

Healios

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

# FY2017 1Q Financial Results

May 12, 2017

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# 1. Financial Highlights

# Statement of income

（Million yen）

| | FY 2016 1Q | FY 2017 1Q | | |
|---|---|---|---|---|
| | | | YoY change | Main reasons for increase/decrease |
| Sales | 20 | 20 | +0 | |
| Operating income | ▲2,114 | ▲490 | +1,624 | Research & Development Cost decreased ＋1,639 |
| Ordinary income | ▲2,128 | ▲525 | +1,603 | - |
| Net income | ▲2,131 | ▲526 | +1,605 | - |
| R&D | 1,980 | 340 | ▲1,639 | MultiStem License-in ▲1,809 |
| Amortization of goodwill | 25 | 25 | – | - |
| Number of employees | 47 | 61 | +14 | - |


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# Balance sheet

（Million yen / %）

| | December 31,2015 | December 31, 2016 | | |
|---|---|---|---|---|
| | | | Change | Main reasons for increase/decrease |
| Current assets | 8,073 (88.0%) | 9,500 (89.9%) | +1,426 | Cash and deposit ＋1,413<br>(Cash and deposit balance 9,240) |
| Non-current assets | 1,101 (12.0%) | 1,063 (10.1%) | ▲37 | |
| Total assets | 9,174 (100.0%) | 10,564 (100.0%) | +1,389 | |
| Current liabilities | 772 (8.4%) | 678 (6.4%) | ▲93 | |
| Non-current liabilities | 2,408 (26.2%) | 2,364 (22.4%) | ▲43 | |
| Total liabilities | 3,180 (34.7%) | 3,043 (28.8%) | ▲137 | |
| Total equity | 5,994 (65.3%) | 7,520 (71.2%) | +1,526 | Capital etc. ＋2,001<br>Earned surplus ▲526 |
| Total assets | 9,174 (100.0%) | 10,564 (100.0%) | +1,389 | |


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# 2. Updates in FY2017 1Q

# 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 | → | | | | | | Business transfer completed on April 30, 2017 |
| | HLM0021 | Cataract surgery | Japan | → | | | | | | |
| | HLM0022 | ILM Peeling | EU | → | | | | | | |
| | HLM0023 | ILM Peeling | US | → | | | | | | |


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# Transfer our business relating to an ophthalmic surgical adjuvant containing BBG250

| 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 date] April 30, 2017

*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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# HLCM051 has been designated as “ SAKIGAKE” Product by MHLW

Somatic stem cell regenerative medicine

HLCM051 MultiStem®



HLCM051 has been designated as “SAKIGAKE Designation System” Product for regenerative & cell therapy by the Ministry of Health, Labor and Welfare (MHLW) on February 28, 2017.

“SAKIGAKE Designation System” （From the website of MHLW）

http://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/dl/140729-01-02.pdf

1) Prioritized consultation (Waiting time: 2months ➡ 1month)
2) Substantial Pre-application Consultation (de facto review before application)
3) Prioritized Review (12months ➡ 6months)
4) Review Partner (PMDA manager as a concierge )
5) Substantial Post-Marketing Safety Measures (Extension of re-examination period)

**Development Process of Introducing Early Approval System for Regenerative Medicine**






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# Results was published in The Lancet Neurology

Somatic stem cell regenerative medicine

HLCM051 MultiStem®



Results from Athersys' Phase 2 trial of MultiStem cell therapy for treating ischaemic stroke patients in the United States and Europe have been published in the peer-reviewed journal, The Lancet Neurology.




“ The Lancet Neurology”
Volume 16, No.5, p360-368, May 2017

Safety and efficacy of multipotent adult progenitor cells in acute ischaemic stroke (MASTERS): a randomised, double-blind, placebo-controlled, phase 2 trial

・It is shown that administration of MultiStem was safe and well tolerated in patients with acute ischaemic stroke.
・ In the paper, Healios' clinical trial was also mentioned; ”further clinical trials evaluating the efficacy of the intervention in an earlier time window after stroke (<36 h) are planned.”


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# Athersys' clinical program for ischemic stroke received Fast Track designation

Somatic stem cell regenerative medicine

HLCM051 MultiStem®



In May 2017, Athersys' clinical program for ischemic stroke received Fast Track designation by U.S. Food & Drug Administration ("FDA") .

"Fast Track" （From the website of FDA）
https://www.fda.gov/ForPatients/Approvals/Fast/ucm405399.htm

Fast track is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need. The purpose is to get important new drugs to the patient earlier. Fast Track addresses a broad range of serious conditions.

・More frequent meetings with FDA
・More frequent written communication from FDA
・Eligibility for Accelerated Approval and Priority Review, if relevant criteria are met
・Rolling Review, which means that a drug company can submit completed sections of its Biologic License application (BLA) or New Drug Application (NDA) for review by FDA, rather than waiting until every section of the NDA is completed before the entire application can be reviewed.

* Athersys' development status：They are actively engaged with the FDA and EMA to obtain regulatory alignment for their planned Phase 3 clinical trial for acute ischemic stroke in the United States and Europe.


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# Business and Capital Alliance Contract with Nikon Corporation

Healios promotes the search and development of new seeds in the regenerative medicine field

Nikon supports these new seeds from the viewpoint of contract manufacturing of cells/ cell quality evaluation with image analysis etc.

[Capital Alliance]

Number of new issued shares: 1,034,700 common shares
Total issue price：2,000,107,200Yen.

[The purpose of the funds]

| | Billion yen |
|---|---|
| License fee to introduce new seeds and development fee | 1.99 |


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# The issuance of stock acquisition rights

Amount of fund raisings：Approximately 13 billion yen
(The amount could change depending on the share price trend going forward.)

