

Healios

“To be the change in an ever evolving world
through enrichment of living”

FY2016 Financial Results

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1. Financial Highlights

Statement of income

(Million yen)

	FY 2015	FY 2016		
			YoY change	Reasons for increase/decrease
Sales	98	77	▲21	
Operating income	▲1,060	▲3,507	▲2,447	Research & Development Cost ▲2,330
Ordinary income	▲987	▲3,426	▲2,439	-
Net income	▲958	▲3,433	▲2,475	-
R&D	629	2,959	+2,330	Multistem License-in +1,809
Amortization of goodwill	100	100	–	-
Number of employees	44	58	+14	-

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Balance sheet

(Million yen / %)

		December 31,2015	December 31, 2016		
				Change	Main reasons for increase/decrease
	Current assets	9,325 (88.9%)	8,073 (88.0%)	▲1,252	
	Non-current assets	1,162 (11.1%)	1,101 (12.0%)	▲61	
Total assets		10,487 (100.0%)	9,174 (100.0%)	▲1,313	
	Current liabilities	1,080 (10.3%)	772 (8.4%)	▲308	
	Non-current liabilities	29 (0.3%)	2,408 (26.2%)	+2,379	Long-term debt +2,371
Total liabilities		1,110 (10.6%)	3,180 (34.7%)	+2,070	
Total equity		9,377 (89.4%)	5,994 (65.3%)	▲3,383	Earned surplus ▲3,433
Total assets		10,487 (100.0%)	9,174 (100.0%)	▲1,313	

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2. Updates in FY2016

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	→	→	→				**To Clinical stage**
iPSC Regenerative Medicine	HLCR011	Wet AMD	Japan	→						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
Compound drug	HLM0021	Vitreous surgery	Japan	→	→	→	→			Under development at WAKAMOTO Co., Ltd.
	HLM0021	Cataract surgery	Japan	→	→	→				Development will be advanced immediately after licensee is determined.
	HLM0022	ILM Peeling	EU	→	→	→	→	→	→	Launched
	HLM0023	ILM Peeling	US	→	→	→	→			Under development at D.O.R.C.

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FY2016 Updates

Somatic stem cell regenerative medicine	MultiStem®		- Introduced the new pipeline by executing the license agreement with Athersys, Inc. → To the clinical stage - “Placebo-Controlled, Double-Blind, Phase 2/3 Efficacy and Safety Trial of HLCM051 (MultiStem®) in Patients With Ischemic Stroke”
iPSC Regenerative medicine	RPEs in Japan		- Start of C**li**nical studies originally scheduled in 2017 may be delayed due to changes in pre-clinical study plans. - Joint R&D related to pre-transplant immune reaction testing method -February 2017, MHLW approved a clinical research plan. In the near future “Allogeneic×Suspension” RPE cells transplantation will be conducted. **1**
	RPEs overseas		- Optimization of process development is underway at the contract manufacturer
	3D organs (Liver)		- Promotion of collaborative research with Yokohama City University. - Executed a Sublicense Agreement with Takeda Pharmaceutical Company Limited
Compounds	BBG		- Advancement towards GMP production at the contract manufacturers of the drug substance/product - Results of a Phase III investigator initiated trial were published in an academic journal **2**

Collaborative research agreement with Universal Cells

Research for “next-generation iPS cell” that causes no immunorejection will start

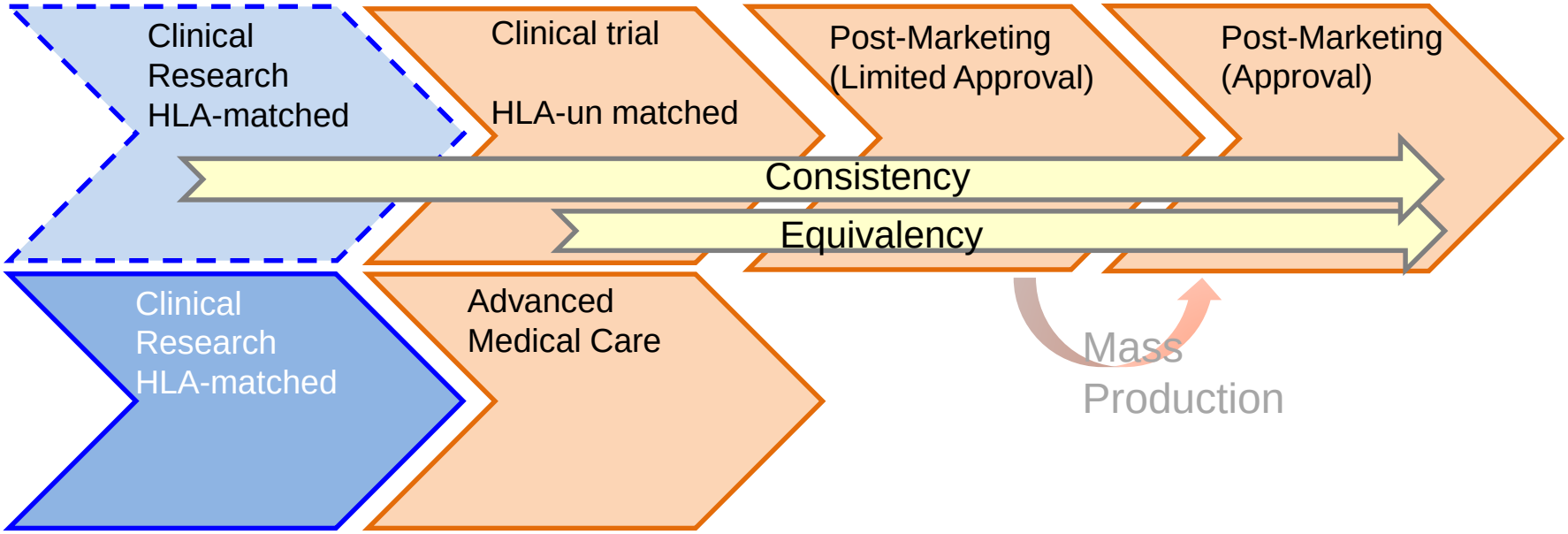
(Note) RPE: retinal pigment epithelium In the clinical research, RPE cells will be manufactured by RIKEN. And HLA matched cells will be transplanted, without using the immunosuppressive agent.

(Sources) MultiStem images = Created by Healios from the images provided by Athersys
“3D organs” image = Takebe,T., et al. Nature Protocols, 9, 396–409 (2014)

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Relationship between Clinical Research and Clinical Trials

1 Regenerative Medicine



Consistency: Causal relationships, common features, points of difference are distinct
Equivalency: No scientifically significant difference, recognized as equivalent

(Note) Prepared by Healios with reference to “Regenerative Medicine & Regulatory Science”, “Technical Guidance for Implementation of Quality, Non-Clinical Safety Testing & Clinical Studies of Regenerative Medicinal Products (Human Cell-Based Manufactured Products): On Quality”, and other materials

This image represents one example of connectivity between clinical research implemented by academia and clinical trials implemented by businesses, in regenerative medicine. It does not mean to imply that all clinical research and clinical trials are related in this fashion.

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Transfer our business relating to an ophthalmic surgical adjuvant containing BBG250

2

Compounds	BBG		Transfer our business relating to an ophthalmic surgical adjuvant containing BBG250

[The transferee] D. Western Therapeutics Institute, Inc.
[Transfer price] A lump sum fee of 1.3 billion yen at the time of transfer. There is also the possibility of receiving milestone payments in line with the progress, etc., of development and out-licensing operations.

[Contract date] January 31, 2017
[Business transfer due date] April 30, 2017 (Planned)

*By receiving lump sum payment at the time of business transfer, Healios expects to post an extraordinary income of approximately 0.6 billion yen in FY2017 ending December.

To concentrate our management resources in cell medicines, and following our mission, “To be the change in an ever-evolving world through enrichment of living,” We have decided to transfer the Business with the goal of moving forward our multilayered, multi-stratified pipeline strategy in therapeutic areas having high unmet medical needs.

