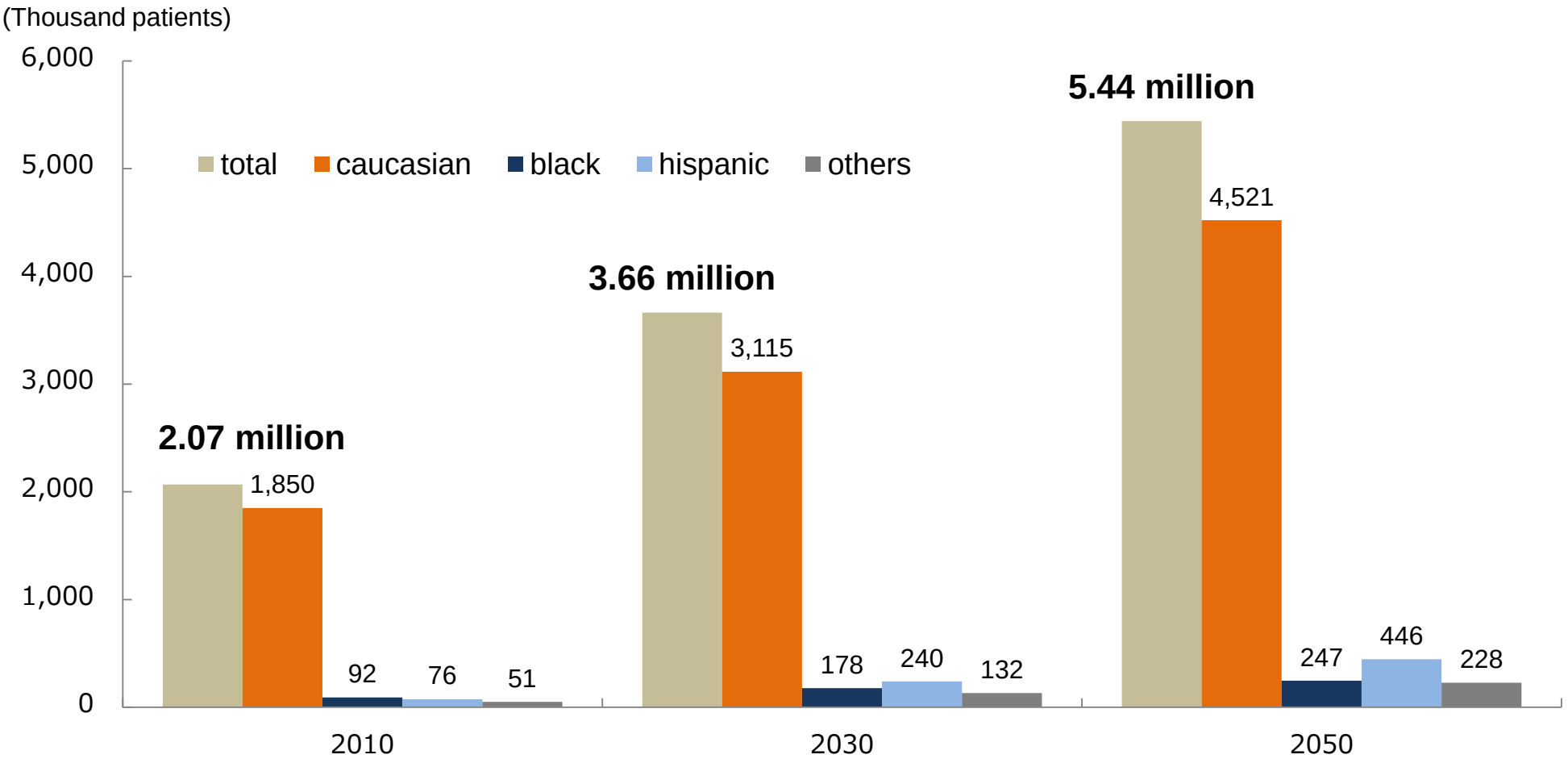
Estimated number of future serious case AMD patients in the US

Expected to increase over medium- to long-term as society ages



(source) National Eye Institute

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Number of AMD patients

Number of both Wet and Dry patients (including mild cases)

（Thousand patients）

	America	Japan	Others
Number of AMD Patients	**10,000**	**9,230**	**13,000**
Number of AMD Patients in Serious Cases	**2,000**	**690**	**2,600-3,220**
Wet-patients in serious cases	**1,000-1,500**	**630**	**1,300-1,950**
Dry-patients in serious cases	**850-900**	**60**	**1,100-1,170**