[As of the end of April 2017]
Number of exercised shares ： 1,000,000 common shares
Amount of fund raisings ： 1.52 billion yen
Number of unexercised latent shares ： 6,145,700 common shares

[The purpose of the funds]

| | Billion yen |
|---|---|
| Development for HLCM051(Ischemic stroke in Japan) | 4.63 |
| Development for HLCR012 (iPSC-derived RPE cells for Dry AMD in US and Europe ) | 1.01 |
| Development for HLCL041(Organ bud) | 0.78 |
| License fee to introduce new seeds and development fee | 4.81 |
| Repayment of borrowings | 2.5 |

Disclosed on March 2, 2017


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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<br>• Differentiation and transplant RPE cells from iPSC (aim is to outgrow symptomatic treatment using anti-VEGF medication)<br>• 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<br>• Treatment of transplantation using iPSC derived RPE cells<br>• No effective medication<br>• 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<br>• Mini-liver transplant for patients with congenital abnormalities in specific liver enzymes<br>• Existing treatments cost more than ¥30 million/ year<br>• 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<br>• Cellular medication that improves post-stroke prognosis by suppressing immunoreaction<br>• Hopes are for efficacy during 18-36 hours post-stroke when there is no existing medication<br>• 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<br>• 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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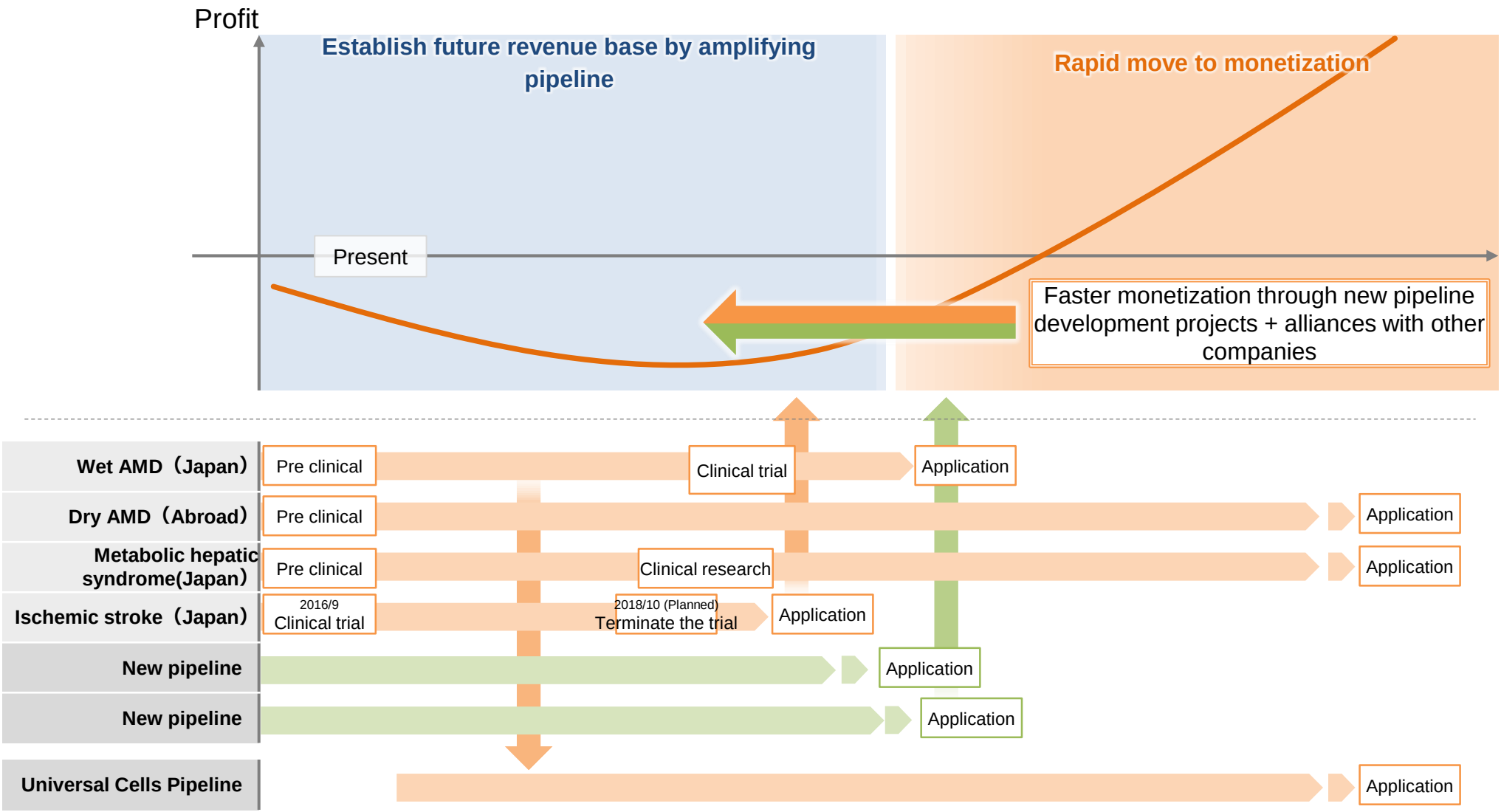
# About introducing new seeds

| | |
|---|---|
| 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. |


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# 3. News Follow-Up

# Image of Development & Revenue Planning






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# 4. Expansion of Cellular Medicine Products

# Image of the Transition of Cellular Medicine Products

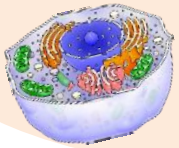
Immunosuppressant

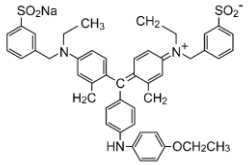
Immune Barrier

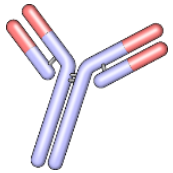
Somatic Stem Cell

ES/iPS Cell

iPS Organ bud





Low molecular drug

Antibody drug

Cellular Medicine Products

Displacement of Function

3D Organ



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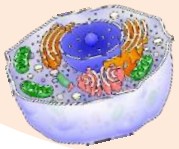
# Image of the Transition of Cellular Medicine Products

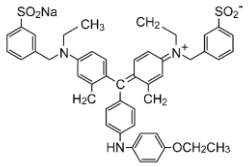
Immunosuppressant

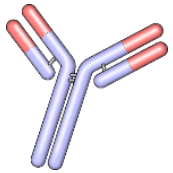
Immune Barrier

Somatic Stem Cell

Universal Cells





Low molecular drug → Antibody drug → Cellular Medicine Products → Displacement of Function → 3D Organ



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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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# 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

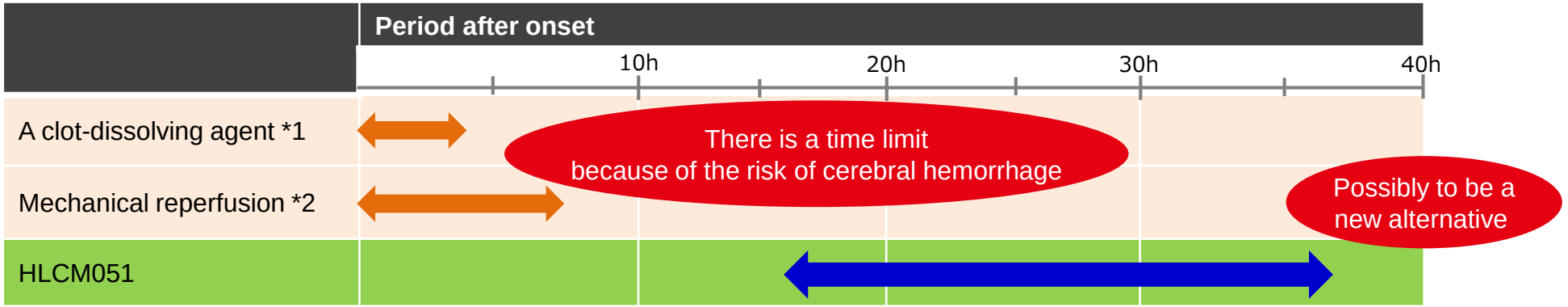
It is estimated that 37.9% of bedridden patients and 21.7% of persons who were in need of care were affected by ischemic stroke



（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.