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3. Expansion of Cellular Medicine Products

Image of the Transition of Cellular Medicine Products

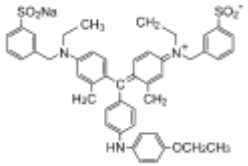
Immunosuppressant

Immune Barrier

Somatic Stem Cell

ES/iPS Cell

iPS Organ bud





Low molecular drug

Antibody drug

Cellular Medicine Products

Displacement of Function

3D Organ

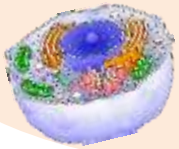
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Image of the Transition of Cellular Medicine Products

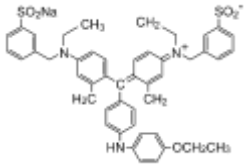
Immunosuppressant

Immune Barrier

Somatic Stem Cell



Universal Cells





3D Organ

Displacement of Function

Low molecular drug

Antibody drug

Cellular Medicine Products

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Healios' approach for Technology for Immune Reaction

Commercialization



Universal Cells

Immunosuppressant

Immune Barrier

Allogeneic iPSC bank

- Genome editing technology
- Pluripotent cells manufactured to avoid transplant rejection

Autologous

- HLA matched iPSC
- Pre-transplant immune reaction testing

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4. Direction of Future Business

Directions in Future Business　Summary

Development of existing pipelines	Development of treatment for AMD using iPSC derived RPE cells: Currently in preclinical testing, moving ahead to clinical trials under partnership with DSP.
	Development of treatment for ischemic stroke using somatic stem cells: Entered clinical trial phase in 2nd half of 2016, solid progress facing about two years of testing.
	Development of treatment for metabolic hepatic syndrome using organ bud Technology: Though currently still in the research stage, pressing forward with development towards preclinical testing.
Introducing new pipelines	Priority is given to bringing in projects with an early expected payoff and synergy with existing pipeline projects
	Selection of new pipeline projects that are unique with no competition on the market, not just iPS cell-related, but including clinical pipeline projects and technology optimal for realistic fulfillment of select unmet patient medical needs.
	Next generation iPS cells with Universal Cells' technology to avoid transplant rejection are to be established as defacto standard, replacing predecessor ES / iPS products on the market.
Enforce of organization	Further strengthen R&D and manufacturing, looking into partnerships or M&A with other companies as options.
Financial arrangement	Continue to practice steady cash management while seeking new income opportunities in addition to funding already raised plus income from existing partners.

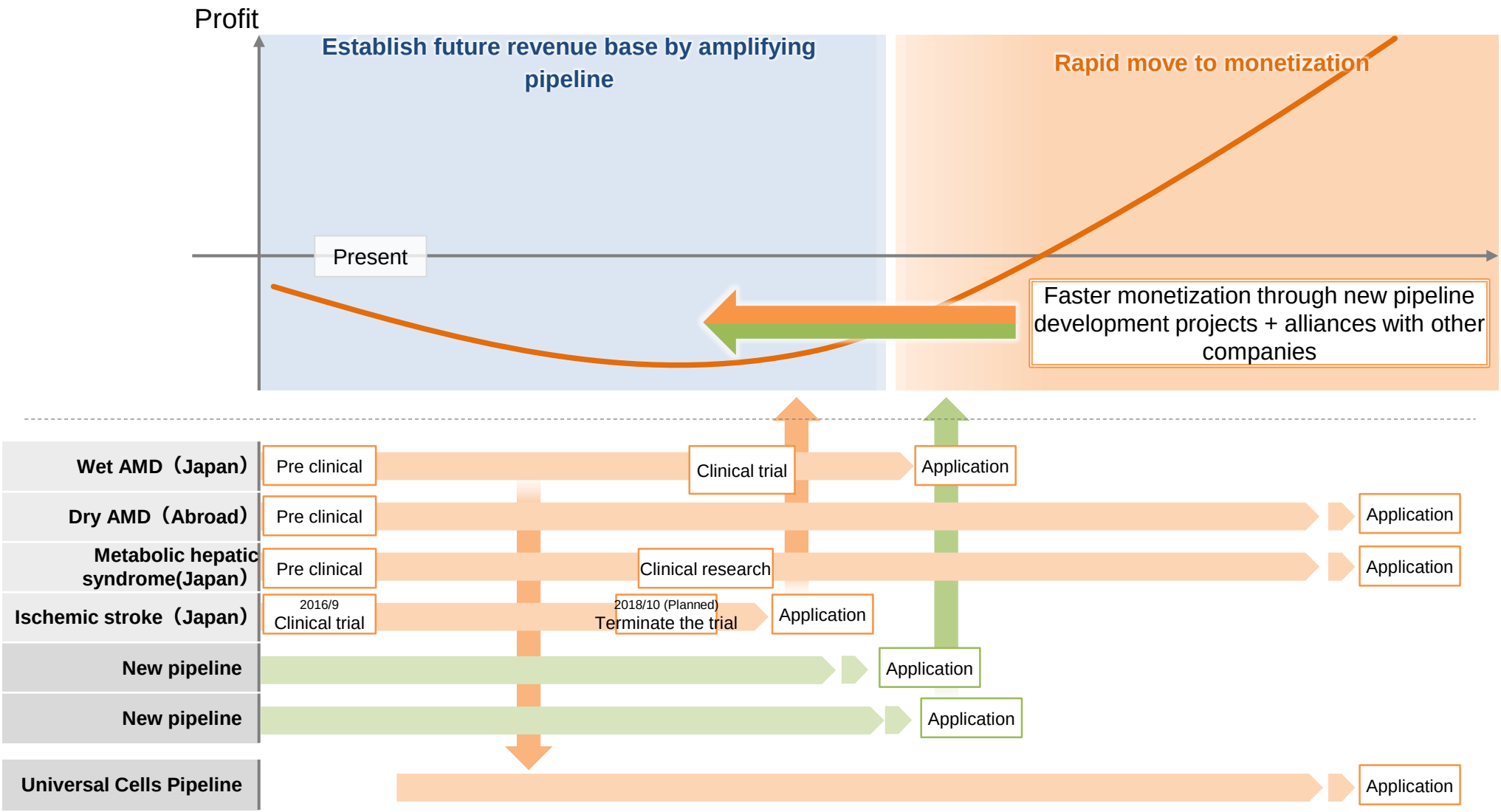
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Directions in Future Business　Existing pipelines

Indications	Stage	Outline	Development funds
Wet AMD	Pre clinical	• About 600,000 patient subjects in Japan • Differentiation and transplant RPE cells from iPSC (aim is to outgrow symptomatic treatment using anti-VEGF medication) • In joint development with DSP	Financing based on joint development with DSP Fundraising completed with 2015 listing
Dry AMD	Pre clinical	• About 5million patient subjects all over the world • Treatment of transplantation using iPSC derived RPE cells • No effective medication • Selection of development partner in process	Plan to prepare subsequent development costs through alliances, etc.
Metabolic Liver Disease	Pre clinical	• About 30 patient subject in Japan, over 400 in the world • Mini-liver transplant for patients with congenital abnormalities in specific liver enzymes • Existing treatments cost more than ¥30 million/ year • Yokohama City University plans to start clinical research in 2019	Partial research costs already been raised. Plan to prepare subsequent development costs through alliances, etc.
Ischemic Stroke	Clinical stage	• About 60,000 patient subjects in Japan • Cellular medication that improves post-stroke prognosis by suppressing immunoreaction • Hopes are for efficacy during 18-36 hours post-stroke when there is no existing medication • In clinical trials since 2016. Testing assumed to take place for about two years	License fees and partial development funding already raised through loans. Next milestone is slated payment of about US$30 million.
ILM Peeling,etc（BBG）	Business transfer	• January 2017, decided to transfer the business to DWTI • A lump sum fee of 1.3 billion yen at the time of transfer, There is also the possibility of receiving milestone payments.	-

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Image of Development & Revenue Planning



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5. Details of Somatic Stem Cell Regenerative Medicine

Introduced New Pipeline: HLCM051 in January 2016

Athersys inc.



