Challenge for Innovation

- Building Resilience for Sustainable Growth -

R&D Meeting on July 10, 2014
Yoshihiko Hatanaka
President and CEO
Astellas Pharma Inc.

Cautionary Statement Regarding Forward-Looking Information

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Actual financial results may differ materially depending on a number of factors including adverse economic conditions, currency exchange rate fluctuations, adverse legislative and regulatory developments, delays in new product launch, pricing and product initiatives of competitors, the inability of the company to market existing and new products effectively, interruptions in production, infringements of the company's intellectual property rights and the adverse outcome of material litigation.

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Focus Therapeutic Area in Research and GCL Model

Concentrate management recourses on innovative drug business

Focus Therapeutic Area in Research

- Urology
- Transplantation
- Oncology
- Immunology & Infectious Diseases
- Neuroscience
- DM Complications & Kidney Diseases

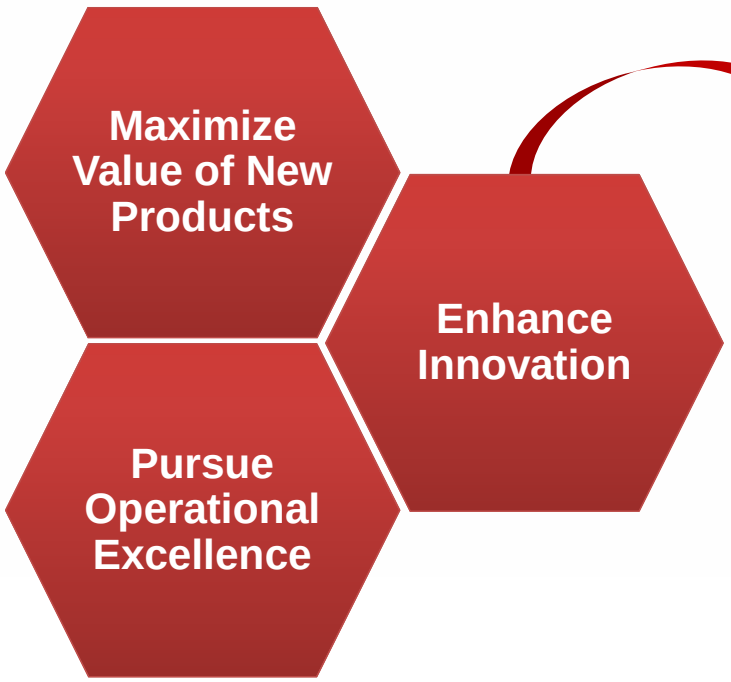
Current GCL

Third GCL

Global Category Leader (GCL)

Strategic Priorities for Sustainable Growth

Resiliently Respond to the Changing Environment and Aim for Sustainable Growth

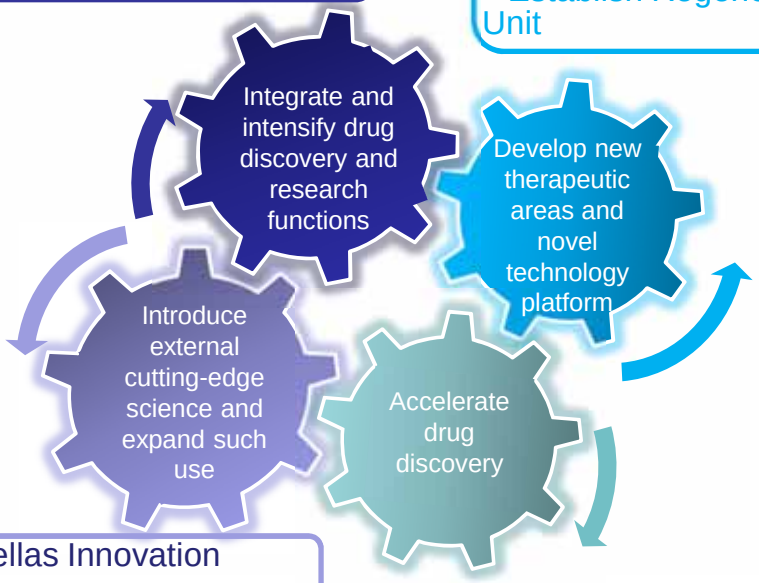


- Reshape research framework (I)
- Develop *Network Research System* by more utilizing external resources (II)
- Develop new therapeutic areas and novel technology platform (III)
- Accelerate R&D project (IV)
- Enrich R&D pipeline

I. Reshape Research Framework

・Reorganize Drug Discovery Research functions
・Develop *Network Research System*

・Cooperate with various partners
・Expand activities of Frontier Disease Research
・Establish Regenerative Medicine Unit



・Establish Astellas Innovation Management

・Enhance research management
・Introduce multiple R&D pathways

II. Develop *Network Research System* by More Utilizing External Resources

Best Science Seek world class cutting-edge innovation

Best Talent Bring together leading talent from Astellas, biotech and academia, etc.

Best Place Adopt the most suitable Astellas or third-party location worldwide

Target **Candidate** **FIM** **POC** **Pivotal** **NDA** **Launch**

Innovation outside Astellas | Biotech, VC, Academia,CRO, KOL, etc.

Search, Evaluate, Negotiate

Astellas Innovation Management | **Licensing & Alliances**

astellas INNOVATION MANAGEMENT AIM

FIM: First in man
POC: Proof of concept
NDA: New drug application
VC: Venture capital
CRO: Clinical research organization
KOL: Key opinion leader

III. Develop New Therapeutic Areas and Novel Technology Platform

Challenge with *Network Research System*
(Best Science, Best Talent, and Best Place)

Immuno-Biological Laboratories
(Gunma)
Transgenic silkworms

Cytokinetics
(San Francisco)
Muscle weakness diseases

Mitokyne
(Boston)
Mitochondria-related diseases

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(Tsukuba)
Regenerative Medicine Unit