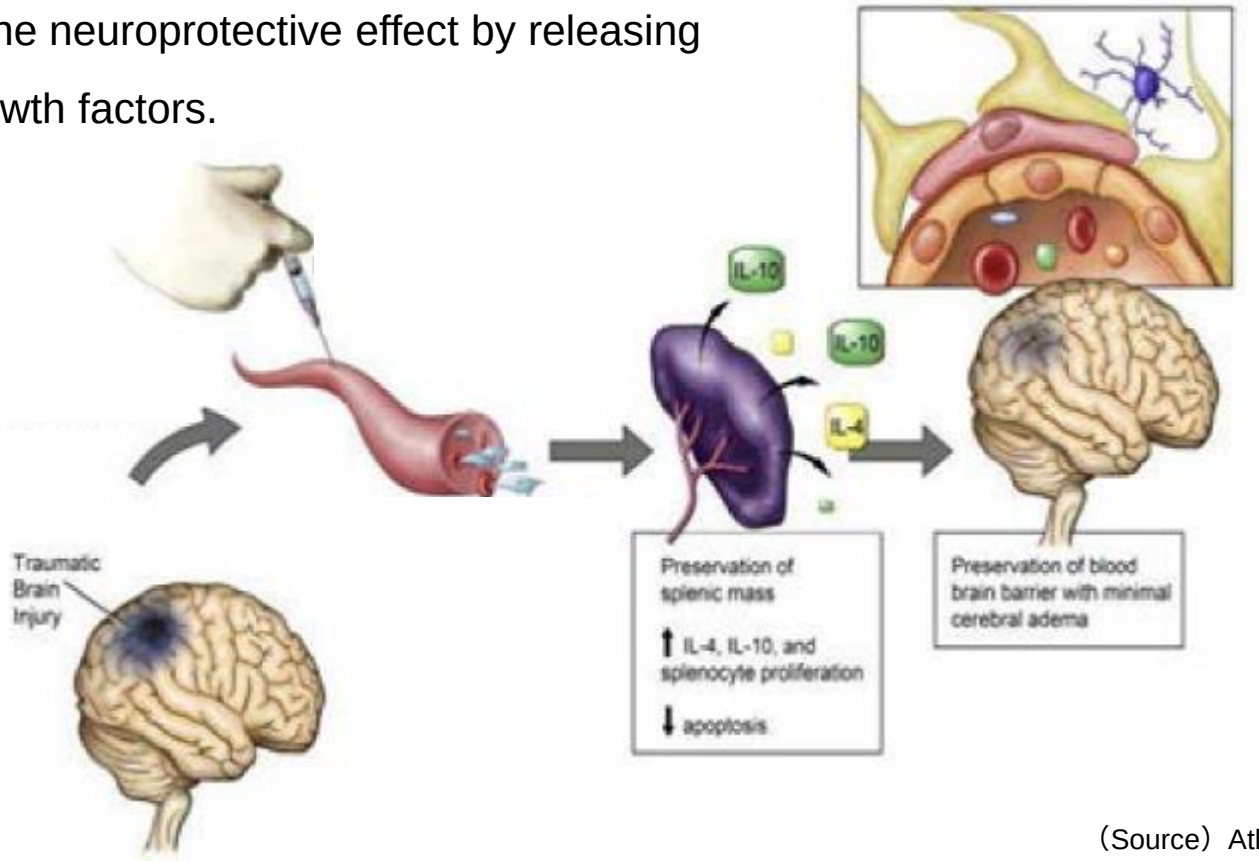
(Note)Calculated using 2013 and 2014 fiscal year-end exchange rates.


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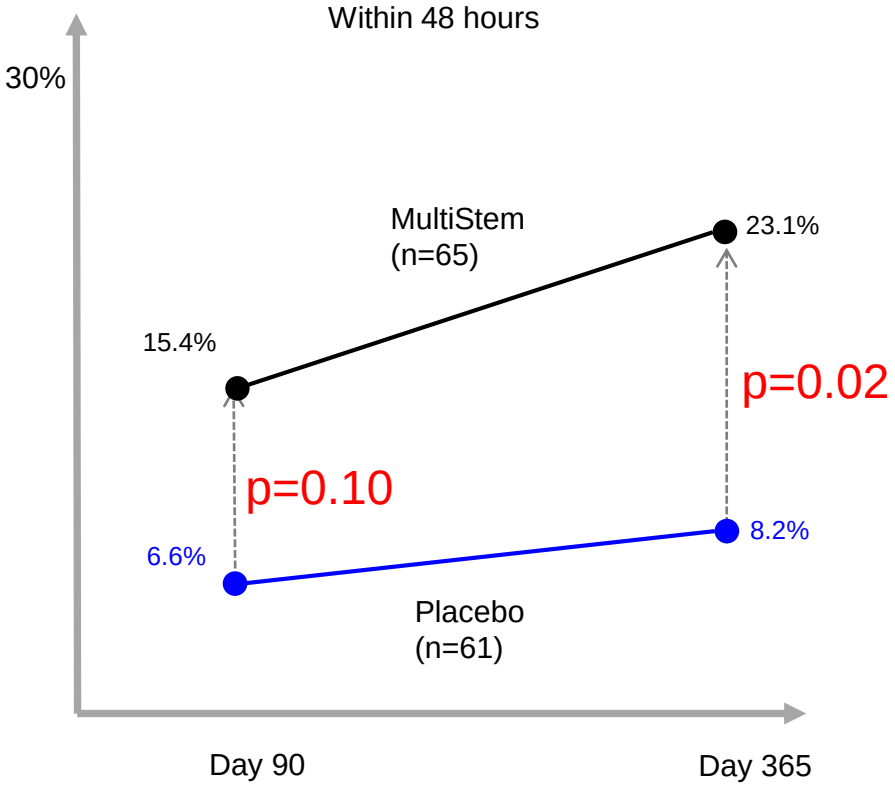
# Study Design Based on the Result of the Phase II Study by Athersys in Europe and America