※According to research by Hisayama Kyushu University Graduate School of Medicine in Fukuoka (based on a comprehensive study), the total number of patients in Japan is calculated, estimating the total number of first-stage age-related macular degeneration and latter stage of age-related macular degeneration based on population statistics (2007). Also, the Disease Information Center announced that the number of patients suffering serious cases is approximately 690,000. The total number of patients in the US, which the National Eye Institute reports, includes the total number of age-related macular degeneration patients in mild cases and patients with visual field defects. Also, our company calculated the total number of Dry/Wet patients based on the incidence rates presented by AMDF (2010). Our company calculated the total number of patients in Europe based on incidence rates in each grade of European population statistics （2010)

※source: Prevalence of age-related maculopathy in older Europeans: the European Eye Study (EUREYE).Source: Arch Ophthalmol. 2006 Apr;124(4):529-35

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Market scale of AMD

Annual sales of medicinal treatments of Wet AMD: 8.44 billion USD.
No medicine for Dry AMD.

Condition	Medicine / Effect	Year	America	Japan	Others	Total
Wet	Anti-VEGF Medicine/ Restraint of New Blood Vessels	2016	**4,729 million USD**	**580 million USD**	**3,127 million USD**	**8,436 million USD**
Dry			**No Medicine**			

(source) Market scale was calculated using official materials from drug companies (Roche Diagnostic, Novartis, Regeneron, Bayer HealthCare, Santen Pharmaceutical Co., Ltd). Calculated using 2016 fiscal year-average exchange rates.

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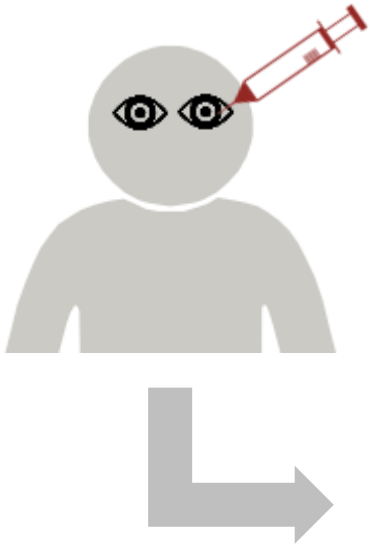
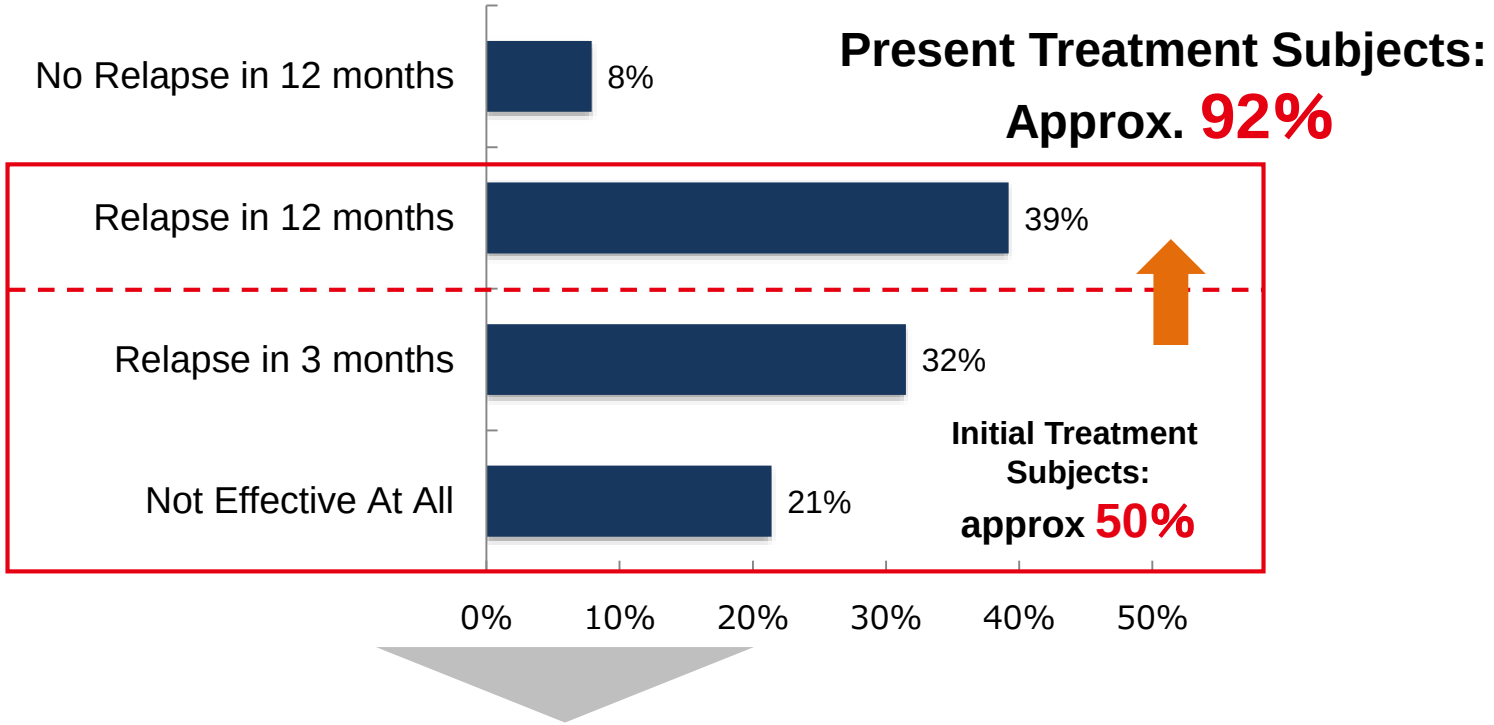
Treatment subjects for Wet AMD