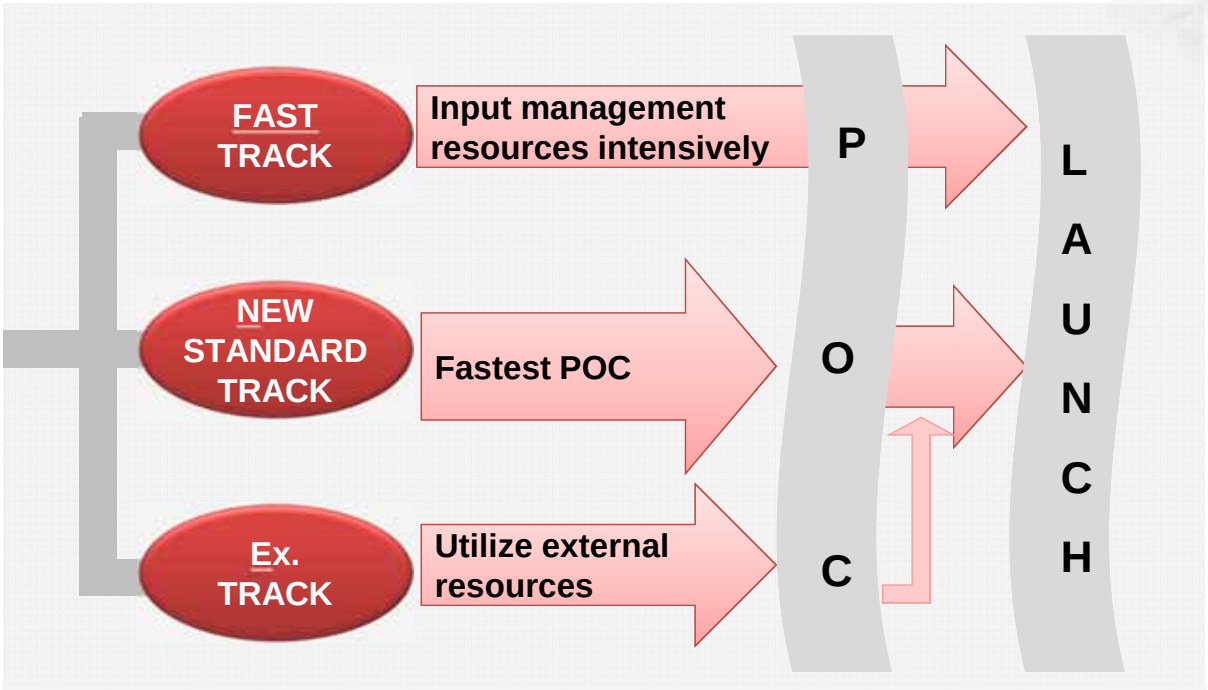
Ambrx
(San Diego)
Next generation ADC

ClearPath
(Maryland)
RSV(Respiratory syncytial virus) vaccine

Daiichi Sankyo
(Tokyo)
Compound library sharing

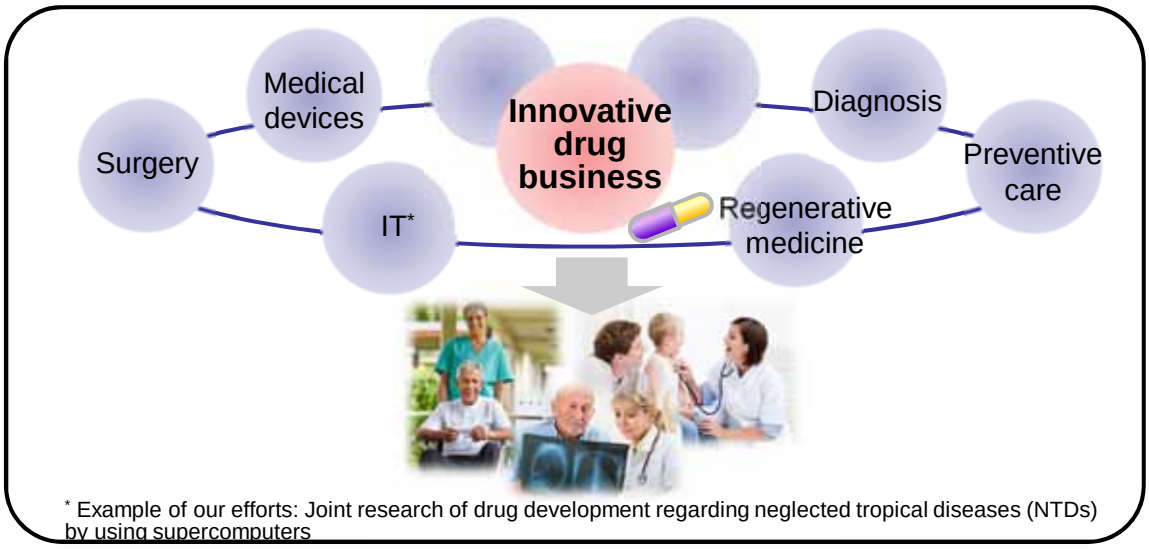
Lieber Institute for Brain Development
(Maryland)
Novel CNS drug

IV. Accelerate R&D Project (Project FASTEN)



Provide a New Value

Continuously deliver new solutions for patients with the innovative drug business as the core



* Example of our efforts: Joint research of drug development regarding neglected tropical diseases (NTDs) by using supercomputers

Establish an internal special unit in order to create new business

- **Make use of Astellas' advantages developed through innovative drug business for expansion into other products than disease treating agents**
- **Actively promote external collaborations including those with companies outside of pharmaceutical industries**
- **Deliver new solutions through introduction of revolutionary technologies**

Deliver Solutions in Surgery: Collaborative Research with Immuno-Biological Laboratories regarding Human Fibrinogen

Transgenic silkworm technology

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Collaborative research for productization

Revolutionary method that allows efficient production of human fibrinogen

- **Succeeded in making complicated protein (difficult with microorganisms)**
- **No risk of virus contamination and stable supply**

- **Decided further develop collaborative research following completion of primary investigation of characteristics**

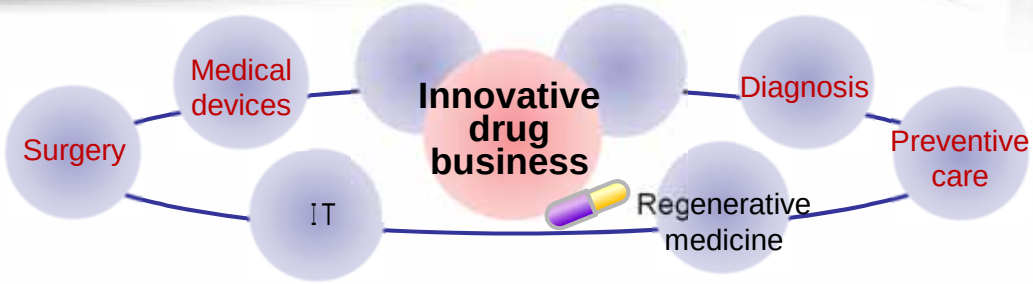
⇒ **Aim to launch by around 2020**

Fibrinogen

- Fibrinogen is used for adhering/closing tissues and arresting bleeding, as a core molecule for blood coagulation.
- Currently used pharmaceutical preparation is derived from human blood.
- The market of fibrinogen-containing products in the world is expected to grow to over 100 billion yen by 2018 (source: Evaluate Pharma).