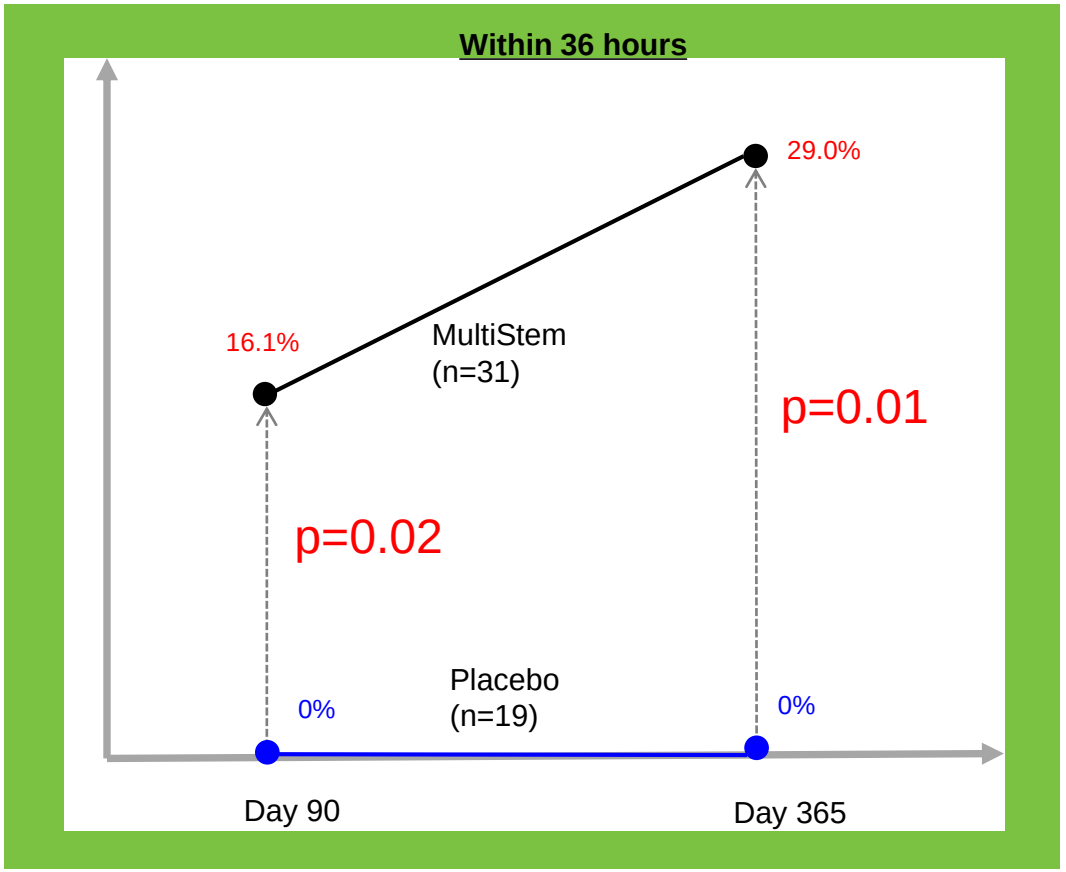
Somatic stem cell regenerative medicine

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)

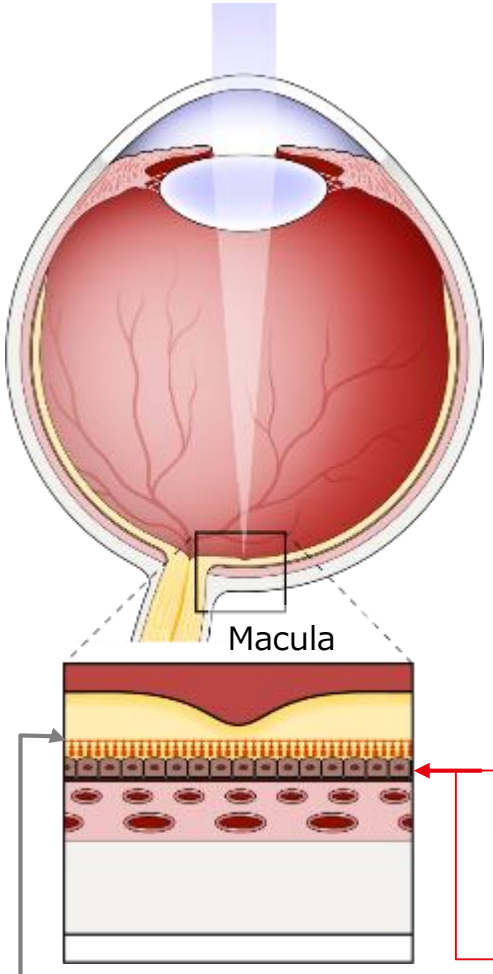


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# 6. Details of iPSC Regenerative Medicine

# Explanation of AMD Pathological Condition

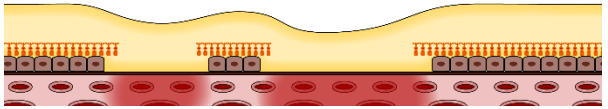
## AMD causes RPE Cells to degenerate, which will damage functions