（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 stably frozen 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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Outline of Ischemic Stroke in Japan

Ischemic stroke

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

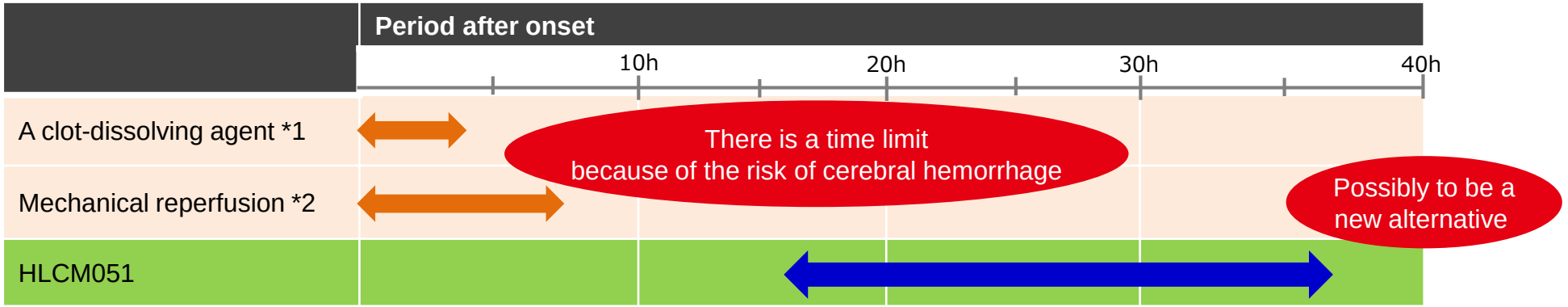
It is estimated that 37.9% of bedridden patients and 21.7% of persons who were in need of care were affected by ischemic stroke



（Source）Athersys

Treatment in accordance with the period after onset

■ Expected development of a new therapy that can be used during a longer period after 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 recovering 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 (year)	**230,000 – 330,000**	Annual medical costs for ischemic stroke estimated at 1070.7 billion yen（2009）
Severe patients（atherothrombotic and cardiogenic cerebral infection)	**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 the 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 estimate 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 result of its market research.

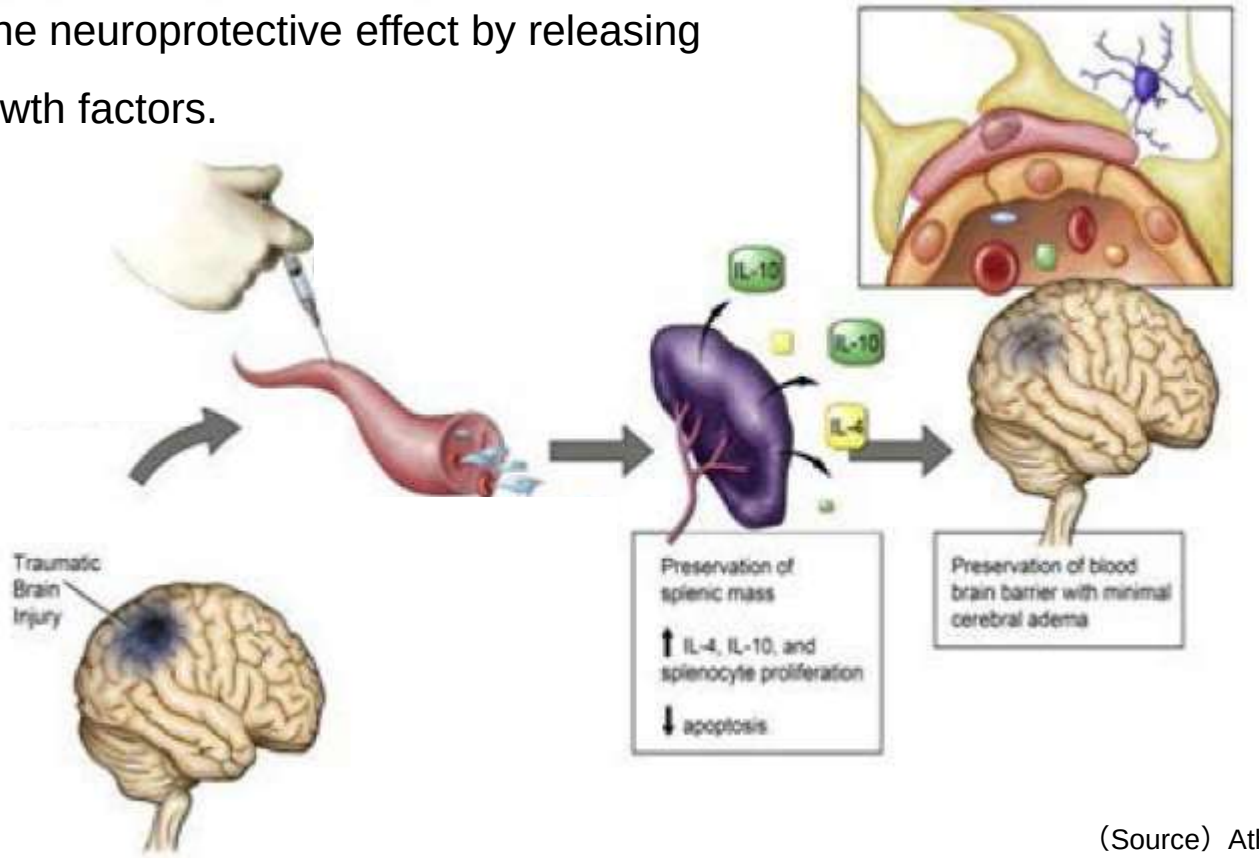
(Note)Calculated using 2013 and 2014 fiscal year-end exchange rates.

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Mechanism of treatment using HLCM051

Exhibits its therapeutic efficacy by suppressing inflammation and immune reactions and stimulating the formation of neuroprotective substances

- 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.



（Source）Athersys

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HLCM051 to Clinical Stage

Somatic stem cell regenerative medicine

HLCM051
MultiStem®



Clinical trial protocol notification was submitted to PMDA. A 30-day review period was completed for the clinical study initiation.

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

Study Design

Subjects: Patients with onset of ischemic stroke within 18 to 36 hours prior to the start of the administration of the investigational product

Enrollment: 220 (HLCM051 group [n=110], or placebo group[n=110], randomized)

Study period: Approximately 2 years

Primary Endpoint: Proportion of subjects with an excellent outcome defined by the functional assessments on Day 90.

*Excellent Outcome

"Excellent Outcome" is defined as achieving mRs ≤1, NIHSS ≤1, and BI ≥95 in mRS, NIHSS, and BI, the three major indices of functional assessments for stroke patients.