Patients recurring within 1 year, which is the case for approx. 92% of Wet AMD Patients, are the candidates for treatment.



Recurrence frequency after receiving anti-VEGF medication



Present Treatment Subjects:
Approx. 92%

Initial Treatment Subjects:
approx 50%

QOL of continuously medicated patients is not high.

(source) 13th Annual Meeting of The Japanese Society for Regenerative Medicine March 19th 2014, Thurs, 12:00～12:50
Approach to Clinical Application of iPS cells Institute of Physical and Chemical Research, Mandai Michiko

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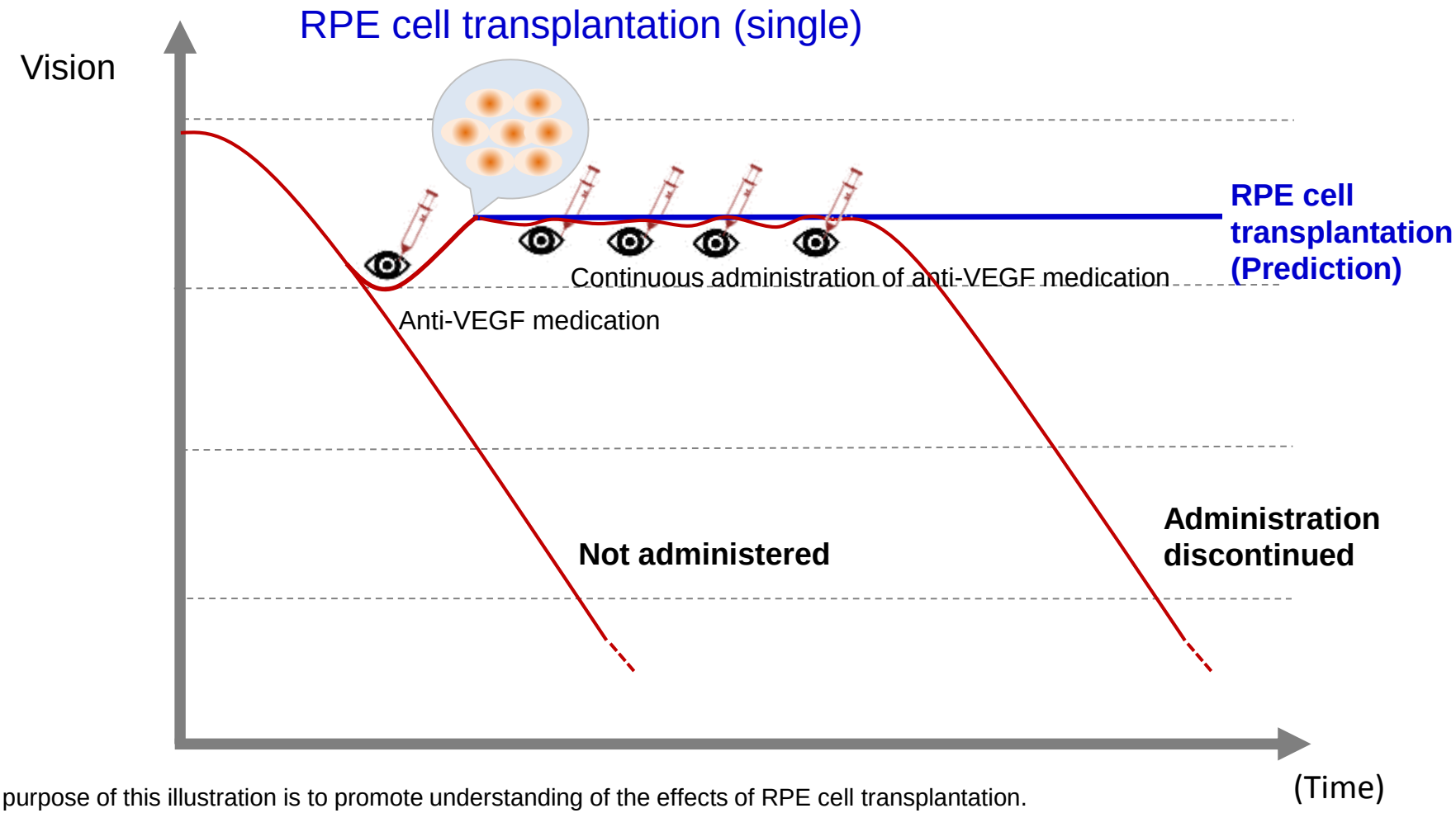
Good vision can be maintained with early treatment