**Regular Macular Part**

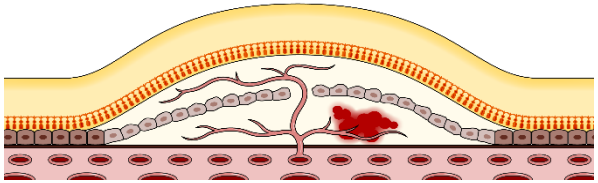
### Developed Dry AMD

**Immunity Barrier Maintained → Visual Cell Degenerative Disease → Dry AMD**



### Wet AMD

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

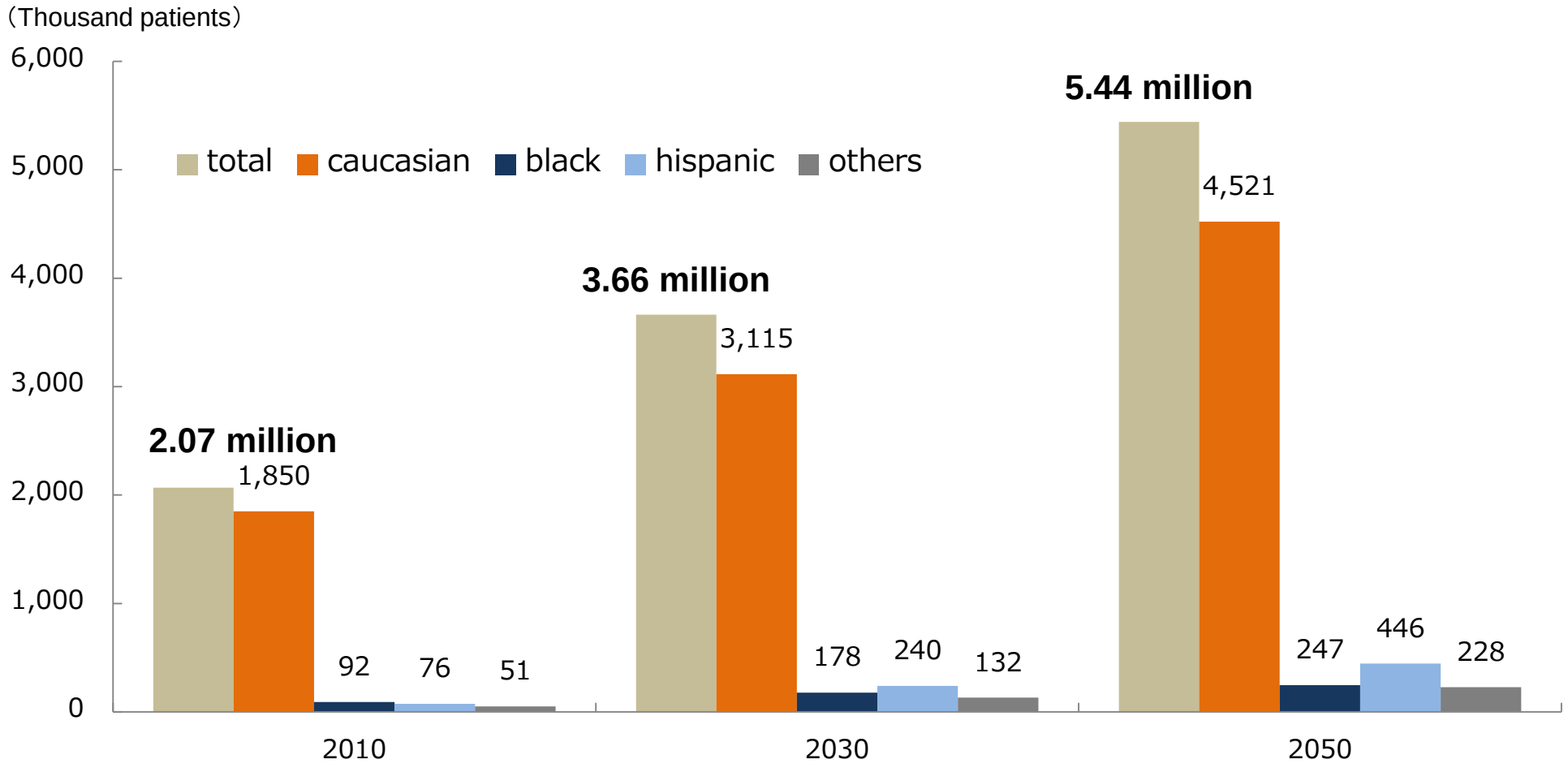




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# Estimated Number of AMD Future Patients in Serious Cases in US

## 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** | | | |

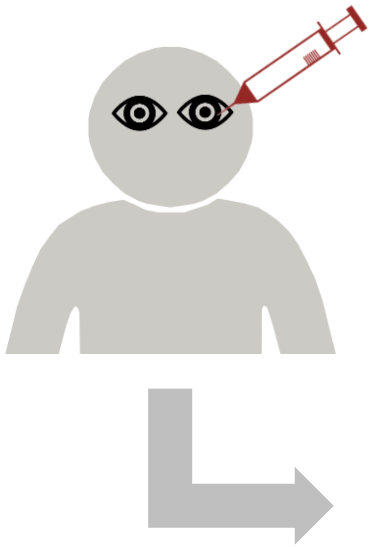
(source)Market scale was calculated using official materials from drug companies (Roche Diagnostic, Novartis, Regeneron,Bayer HealthCare, Santen Pharmaceutical Co., Ltd). Calculated using 2014 fiscal year-end exchange rates.



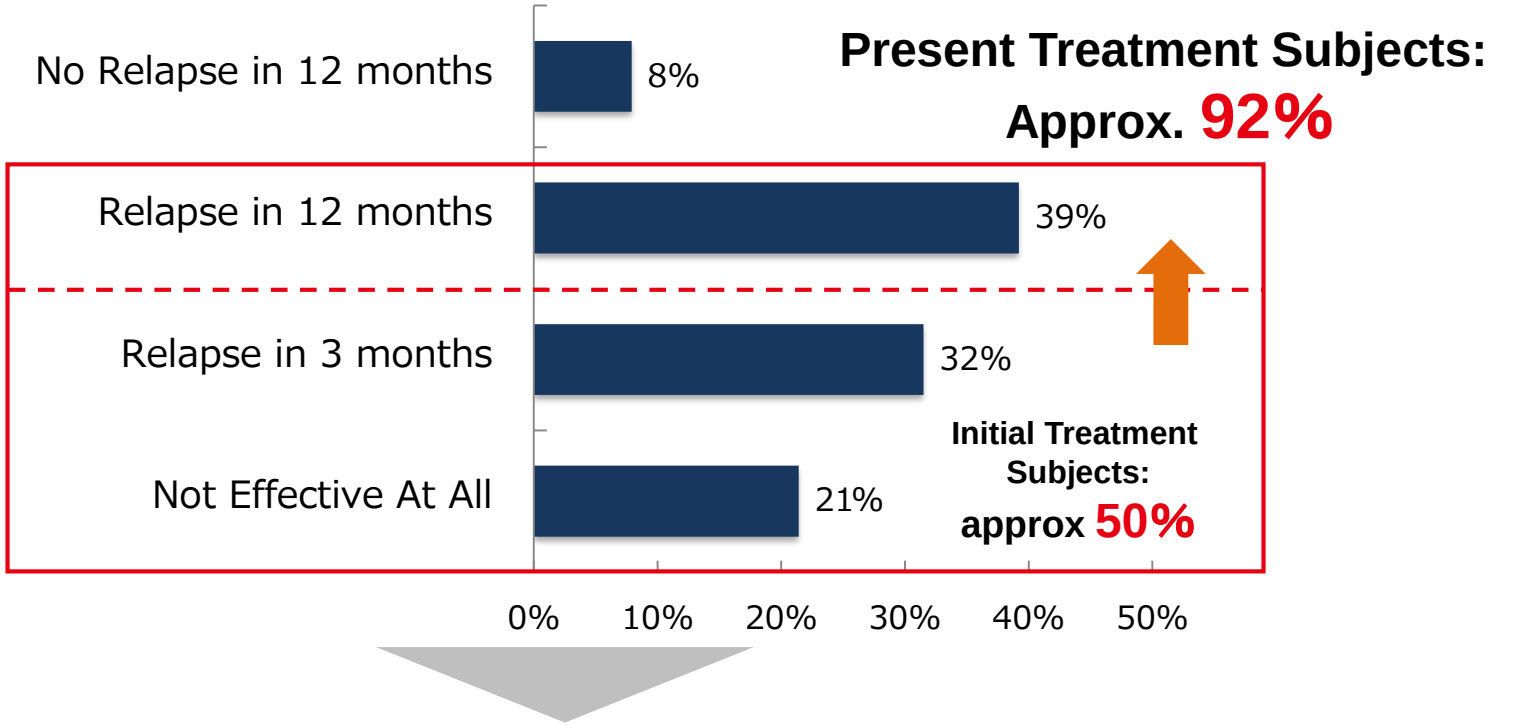
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# Treatment Subjects for Wet AMD