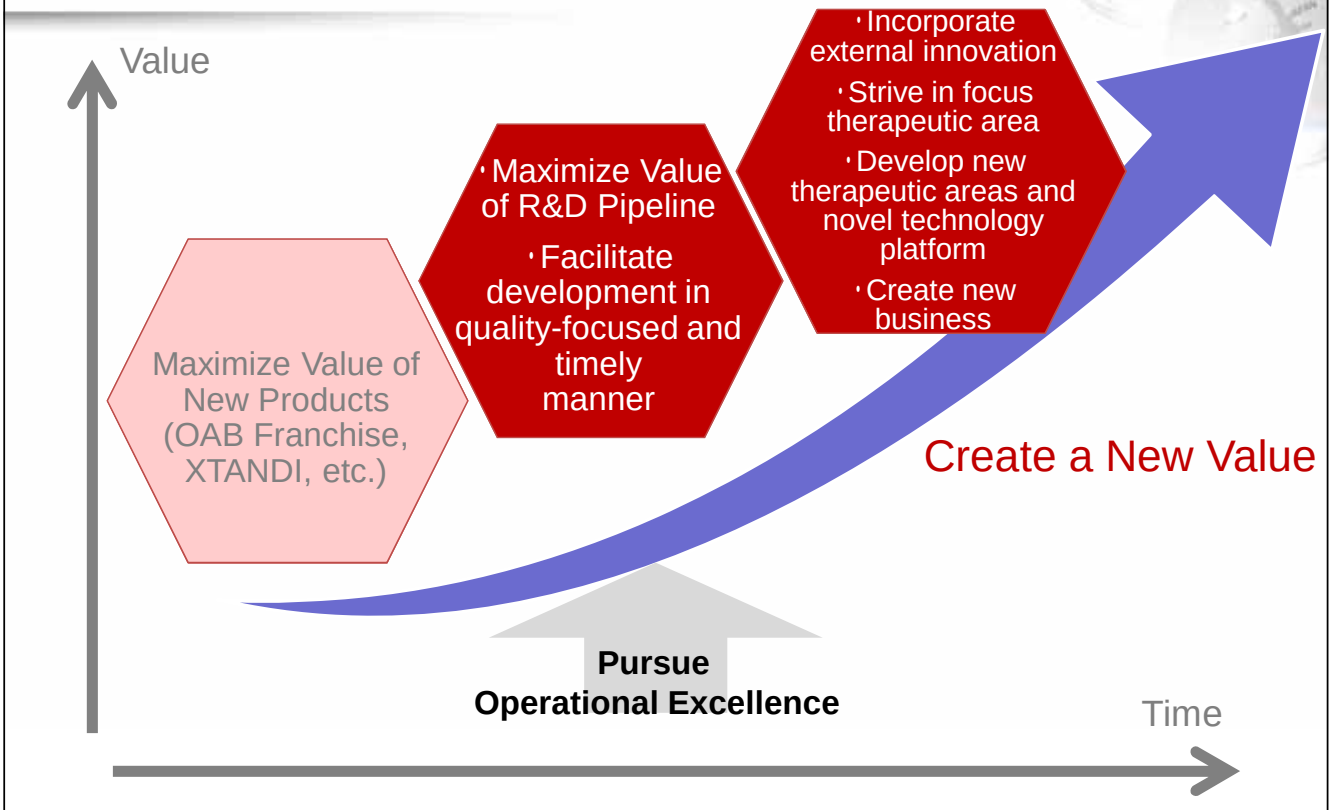
Other Initiatives



Products combined with medical devices	• **Create new therapeutic fields through combination of drugs and medical devices** • **Provide new therapeutic methods in urology**
Expansion to diagnosis and preventive care	• **Provide more accurate early diagnosis methods for localized primary tumor and micro-metastasis (make use of antibody technology)**
Solutions to surgery needs	• **Provide products that will contribute to reduction of surgery time and better outcome** • **Perioperative period management**

Provide high value-added

Aim at Sustainable Growth of Enterprise Value



Transform innovation into value that will benefit patients



Changing tomorrow

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Initiatives in Drug Discovery Research

- Reshape research framework, aim for further innovation -

July 10, 2014
Wataru Uchida, Ph.D.
Senior Vice President,
President, Drug Discovery Research
Astellas Pharma Inc.

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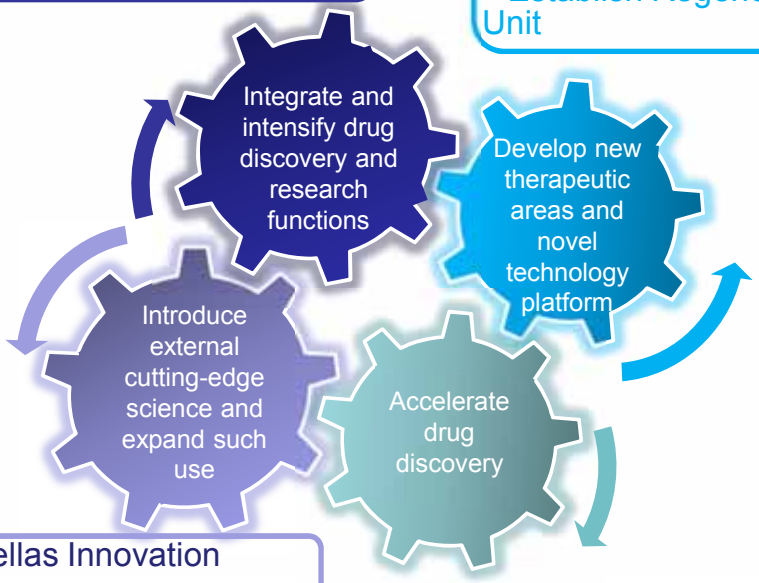
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Reshape Research Framework

- Reorganize Drug Discovery Research functions
- Develop *Network Research System*

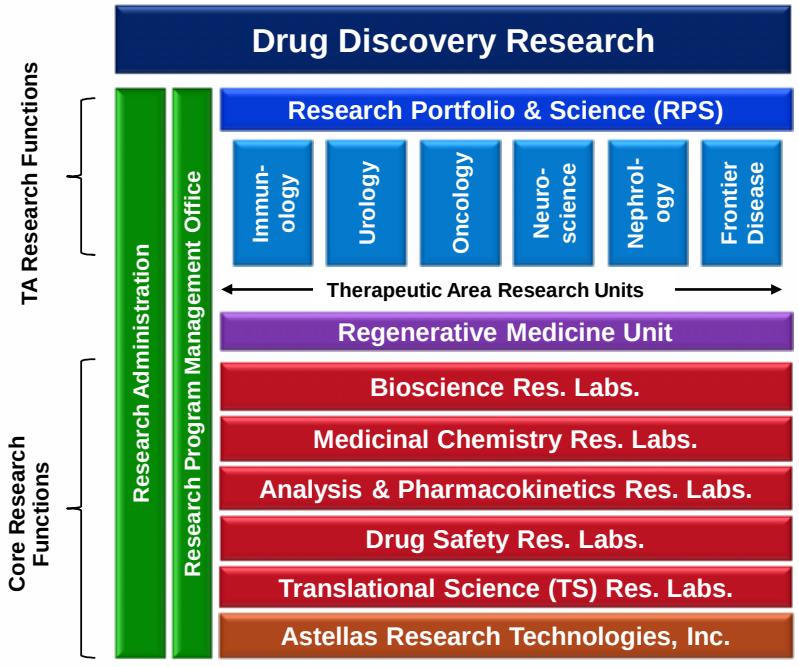
- Cooperate with various partners
- Expand activities of Frontier Disease Research
- Establish Regenerative Medicine Unit



- Establish Astellas Innovation Management

- Enhance research management
- Introduce multiple R&D pathways

Restructure Organization



RPS possesses two important functions of managing research portfolio and fostering/capturing innovation. The latter is carried out in close coordination with Astellas Innovation Management..