* The purpose of this illustration is to promote understanding of the effects of RPE cell transplantation.
Changes in vision with the administration of anti-VEGF medication vary according to patient symptoms and administration frequency.

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Guide to medicine price – Approach based on the cost of existing treatment

Anti-VEGF medicine mostly continues from the beginning of treatment until death

Annual Medical Expense

Unit Price of Anti-VEGF + Treatment Price
160,000 yen

✖

Annual Recommended Medication Protocol
6 Times

=

Annual Medical Expense
1,000,000 yen

Estimate of Lifetime Medical Expense

On the Assumption of Average Life Span (Japan): 80years old (Male) / 86 years old (female)

Estimate of Lifetime Medical Expense

Continuous Treatment for **50-year old Patient Onset** ＝approx. **30years** ✖ **1.02 million yen** = **Approx. 30 million yen**

60-year old Patient Onset＝approx. **20years** ✖ **1.02 million yen** = **Approx. 20 million yen**

(source) Onset Data: National Eye Institute; Average Life Span: The Ministry of Health, Labor and Welfare; Annual Recommended Medication Protocol: Materials Presented by Institute of Physical and Chemical Research

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Status of clinical research by RIKEN etc.

"Clinical research of transplantation of allogeneic induced pluripotent stem cells – derived retinal pigment epithelium (RPE) cells for exudative age-related macular degeneration (AMD)"

March 2017:
Operation on first subject in clinical research using Allogeneic iPSC-derived RPE cell suspension.
November 2017:
Operations using Allogeneic iPSC-derived RPE cell suspension completed on 5 subjects. Continuing follow-up observation for one year.

	Sheet	Suspension
Autologous cells	Operation on 1 subject (in 2014)	To be determined.
Allogeneic cells	To be determined	Operations on 5 subjects (in 2017)

January 2018:
In one case an epiretinal membrane, deemed to be one of causes of retinal edema, was removed to improve symptoms during the clinical research.

Dr. Takahashi from RIKEN explained that "The adverse effect was not imminent or urgent in nature. This event will not have any impact to our clinical studies in the future."

(Sources) Created by Healios from the data at a press conference by RIKEN

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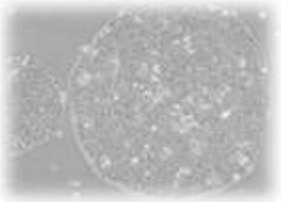
6. Expansion to 3D Organs (Liver)