(Source) Image: prepared by Healios based on the materials provided by Athersys

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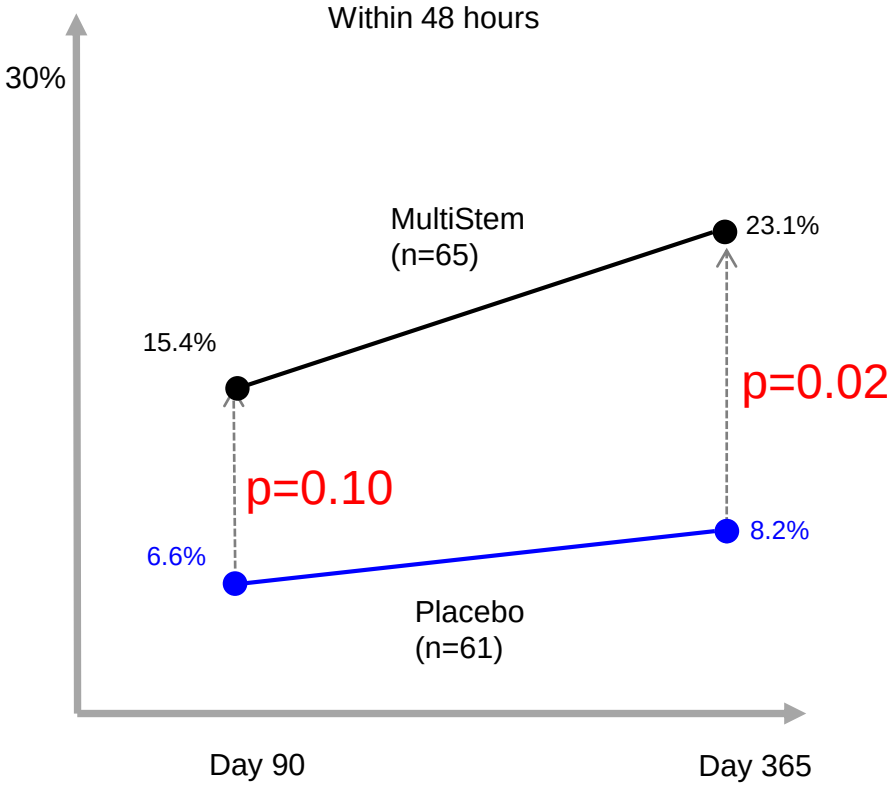
Study Design Based on the Result of the Phase II Study by Athersys in Europe and America

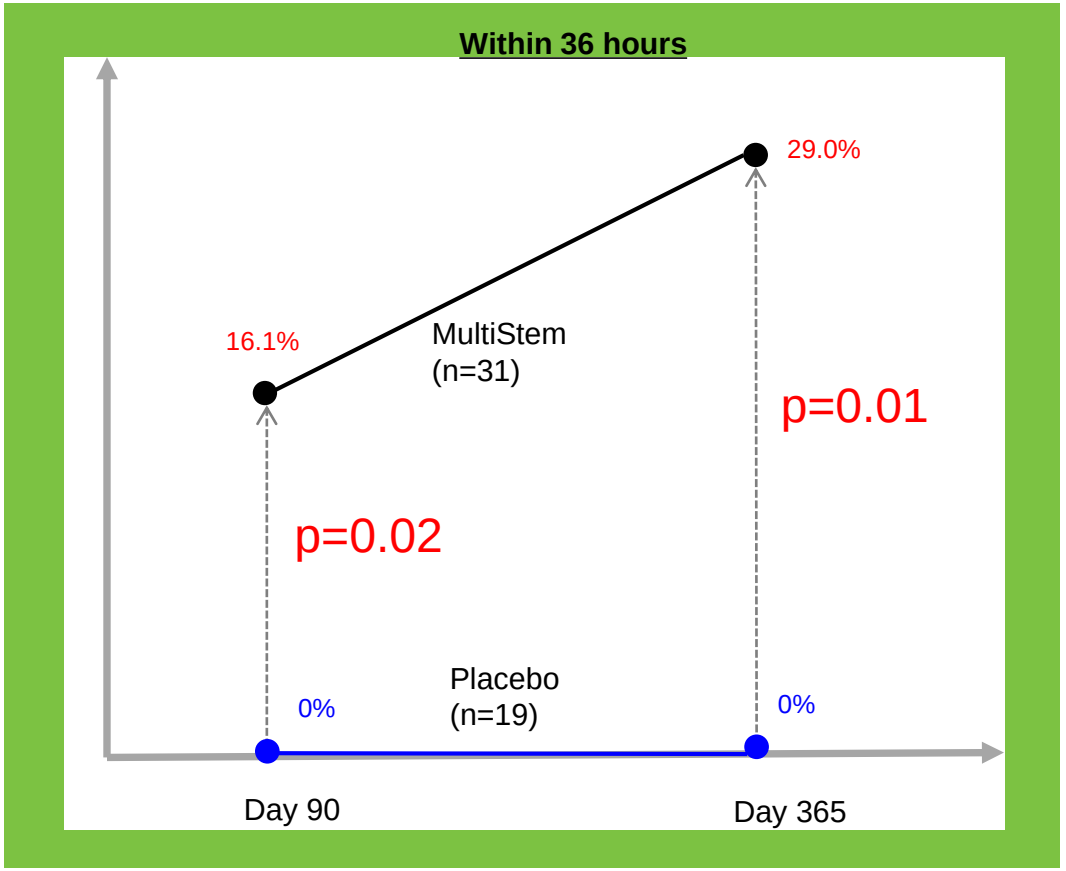
Somatic stem cell regenerative medicine

HLCM051
MultiStem®



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 had received MultiStem within 36 hours of the onset of cerebral infarction.





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

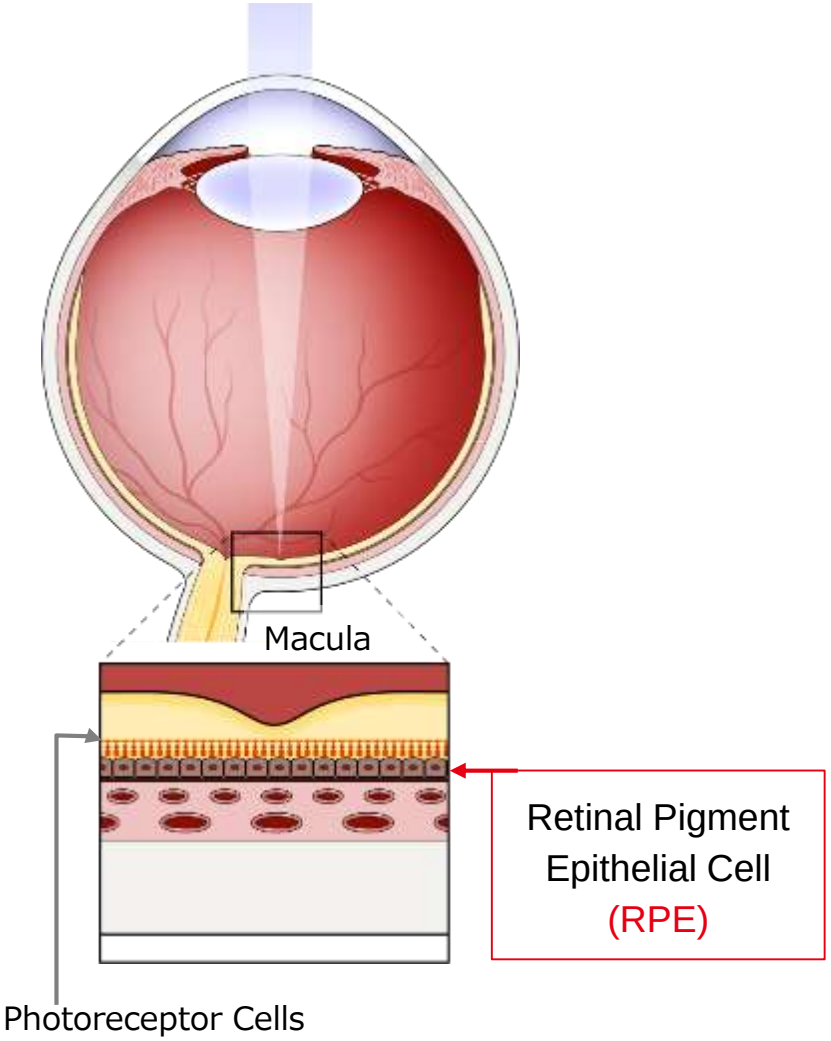
(Note) Excellent outcome = All of the following: mRS ≤ 1, NIHSS ≤ 1, and BI ≥ 95)

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6. Details of iPSC Regenerative Medicine