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



## Recurrence frequency after receiving anti-VEGF medication




**Present Treatment Subjects: Approx. 92%**

**Initial Treatment Subjects: approx 50%**

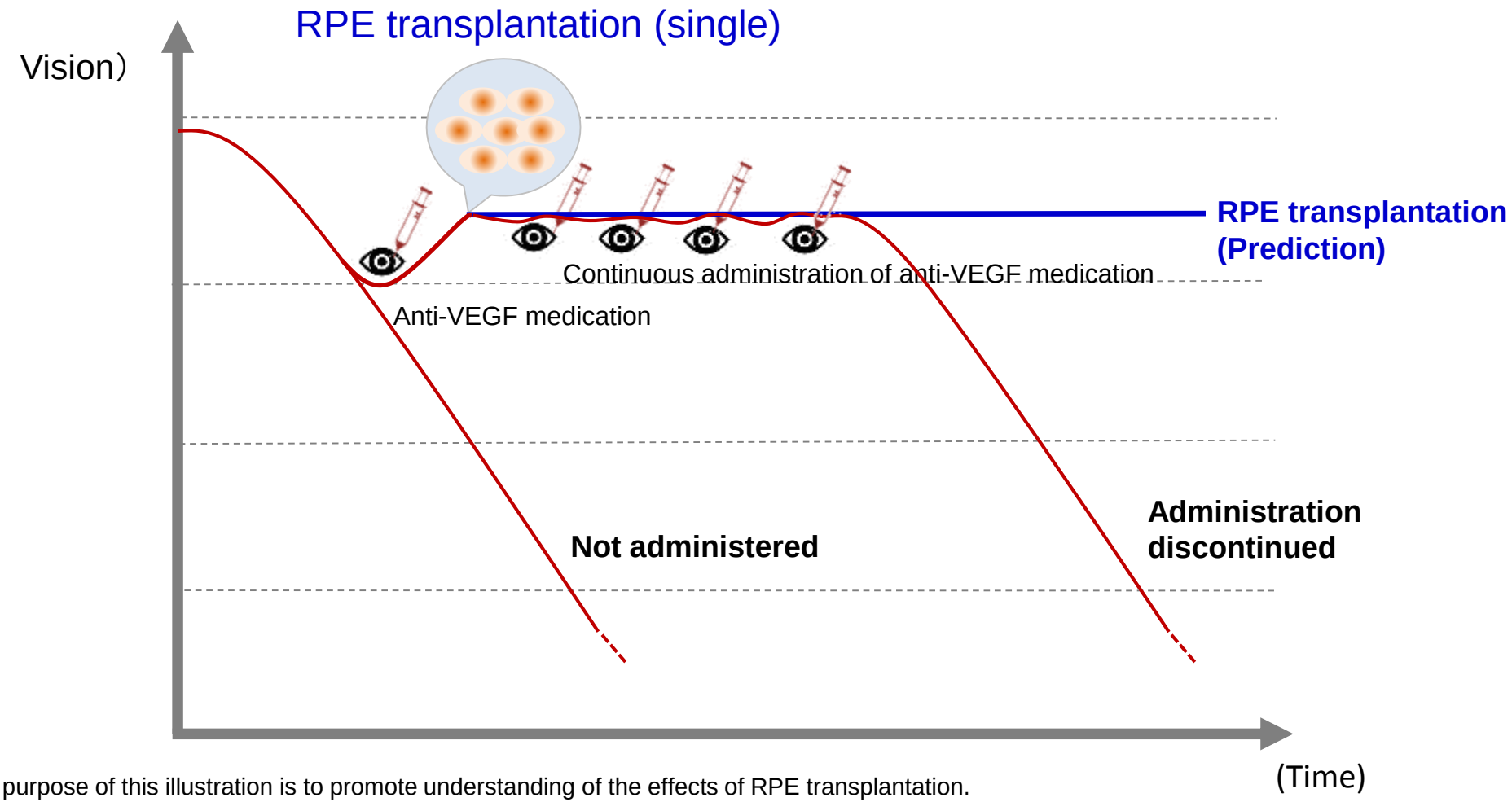
**QOL of Continuously Medicated Patients is not High.**

(source) 13th Annual Meeting of The Japanese Society for Regenerative Medicine March 19th 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