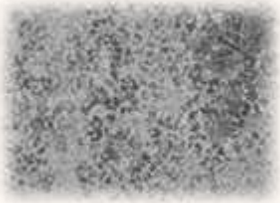
3D organ generation mechanism

Generating "Organ bud" by co-culturing 3 types of cells

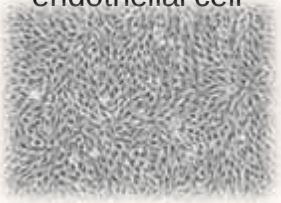
Human iPS cell



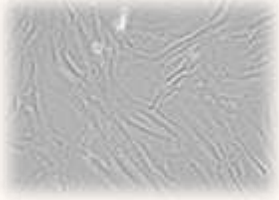
Precursor cell



Vascular endothelial cell



MSC



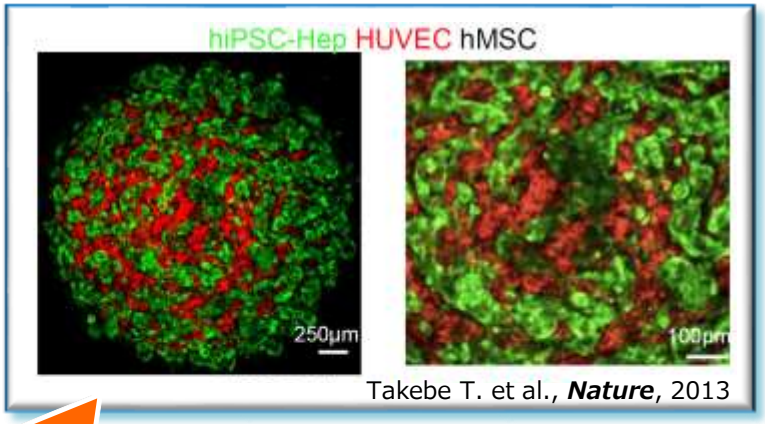
Organ bud*



Organ bud=
Origin of organ

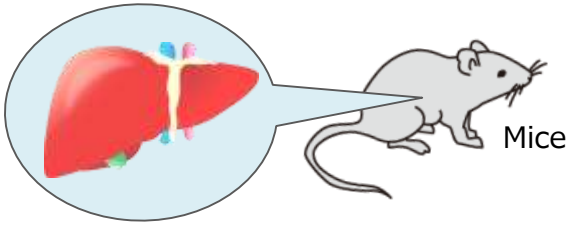


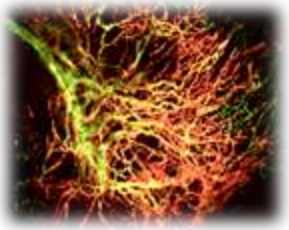
"Elplasia" from Kuraray Co., Ltd.
(http://www.elplasia.com/products/round_bottom/)



Takebe T. et al., ***Nature***, 2013

Cell Transplantation





Containing blood vessels and human liver

Takebe T. et al., ***Nature Protocols***, 2014

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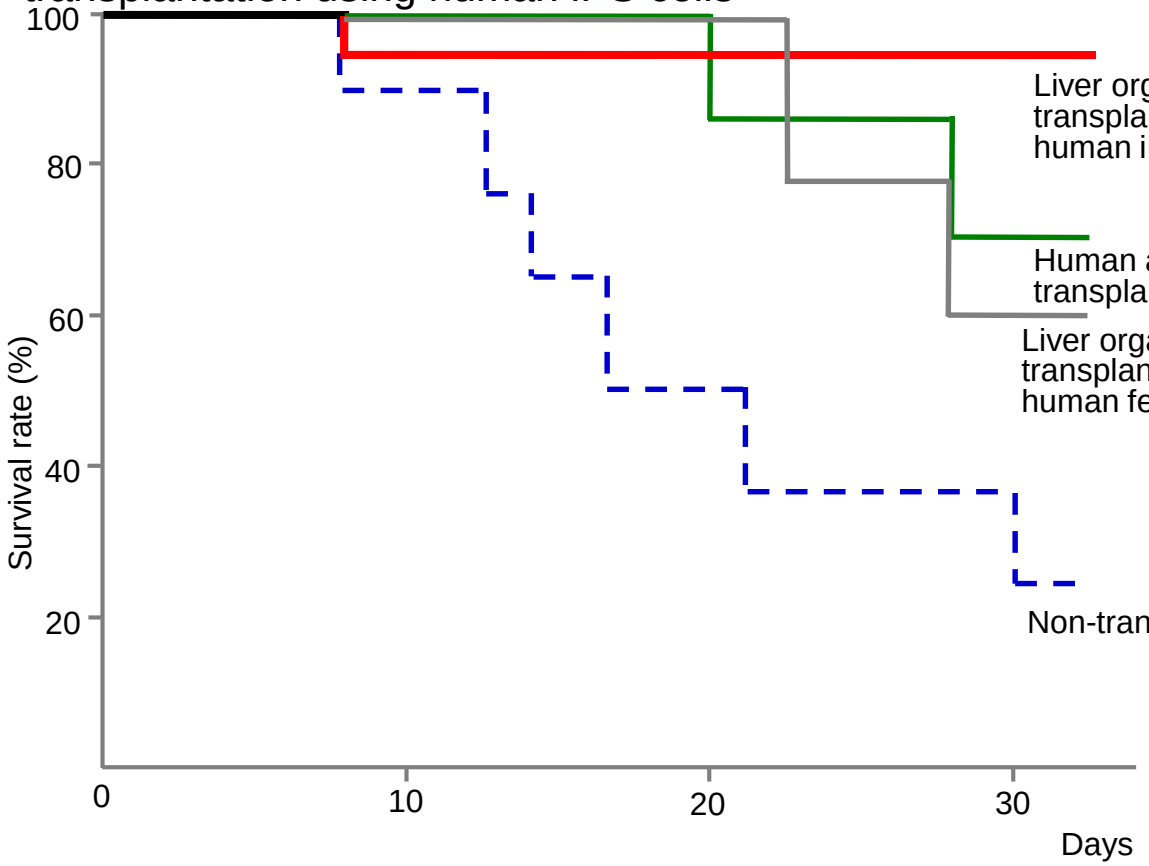
Survival rate of liver failure model mouse