Pharmacology Research Labs. was dissolved and restructured into **TA Research Units** which have enhanced autonomy and accountability

Translational Science-related scientific and managerial capabilities are integrated to form the new **TS Research Labs.**

TA: Therapeutic Area

Develop New Therapeutic Areas and Novel Technology Platform

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Develop New Therapeutic Areas and Novel Technology Platform

Apply recombinant human proteins produced by transgenic silkworms to medicine	• Collaboration for research with Immuno-Biological Laboratories (IBL)
Advance novel therapies for diseases and medical conditions associated with muscle weakness	• Collaboration for R&D and commercialization with Cytokinetics
Discover and develop novel drugs that improve mitochondrial functions	• Collaboration for R&D with Mitokyne (with exclusive right to acquire the company)
Expand our commitment to regenerative medicine	• Establishment of Regenerative Medicine Unit
Develop RSV (Respiratory syncytial virus) vaccine	• Strategic partnership with ClearPath, investing in development of vaccine
Discover and develop novel antibody-drug-conjugates (“ADCs”) in oncology field	• Collaboration for next generation ADC with Ambrx
Seek more chance of innovation by diversifying compound sources	• Compound library sharing partnership with Daiichi Sankyo (400 thousand compounds each other)
Collaborate with academia beyond individual corporate frameworks for discovery of novel CNS drugs	• Participation in LIBD consortium

Develop New Therapeutic Areas：Collaboration with Cytokinetics

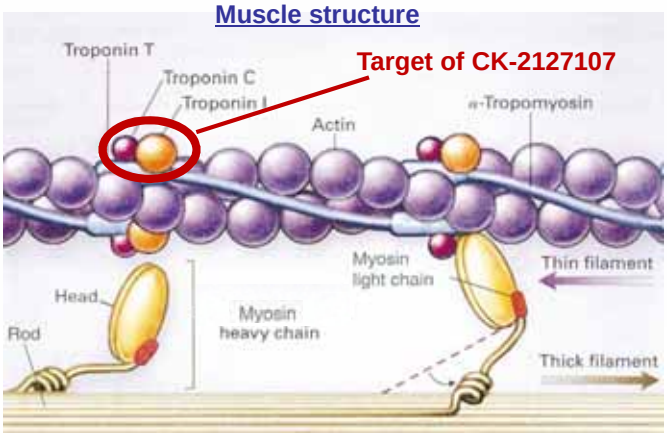
Conduct research/development collaborations with an aim to create new innovative drugs in the field of skeletal muscle diseases.

Skeletal muscle plays a role in various organs and sites in the body. Deterioration of its functions causes various diseases and symptoms.
⇒Aim for the development of skeletal muscle activators that will improve these symptoms.

[Progress]

- **Fast skeletal muscle troponin activator CK-2127107**
  Phase I study showed dose-dependent pharmacokinetics and high tolerability
- **Joint research of follow-up compounds is also progressing smoothly**

Muscle structure



Actin (filament) and regulatory complex

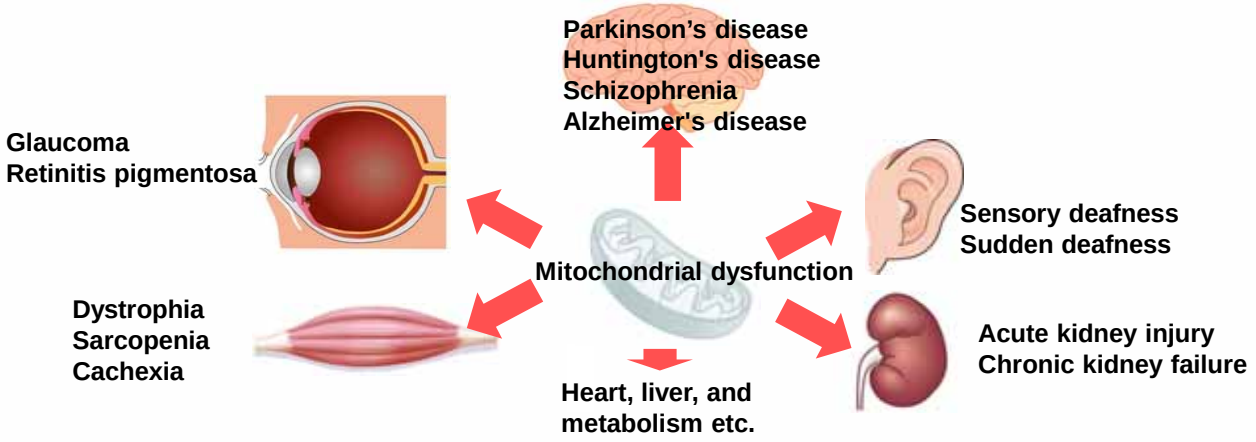
Myosin

Adapted from KAMISAGO *et al.*, *New England Journal of Medicine;* Volume 343 Number 23 : 1695

Develop New Therapeutic Areas：Collaboration with Mitokyne

Conduct research/development collaborations with an aim to create innovative new drugs and establish the leading position in the mitochondria-related diseases field

Mitochondrial dysfunction may cause various diseases



Mitokyne Profile：





- **Mitokyne has completed set up and has initiated research activities.**
- **Its scientific advisors include a Nobel prize laureate Dr. Horvitz.**
- **Nature Biotechnology selected the company as one of the Innovative startups 2013**

Develop Novel Technology Platform: Initiative for Regenerative Medicine

Regenerative Medicine Unit established in April 2014

■Mission

In the field of regenerative medicine and **cell therapy**,

- ✓ Generate product candidates with competitive superiority
- ✓ Establish and maintain technology platform
- ✓ Bear the hub function as the core research unit in Astellas