Explanation of AMD Pathological Condition

AMD causes RPE Cells to degenerate, which will damage functions



Regular Macular Part

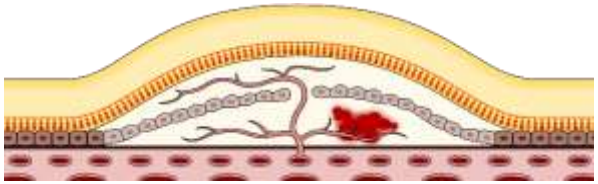
Developed Dry AMD

Immunity Barrier Maintained → Visual Cell Degenerative Disease → Dry AMD



Wet AMD

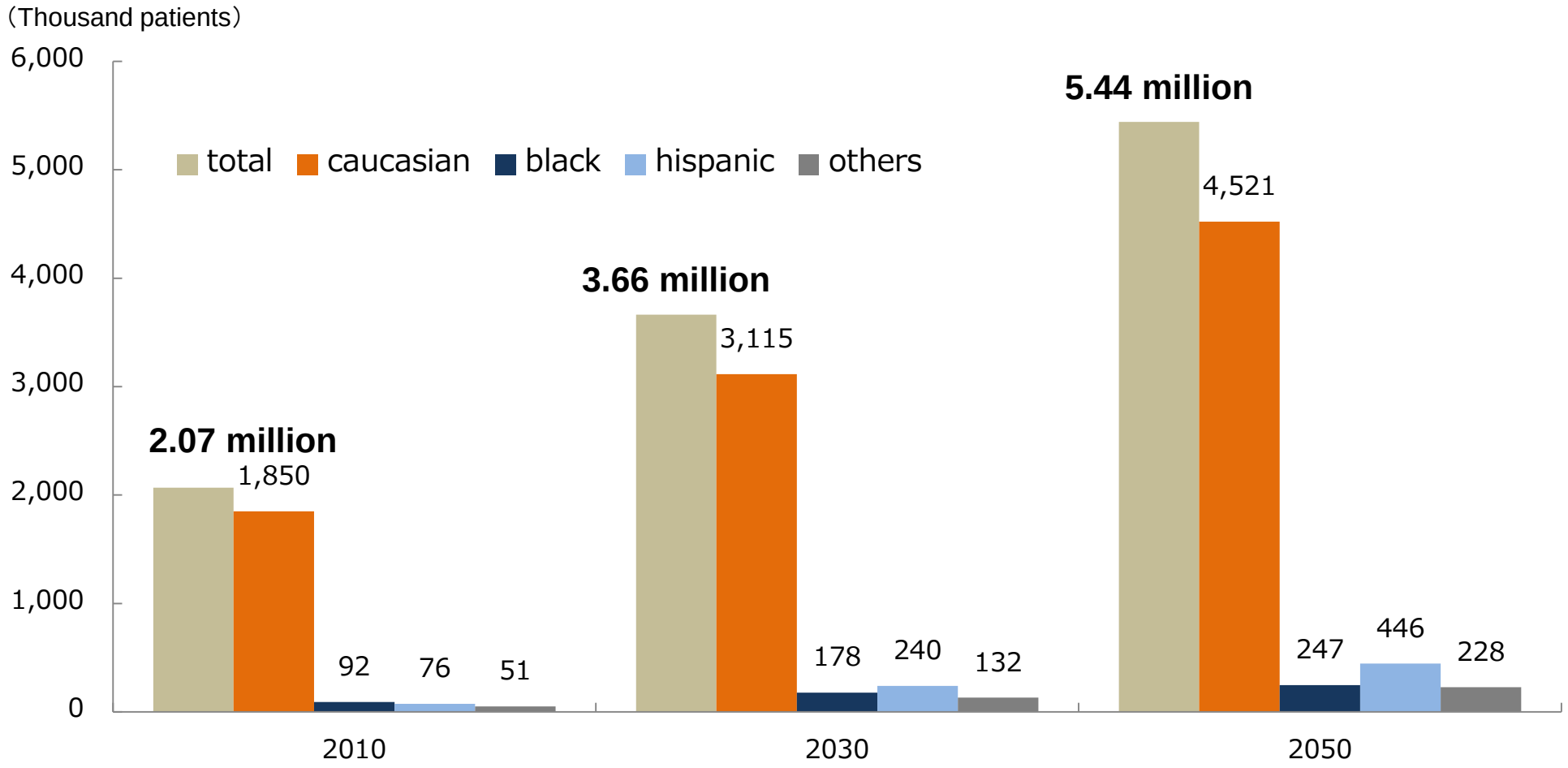
Destruction of Immunity Barrier → Invasion of Immunity Cells → Inflammation → Wet AMD



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Estimated Number of AMD Future Patients in Serious Cases in 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
The Number of AMD Patients	**10,000**	**9,230**	**13,000**
The 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: 831.6 billion yen. No Medicine for Dry AMD.

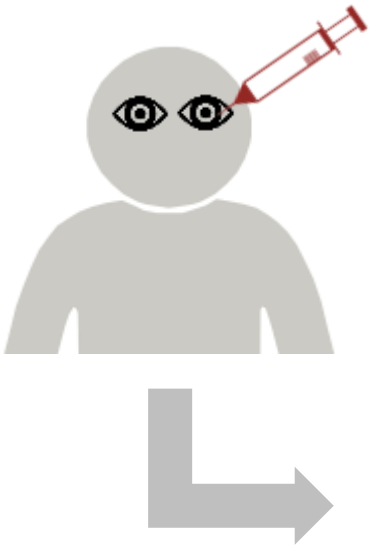
Condition	Medicine/Effect	Year	America	Japan	Others	Total
Wet	Anti-VEGF Medicine/ Restraint of New Blood Vessels	2014	**414.1 billion yen**	**55.7 billion yen**	**361.8 billion yen**	**831.6 billion yen**
Dry	**No Medicine**					

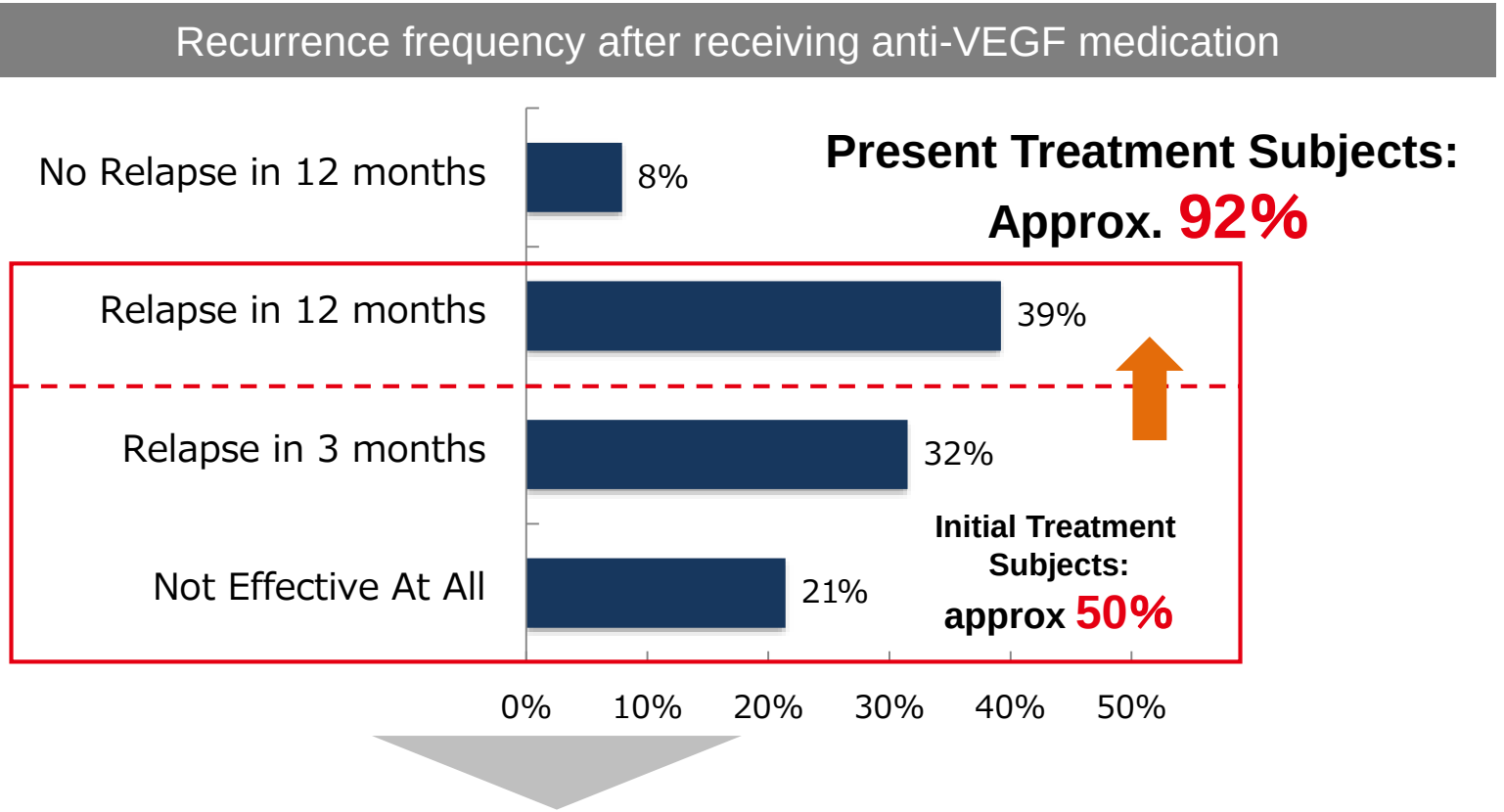
(source)Market scale was calculated using official materials from drug companies (Roche Diagnostic, Novartis, Regeneron,Bayer HealthCare, Santen Pharmaceutical Co., Ltd). Calculated using 2014 fiscal year-end exchange rates.