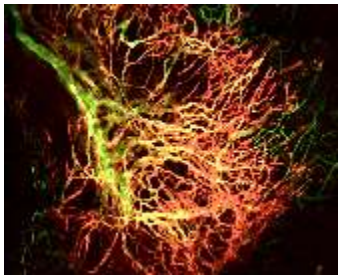
Survival rate improves significantly in transplantation experiments

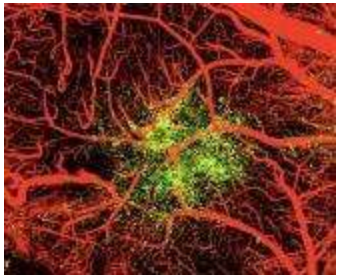
Treatment effects of liver organ bud transplantation using human iPS cells



(Source) Adapted by Healios from Takebe. T, et al. Nature, 499 (7459),（2013)

Process by which organ forms from organ bud links mouse ‘s vascular network autonomously





(Source) Takebe,T., et al.
Nature Protocols, 9, 396–409 (2014)

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Metabolic liver disease in newborns

Yokohama City University planning to start clinical study in 2019

Urea cycle defect

Disease caused by congenital abnormality of enzyme functioning in metabolic pathway (urea cycle), which detoxifies ammonia in the liver and produces urea. Presently, the only definitive treatment available is liver transplantation.

* Even patients with minor conditions require treatment combining food treatment and medication to lower ammonia levels throughout their lives.

Estimated market size of metabolic liver disease in newborns

	US	Japan	Europe	Total
Number of patients (yearly)	**Approx. 160**	**Approx. 30**	**Approx. 230**	**Approx. 420**
Treatment costs (annual) Enzyme replacement therapy	**30 million yen – 50 million yen**			
Estimated annual market scale	**5 - 8 billion yen**	**1 - 1.5 billion yen**	**6 - 11.5 billion yen**	**12 - 21 billion yen**

∗ Number of patients and market size are estimated by Healios based on number of newborns and incidence rate.

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Expansion of Marketability
(Alternative Treatment for Replacing Liver transplantation)

Prospecting R&D for alternative treatment for liver transplantation

	Liver transplantation			Total
	US	Japan	Europe	
Number of patients undergoing treatment (Annual)	**Approx. 6,000**	**Approx. 400**	**Approx. 4,000**	**Approx. 10,000**
Number of patients on waiting list (Annual)	**Approx. 15,000**	**Approx. 400**	**Approx. 4,000**	**Approx. 20,000**