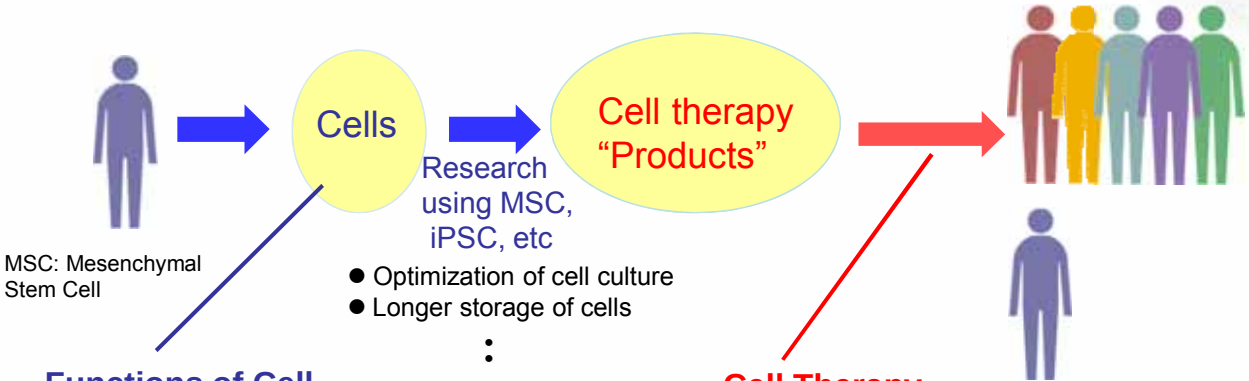
■Organization/management structure

- ✓ Direct reporting to Head of Drug Discovery Research
- ✓ Start with core research members of approximately 20
- ✓ Plan to expand along with the progress of the research

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Concept of Cell Therapy and Target of Astellas

<Expecting its multifunctionality that small compounds or biologics cannot display>



Functions of Cell

- Structural component
- Metabolism/biosynthesis
- Sensor
- Production/release of signaling molecules

Cell Therapy

- Aim to recover /restore the lost function of organ or tissue by disease/aging/accident, by means of cell transplantation (administration)

Cell therapy Astellas targets

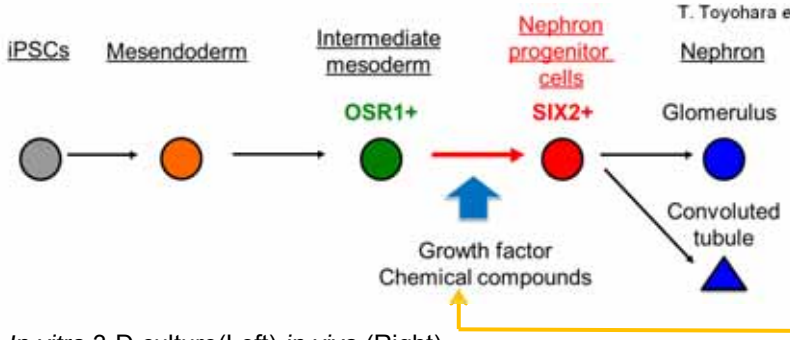
Target indications:	**Those with high unmet medical need such as cardiovascular diseases & cancer**
Short-Mid term goal:	**Recovery of function by paracrine effects of transplanted cells initiate a clinical study in a few years at the earliest.**
Long term goal:	**Recovery of function by transplanted cells themselves**

Result of Research in Regenerative Medicine:
Research Collaboration with CiRA, Kyoto Univ. for Kidney Regeneration

CiRA: Center for iPS Cell Research and Application

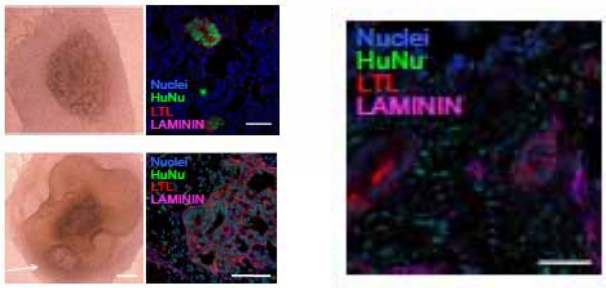
Efficient generation of nephron progenitor cells from iPSC
Progress for drug evaluation, disease model generation and cell therapy

T. Toyohara *et al*, International Society for Stem Cell Research 2013



Developed a method for efficient generation of nephron progenitor cells from intermediate mesoderm

In vitro 3-D culture(Left) *in vivo* (Right)
renal tubule specific protein was expressed and
renal tubule-like structure was formed





Nephron
Nephron is the functional unit of kidney, which has glomerulus and renal tubules. There are about 1 million nephrons in a kidney.

Develop Novel Technology Platform:
Strategic partnership with ClearPath for Vaccine

Develop vaccine business through creative business scheme

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Acquisition right
Fund development

RSV Corporation

Develop vaccine for RSV

ClearPath DEVELOPMENT COMPANY

Robust experience of vaccine clinical development

Manage/Operate

In-license

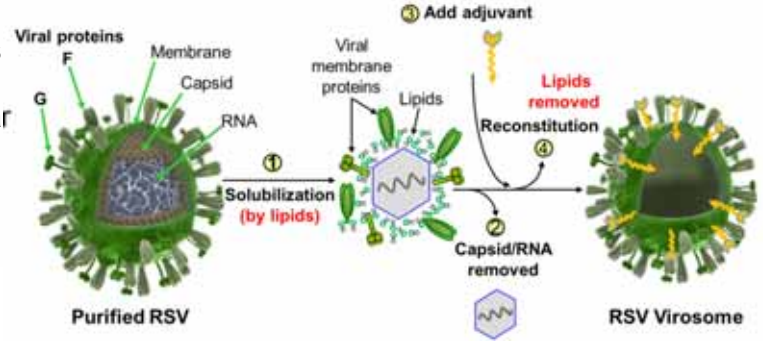
- **Up-front payment**
- **Milestone payments**
- **Royalty**

MYMETICS

Cutting-edge virosome vaccine technology

Virosome：Membrane nanoparticle containing natural surface proteins without genetic material

- Powerful immune responses similar to a normal virus infection due to similar structure to natural RSV
- Enhancement of immune responses by the incorporation of an adjuvant
- No risk of infection due to lack of genetic material



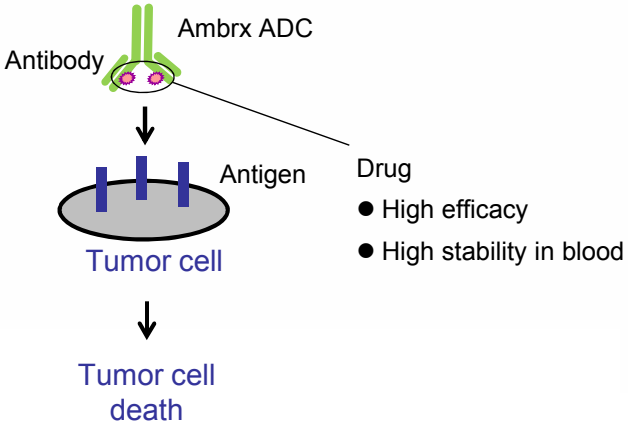
Develop Novel Technology Platform:
Ambrx Next-Generation ADC ("Antibody-Drug Conjugate")