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Treatment Subjects for Wet AMD

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



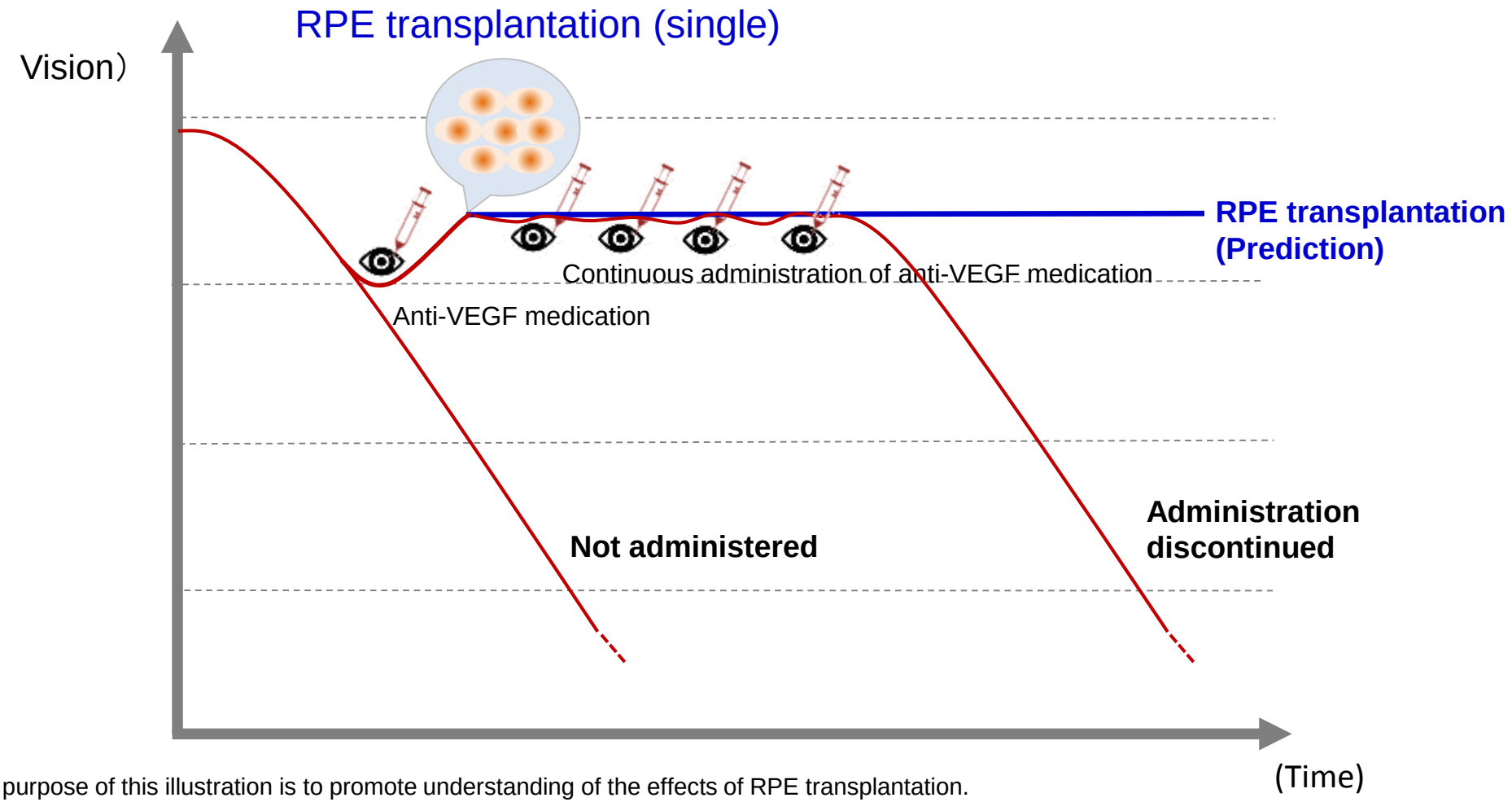


QOL of Continuously Medicated Patients is not High.

(source) 13th Annual Meeting of The Japanese Society for Regenerative Medicine March 19th 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 transplantation.
Changes in vision with the administration of anti-VEGF medication are not the same as the above according to patient symptoms and administration frequency.

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Guide to Medicine Price – Approach from Medical Expense of Existing Health Care

Anti-VEGF Medicine mostly Continues From the Beginning of the Treatment to Death

Annual Medical Expense

Unit Price of Anti-VEGF
170,000 yen

✖

Annual Recommended Medication Protocol
6 Times

＝

Annual Medical Expense
1,020,000 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**