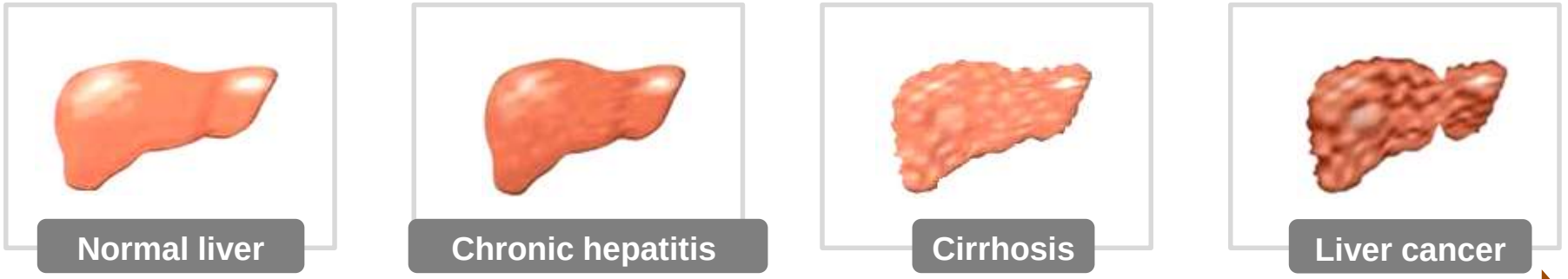
（Source） Compiled by Healios based on materials disclosed by Japanese Liver Transplantation Society, UNOS, Eurotransplan, UK Transplant, Agence de la biomédecine, and Scandia Transplant.

Liver disease drawing attention in future is cirrhosis

Estimated patients with cirrhosis in Japan: 400,000 to 500,000. About 56,000 receive treatment at medical facilities.
Annual deaths in Japan: 17,000 patients.

（Source） Patient Survey 2011 Liver Cancer White Paper 2015

Progress of liver disease



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7. Company Overview

Healios Overview

About Us

Company Name	HEALIOS K.K.（TSE: 4593）
Representative	 Hardy TS Kagimoto, MD Chairman and CEO ■ Succeeded in Developing BBG250 and Realized Sales in Europe
Head Office	World Trade Center Building 15F 2-4-1 Hamamatsucho Minato-ku, Tokyo Japan 105-6115
Paid in Capital	11,360 million yen (As of end of March, 2018)
Number of Employees	75 (As of end of March, 2018)
Research Institution	Kobe and Yokohama
Affiliated Company	SighRegen Co., Ltd. (Joint Venture with Sumitomo Dainippon Pharma Co., Ltd.)
Subsidiary	Healios NA, Inc.

Our Experienced Executive officers

CMO (Chief Medical Officer)	Masanori Sawada, MD, PhD, MBA	■ Osaka University Invited Associate Professor
In charge of overseas development	Al Reaves, PhD	■ Responsible for innovative clinical programs for wet & dry AMD - Lucentis (X-US); Visudyne (global)
In charge of Research and Manufacturing/ Head of Kobe Research Lab.	Kouichi Tamura, PhD	■ Astellas US Director of Laboratories ■ Well-acquainted with Immunosuppressant Research
In charge of Domestic Development	Michihisa Nishiyama	■ Constructed network for Tacrolimus approval and sales at Astellas in the US and Europe
In charge of Administrative field	Ken Ishikawa	■ Striving to strengthen organizational capabilities

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Company History and Societal Trends

2011
- Retina Institute Japan established (currently Healios)
- ◆ Certified as RIKEN Venture

2012
- ○ Prof. Shinya Yamanaka wins Nobel Prize in Physiology or Medicine

2013
- ○ Act on the Safety of Regenerative Medicine, Pharmaceutical and Medical Device Act established
- ◆ Patent licensing agreement with RIKEN
- ◆ Joint development agreement with Sumitomo Dainippon Pharma

2014
- ○ RIKEN Conducts 1st transplantation surgery in world's first clinical study using iPS cells
- ■ Joint research on organ bud with Yokohama City University

2015
- ○ RIKEN announces good follow-up results 1 year after administration in clinical study
- ✓ Listed on MOTHERS

2016
- ● HLCM051 Patent licensing agreement with Athersys
- ■ Collaborative research agreement with Universal Cells

2017
- ○ RIKEN Conducts 1st transplantation surgery in world's first clinical study using allogeneic iPS cells
- ✓ Business and capital alliance agreement with Nikon
- ✓ BBG business transfer
- ● HLCM051 First patient In

2018
- ✓ Healios N.A
- ■ Strategic investment in GAIA BioMedicine
- ■ Strategic Investment in Athersys

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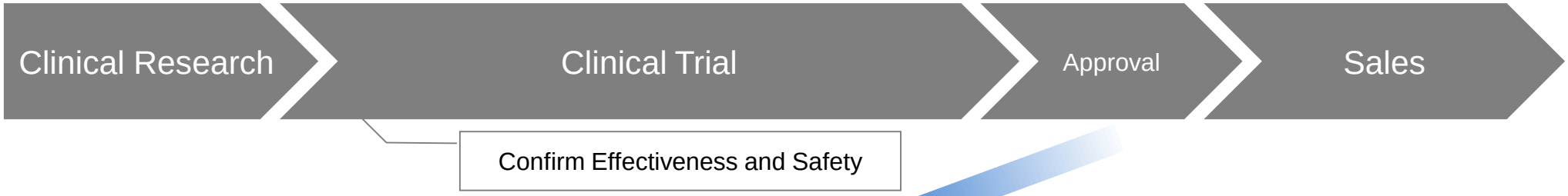
8. Circumstances of Regenerative Medicine