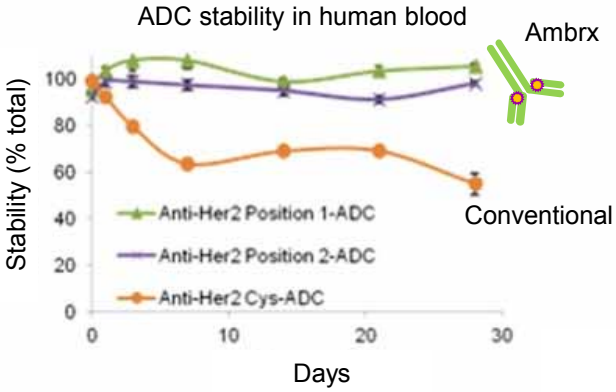
Introduce new ADC technology with increased blood stability

Conventional ADC
Conjugate drug on natural amino acid residues of antibody
- Non-specific conjugation

Ambrx ADC
Incorporate non-natural amino acids into antibody and conjugate drug to the sites
- Site specific ADC → high efficacy
- High stability in blood → low side effects

Ambrx ADC is expected to be an anti-cancer drug with more efficacy and better safety profile





Jackson D. *et. al., PLoS One*. 2014;
(reported by Agensys and Ambrx)

Initiatives in Technology Platform and Focus Therapeutic Areas

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Initiatives in Technology Platform: Precision Medicine/ Omics

Using cutting-edge Omics technologies, gain insight of diseases and actively search for drug targets/biomarkers



Analysis of Clinical sample



Progress of technologies

Collaboration with Academia



Data analysis by bioinformatics (processing information rapidly increasing)

New Technology (-omics, genome editing)
drug target/biomarker

Chemical proteomics
mechanism of drug action

Expression proteomics
mechanism of disease

Boost up
Precision Medicine
Drug Discovery

Initiatives in Technology Platform: Antibody Drug Discovery and Structure Prediction

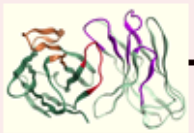
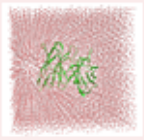
Using cutting-edge IT technologies, increase accuracy of antibody structure prediction
Promote creation of next generation antibodies

Benefits from IT revolution and Big Data

Next generation antibody drug discovery

Development of antibody informatics

3D modeling **dynamic simulation**

Antibody Sequence → Prediction →  → Prediction → 

(1D information) (3D information) (4D information)

IBC's 24th Antibody Engineering and Therapeutics

International competition of antibody structure prediction
(The second competition in December 2013)

- **A team of Osaka University, National Institute of Biomedical Innovation, and Astellas predicted most correctly.**

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Achievement in Oncology Research:
ASP2215 (Novel FLT3/AXL Inhibitor)

ASP2215, a FLT3/AXL inhibitor, showed potent antileukemic activity against AML with either or both FLT3-ITD and FLT3-D835 mutations.

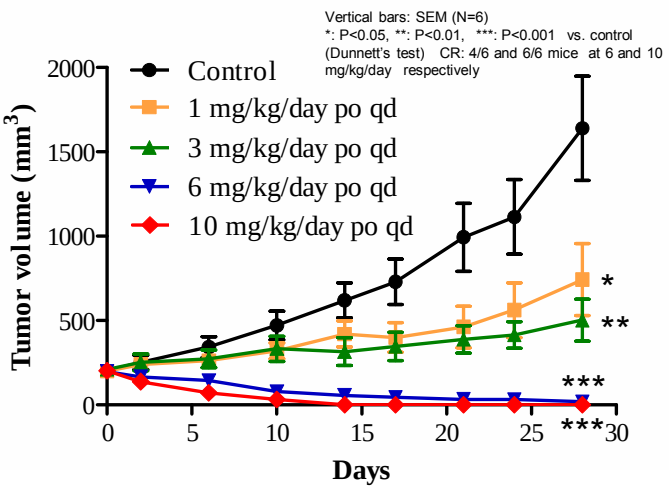
Mori *et al*., 2014 ASCO Annual Meeting

Kinase inhibitory profile

Kinase	IC_{50} (nmol/L)
FLT3	0.29
LTK	0.25
ALK	0.42
AXL	0.70
TRKA	1.1
RET	1.8
ROS	1.5
MER	2.9
c-KIT	230

ASP2215 is a potent FLT3/AXL inhibitor.

Antitumor activity of ASP2215 in mice xenografted with MV4-11 cells



ASP2215 induced complete remission in mice FLT3-ITD xenograft model at does of 6 mg/kg and above.

Achievement in Oncology Research:
ASP8273 (Novel Mutant-Selective Irreversible EGFR Inhibitor)

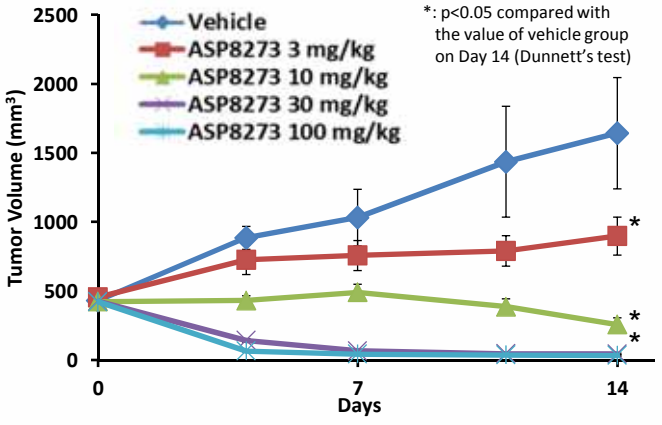
ASP8273 showed antitumor activity in NSCLC xenograft model with EGFR T790M/L858R and higher affinity to these mutations than wild type.

Binding Affinity (KINOMEscan®)

EGFR	Kd (nM)
wild type	140
T790M/L858R	0.22

ASP8273 showed higher affinity to EGFR T790M/L858R than wild type EGFR.

Tumor Regression



ASP8273 induced tumor regression in NSCLC xenograft model with T790M/L858R at doses of 10 mg/kg and above.

Sakagami *et al*., AACR Annual Meeting 2014

Summary

Reshape research framework, aim for further innovation

- More utilizing external resources with *Network Research System*
- Develop new therapeutic areas and novel technology platform
- Continue enhancing current technology platform and focus therapeutic areas

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Our Pipeline

Bringing innovative therapeutics to patients

July 10, 2014
Sef Kurstjens, M.D., Ph.D.
Chief Medical Officer, Astellas Pharma Inc.
President, Astellas Pharma Global Development, Inc.