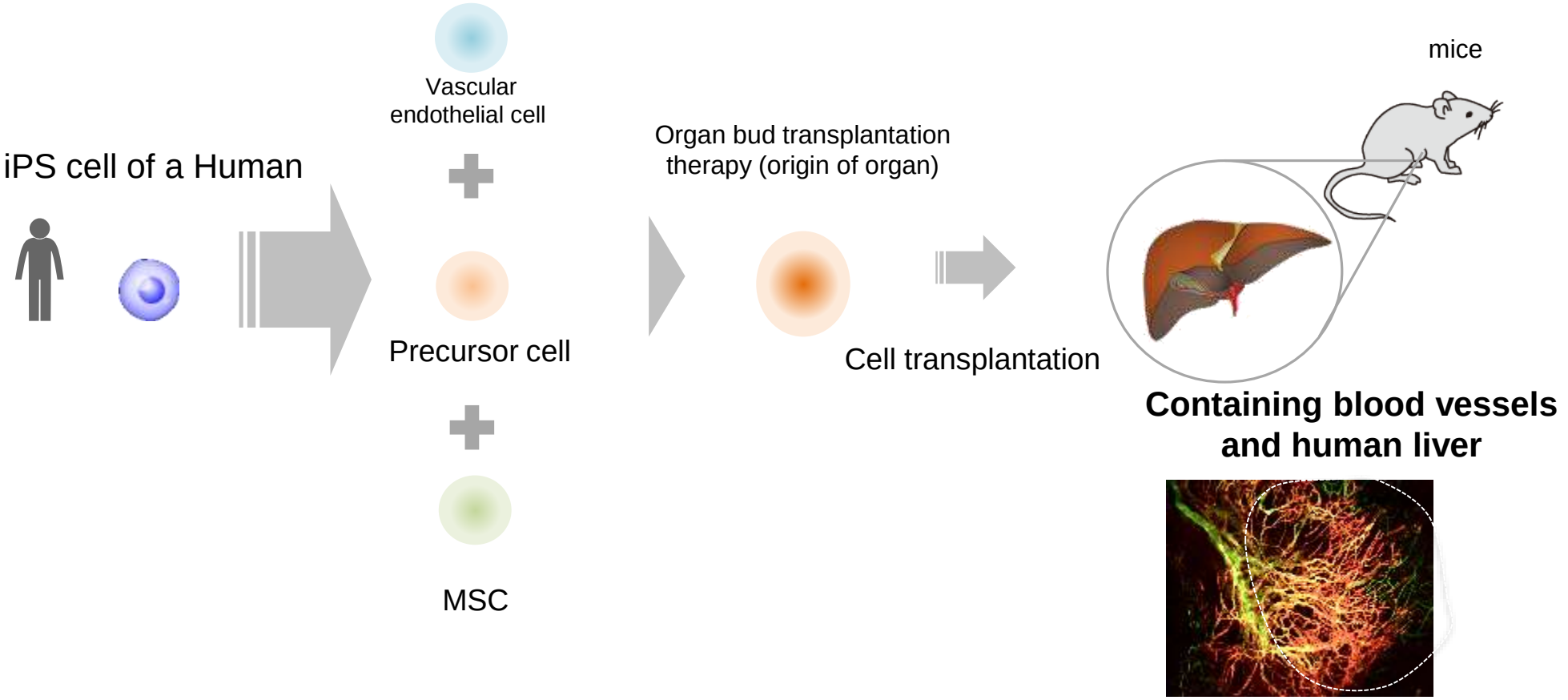
(source) Onset Data: National Eye Institute; Average Life Span: The Ministry of Health, Labor and Welfare; Annual Recommended Medication Protocol: Materials Presented by Institute of Physical and Chemical Research

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7. Expansion to 3D Organs（Liver）

3D Organ Generation Mechanism

Generating “Organ bud” by co-culturing 3 types of cells



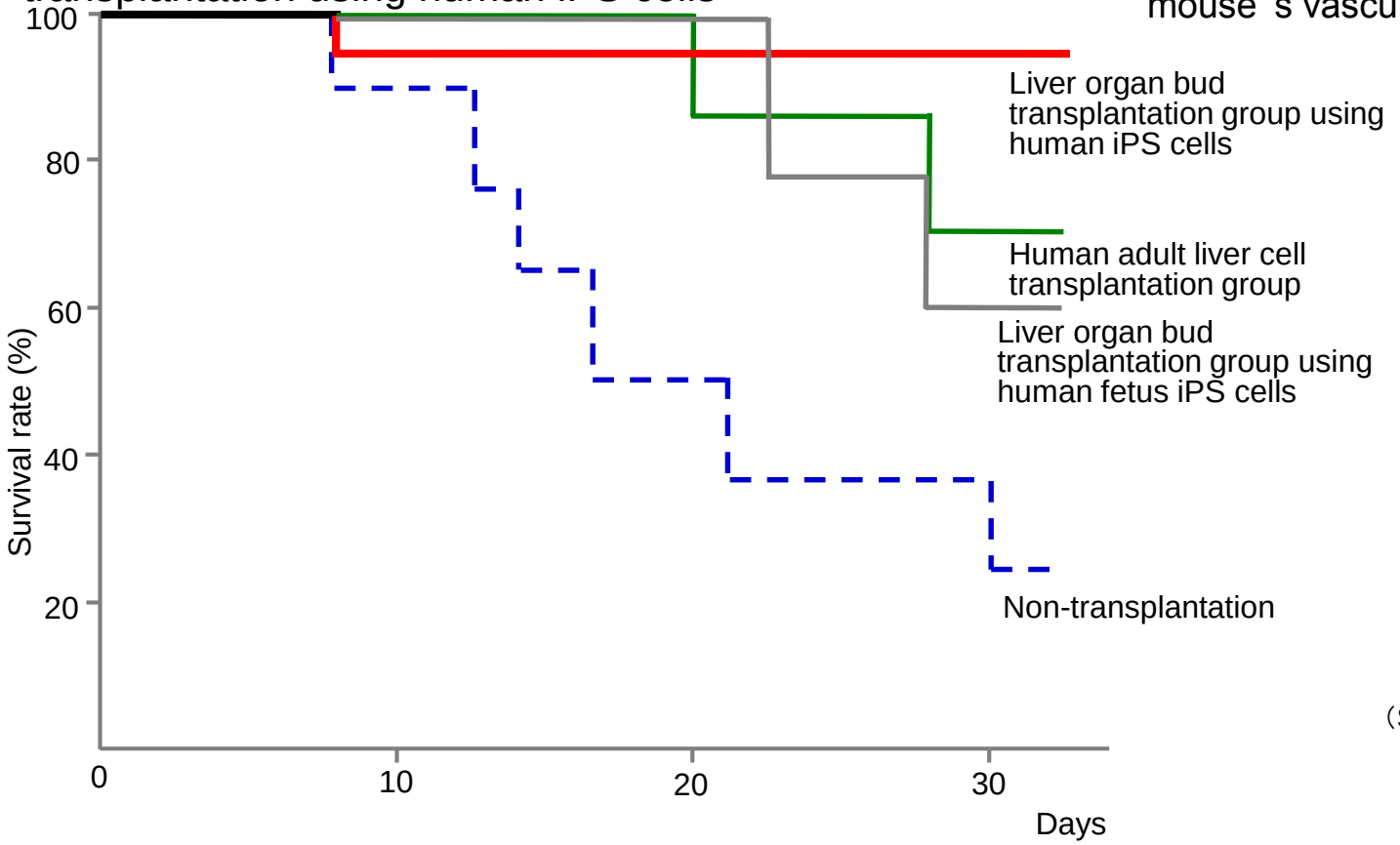
（Source）Takebe,T., et al. Nature Protocols, 9, 396–409 (2014)

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Survival Rate of Liver Failure Model Mouse

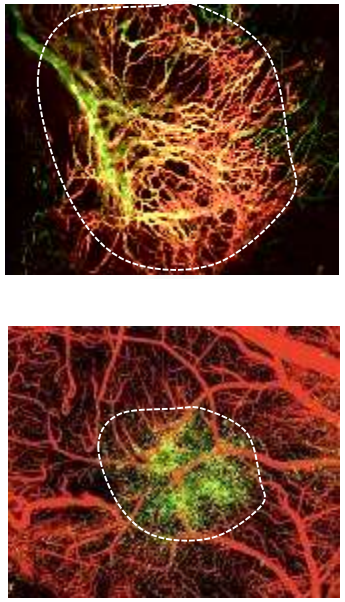
Survival rate improves significantly in transplantation experiments

Treatment effects of liver organ bud transplantation using human iPS cells



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

Process in which organ formed from organ bud links mouse ‘s vascular network autonomously



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

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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 (year)	**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, incidence rate.

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8. Company Overview

Healios Overview

About Us

Company Name	HEALIOS K.K.（TSE: 4593）
Representative	Hardy TS Kagimoto,MD　President and CEO
Head Office	World Trade Center Building 15F 2-4-1 Hamamatsucho Minato-ku, Tokyo　Japan 105-6115
Paid in Capital	5,387million yen(As of end of September, 2016)
Research Institution	Kobe and Yokohama
Number of Employees	53　(As of end of September, 2016)
Affiliated Company	SighRegen Co., Ltd. (Joint Venture with Sumitomo Dainippon Pharma Co., Ltd.)