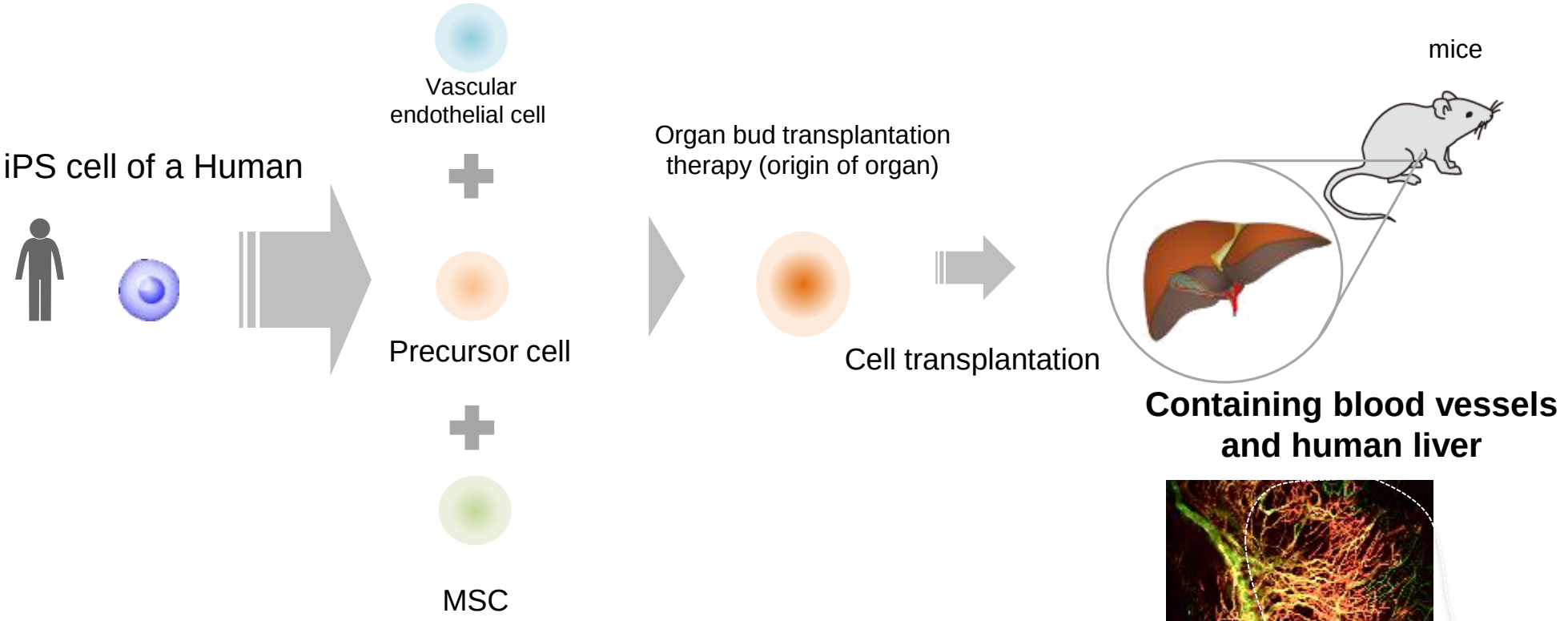


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# 7. Expansion to 3D Organs（Liver）

# 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)

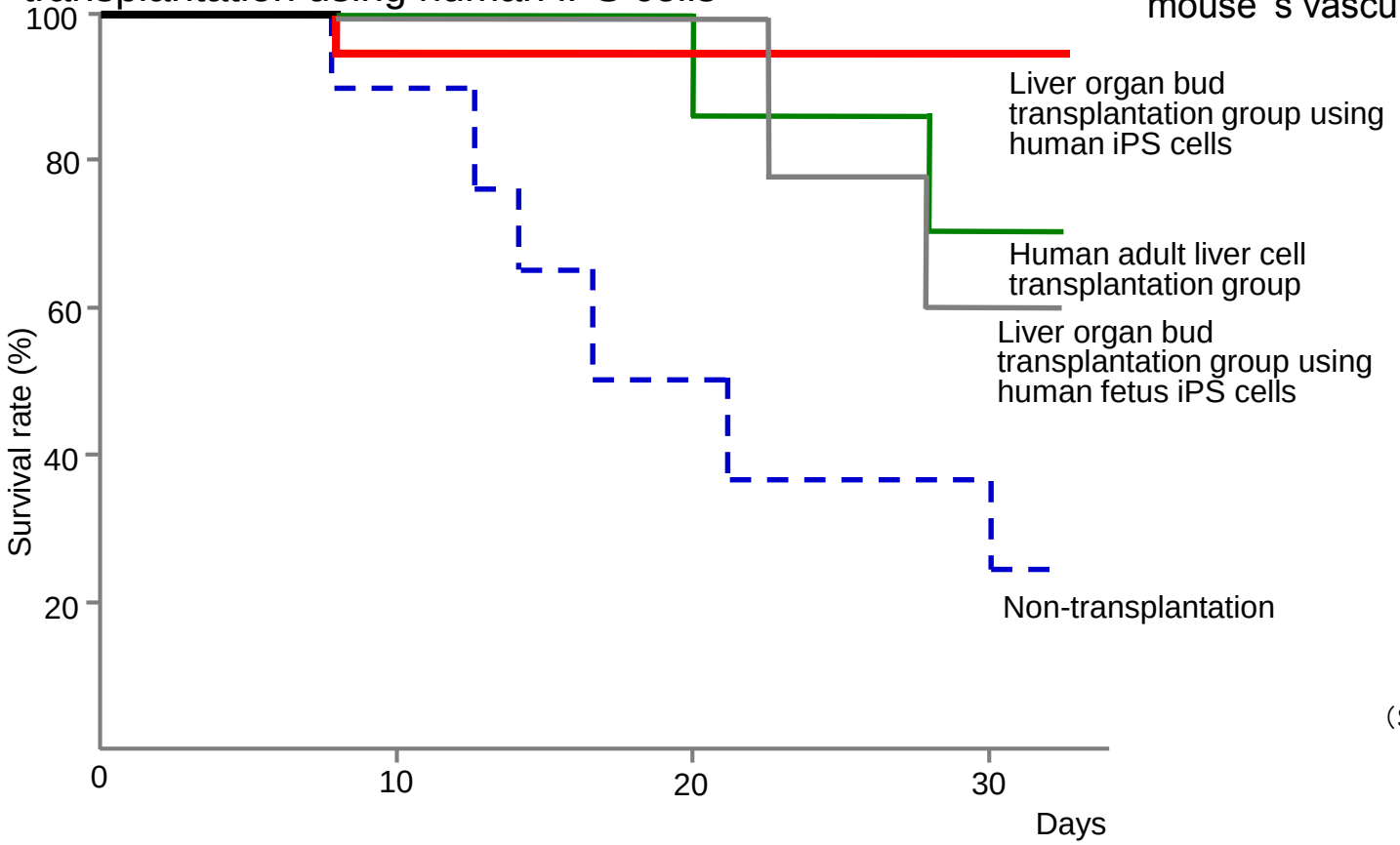


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# Survival Rate of Liver Failure Model Mouse

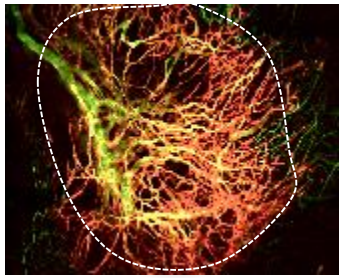
## Survival rate improves significantly in transplantation experiments