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Agenda

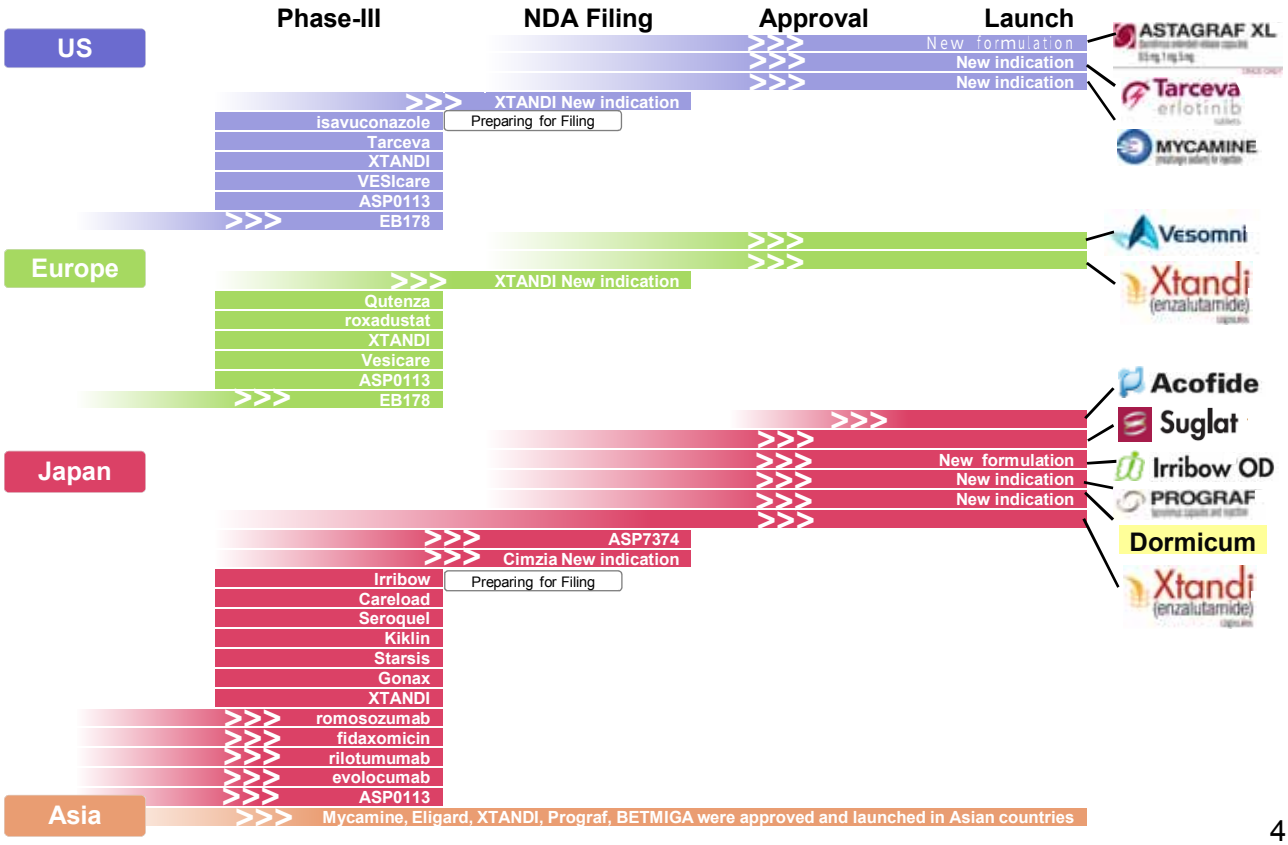
1. Development at Astellas
2. Oncology
3. Urology and Nephrology
4. Immunology (Including Transplantation) and Infectious Diseases
5. Japan Development
6. Summary

Astellas Global Development Purpose Statement

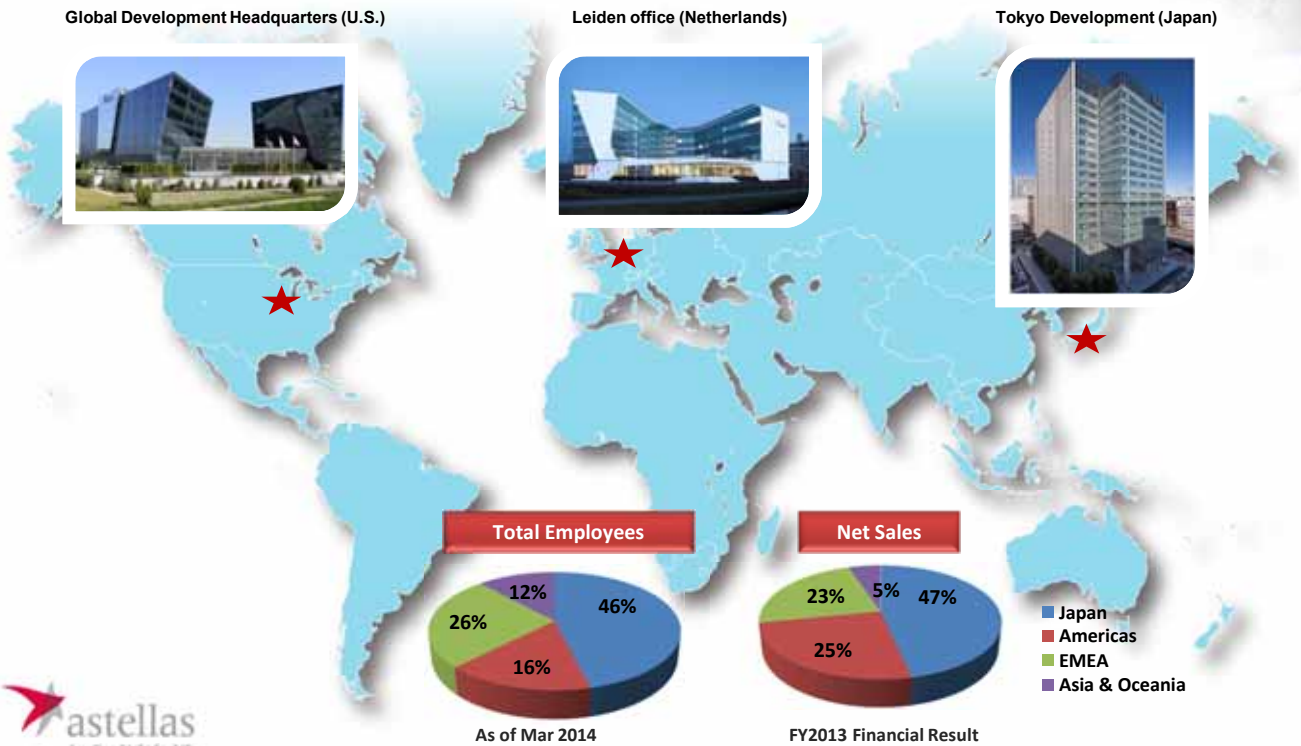
Bringing innovative therapeutics to patients

- by maximizing the potential of the Astellas portfolio
- in a quality-focused, cost-efficient and timely manner
- through achieving regulatory approvals with commercially desirable labels

Progress of Many Late Phase Compounds since April 2013



Global Presence of Astellas Global Development



Development in Astellas - Profile of core TA heads

Claire Thom, PharmD [Oncology]

- 24 years of experience in the pharmaceutical industry, holding a variety of roles in Medical and Scientific Affairs, Research and Development, Marketing/New Product Planning and Portfolio Management

Michael Allen, MD, FRCP, FFPM [Urology/Nephrology]

- 25 years of experience in the pharmaceutical industry involving all stages of Development and multiple therapeutic areas including Urology, Nephrology and Cardiovascular

Bernhardt Zeiher, MD, FACP, FCCP [Immunology and Infectious Diseases]

- 15 years of pharmaceutical industry experience across multiple therapeutic areas, including Sepsis, Acute Lung Injury, Pain, Rheumatology, Transplant and Infectious Diseases. Board certified in internal medicine, pulmonary medicine and critical care.