Our Experienced Team

President and CEO
Hardy TS　Kagimoto, MD



- Succeeded in Developing BBG and Realized Sales in Europe

Director Overseas　Development
Al Reaves, Ph.D



- Responsible for innovative clinical programs for wet & dry AMD - Lucentis (X-US); Visudyne (global)

Director of Laboratories in Kobe , Research and Manufacturing
Kouichi Tamura, Ph.D



- Astellas US Director of Laboratories
- Well-acquainted with Immunosuppressant Research

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A Stronger Force in Development



Director Domestic Development

Michihisa Nishiyama

Appointed in 2016

- Constructed Network for Tacrolimus Approval and Sales at Astellas in the US and Europe

Substantially enhanced development force in a short time



Joined 2013

- R&D ophthalmologic drugs at Japanese pharma company



Joined 2015

- International development at major Japanese pharma



Joined 2016

- Development of stroke medication at major Japanese pharma



Joined 2014

- Development at a major foreign pharma



Joined 2016

- International development with a major medical equipment maker



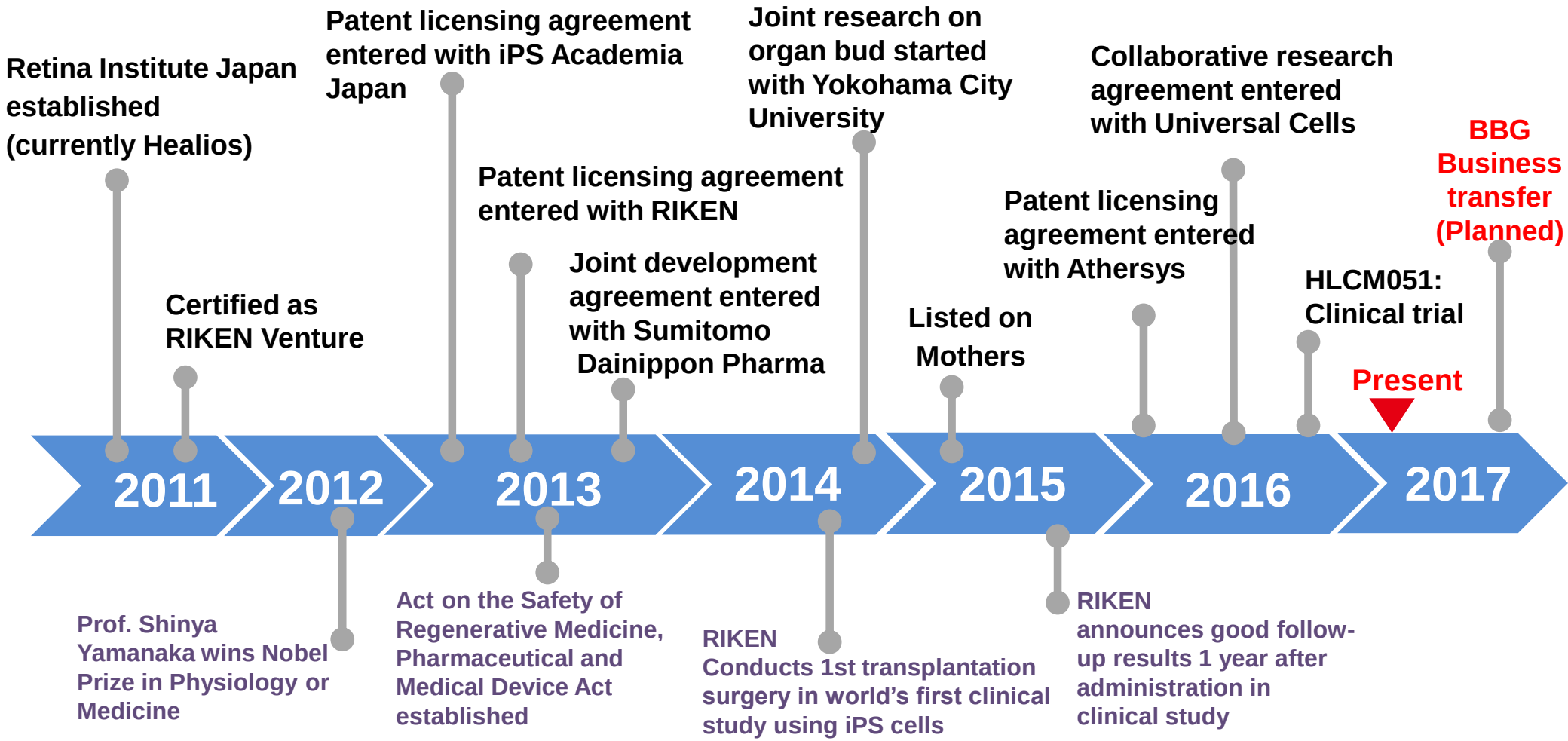
Joined 2016

- Development + marketing at major Japanese pharma

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Company History and Social Trends

Pioneer of iPSC regenerative medicine development



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9. Circumstance of Regenerative Medicine

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

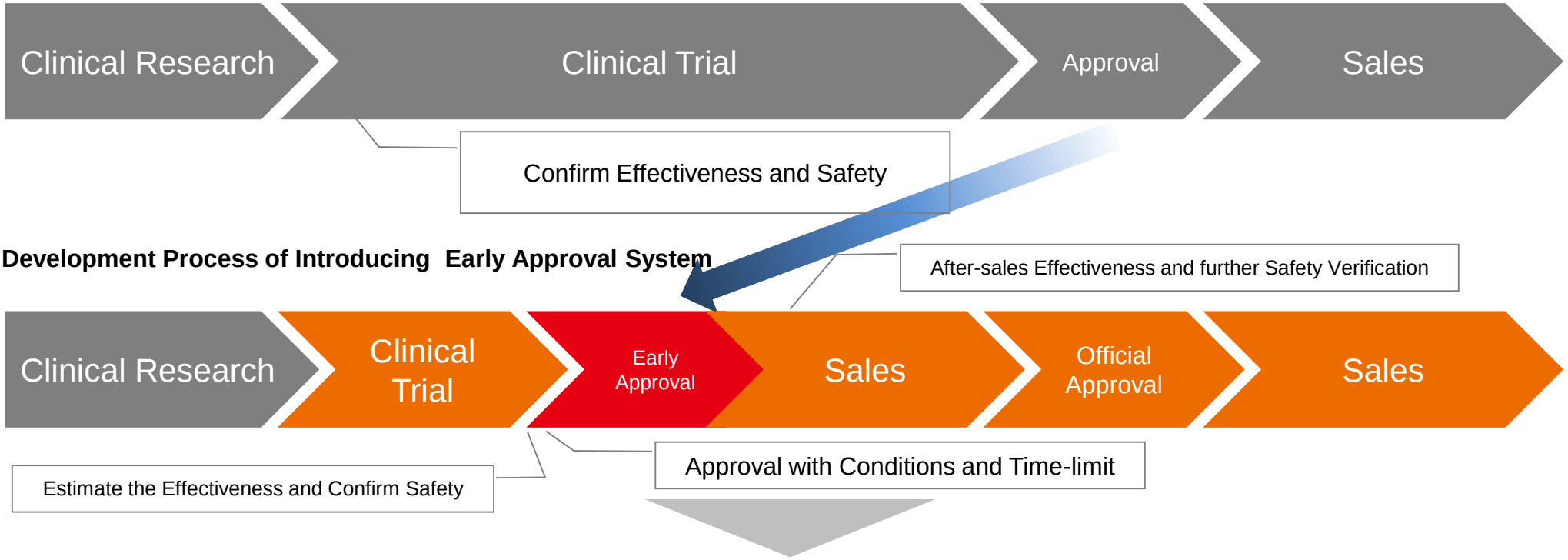
* The price of new drugs is basically calculated according to the prices of official articles with similar efficacy (price determination by comparable drug). However, if there are no appropriate similar official articles, required costs are added in the calculation of prices (cost accounting system).

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Historical Alleviation of Regulations

Japanese Government Revises Regulations to Put Japan at the Forefront

Process of the Development So Far



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

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Descriptions on 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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