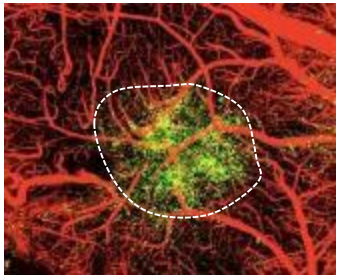
Treatment effects of liver organ bud transplantation using human iPS cells




（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<br>2-4-1 Hamamatsucho Minato-ku, Tokyo　Japan 105-6115 |
| Paid in Capital | 6,394million yen(As of end of March, 2017) |
| Research Institution | Kobe and Yokohama |
| Number of Employees | 61　(As of end of March, 2017) |
| Affiliated Company | SighRegen Co., Ltd. (Joint Venture with Sumitomo Dainippon Pharma Co., Ltd.) |

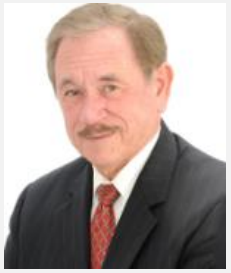
## Our Experienced Team

**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



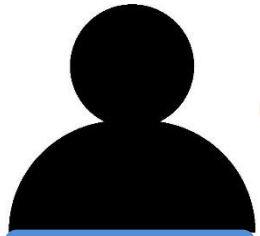
**Director Domestic Development**

**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



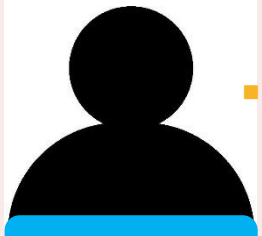
Joined 2013

- R&D ophthalmologic drugs at Japanese pharma company



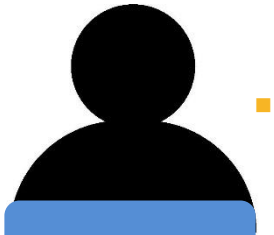
Joined 2015

- International development at major Japanese pharma



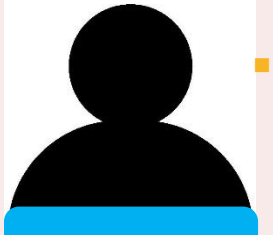
Joined 2016

- Development of stroke medication at major Japanese pharma



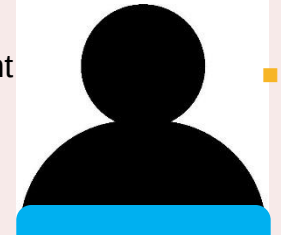
Joined 2014

- Development at a major foreign pharma



Joined 2016

- International development with a major medical equipment maker



Joined 2016

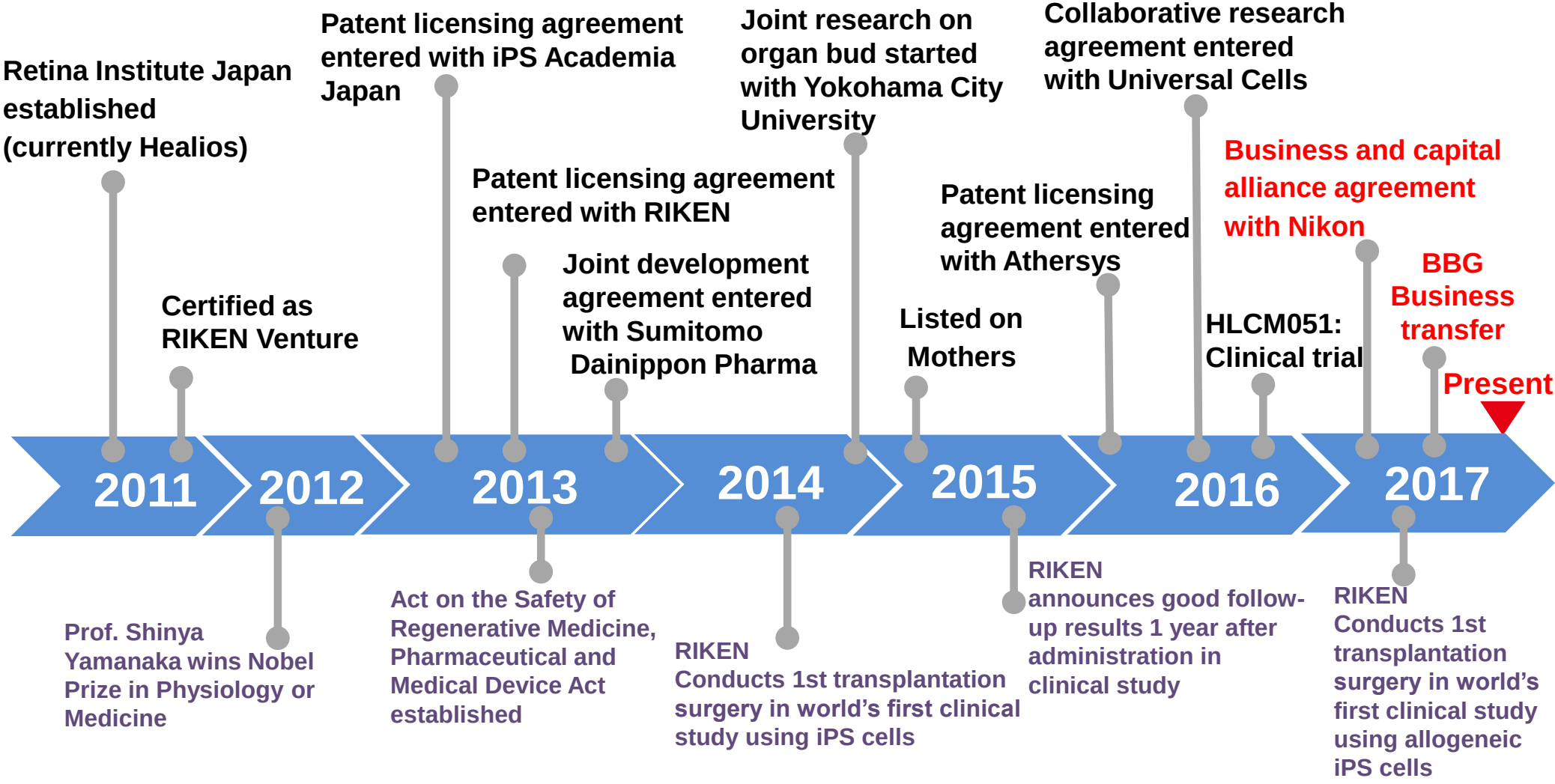
- Development + marketing at major Japanese pharma



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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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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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