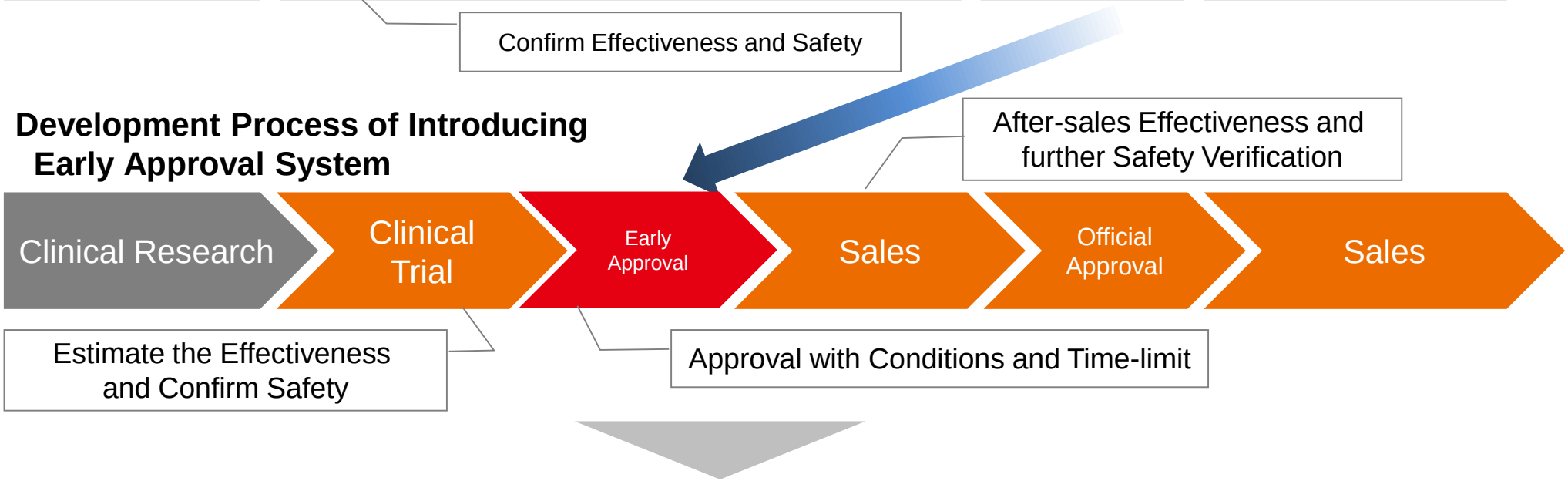
Historical Alleviation of Regulations

Japanese Government Revises Regulations to Put Japan at the Forefront

Process of the Development So Far



Development Process of Introducing Early Approval System



- Drastic reduction in the treatment period and number of patients with ‘Early Approval System’ .
- Insurance is listed at ‘Early Approval’ stage.

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Rapid impact of modified regulations

Approval of regenerative medicine products, September 2015

Product Name	Temcell® HS Injection	Heart Sheet
Company	JCR Pharmaceuticals	Terumo
Indications	Acute GVHD after hematopoietic stem cell transplantation	Severe heart failure due to ischemic heart disease
Price	13.9 million yen	14.76 million yen
Important Point	First allogeneic cell-based regenerative product	First conditional approval

(note) Calculated using 2013 and 2014 fiscal year-end exchange rates.

Price calculation method prospects

Cost accounting system

* The price of new drugs is basically calculated according to the prices of official articles with similar efficacy (price determination by comparable drug). However, if there are no appropriate similar official articles, required costs are added in the calculation of prices (cost accounting system).

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Descriptions of future events, etc. in this document include Healios' assumptions, prospects, etc. based on information which could be acquired at the time this document was presented. For this reason, actual performance, development progress, etc. may differ from those described in this document according to the outcome of R&D in the future, the actions of regulatory authorities, etc. in the future, and uncertain/pending factors as of this point.

Also, this document contains information on regenerative medicine and medical equipment that are currently under development or already on the market. Such information is not intended for promoting advertising or providing medical advice.

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