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TA: Therapeutic area

Quality Global Development Plans Aligned with TA Strategies

Urology/Nephrology

- Maximize the value of urology franchise
- Progress R&D projects in next generation diseases in urology
- Build a pipeline in nephrology

Immunology and Infectious Diseases

- Maintain Transplant market leadership and expand into disorders seen in transplant recipients
- Build a global immunology portfolio

Oncology

- Establish cornerstone assets
- Follow the biology
- Pursue accelerated R&D pathways

Japan Development

- Expand to Asia for maximizing product value
- Exploit Japan development capabilities
- Support both local and global commercial needs
- Collaborate with DDR on Frontier diseases

Maximize Product Value

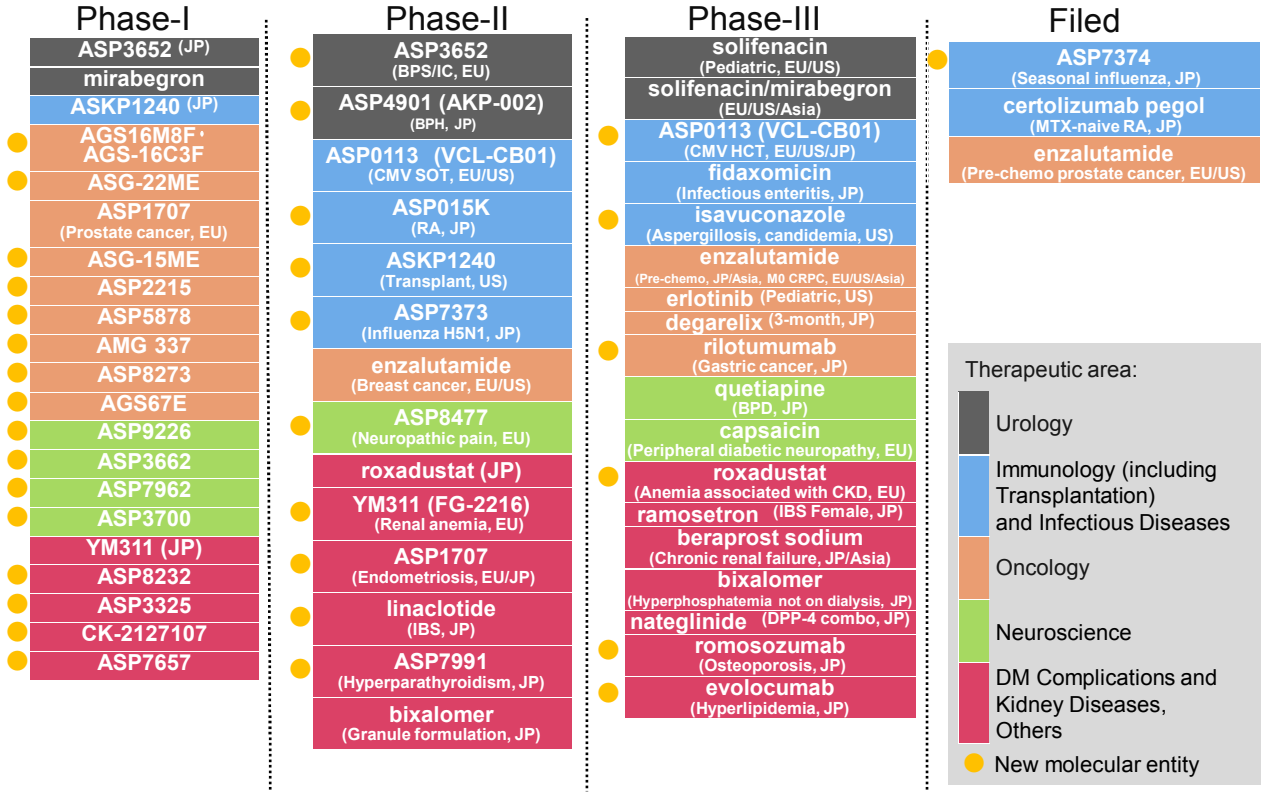
Address Unmet Medical Need

Achieve Operational Excellence

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DDR: Drug discovery research

Status of Astellas' Pipeline



BPS/IC: Bladder pain syndrome/Interstitial cystitis, BPH: Benign prostatic hyperplasia, RA: Rheumatoid arthritis, CMV: Cytomegalovirus, SOT: Solid organ transplant, IBS: Irritable bowel syndrome, MTX: Methotrexate, HCT: Hematopoietic cell transplant, M0 CRPC: Non-metastatic castration-resistant prostate cancer, BPD: Bipolar disorders, CKD: Chronic kidney disease,

ONCOLOGY

Oncology Pipeline

Stage in the most advanced territory

	Project	Target Cancer	Characteristics	PI	PII	PIII	Filed
Small molecule	Enzalutamide (XTANDI)	Prostate cancer (pre-chemo, non-metastatic), Breast cancer (BC)	Androgen receptor inhibitor	Pre-chemo: EU/US/JP/Asia			Filed in US/EU
				Non-Metastatic: EU/US/Asia			
				BC:US/EU			
	Erlotinib (Tarceva)	Pediatric ependymoma	HER1/EGFR tyrosine kinase inhibitor	US			
	Degarelix (Gonax)	Prostate cancer	1st GnRH antagonist in Japan	3-month: JP			
	ASP1707	Prostate cancer*	Oral GnRH antagonist				
	ASP2215	Acute myeloid leukemia	FLT3/AXL inhibitor				
	ASP5878	Cancer					
	AMG 337	Gastric cancer	MET inhibitor	JP			
	ASP8273	Non-small cell lung cancer	EGFR T790M inhibitor				
Antibody	Rilotumumab AMG 102	Gastric cancer	Anti-HGF monoclonal antibody	JP			
	AGS-16M8F/ AGS-16C3F	Renal cancer	Antibody utilizing ADC (target: ENPP3)				
	ASG-22ME	Solid tumors	Antibody utilizing ADC (target: Nectin-4)				
	ASG-15ME	Bladder cancer	Antibody utilizing ADC (target: SLITRK6)				
	AGS67E	Lymphoid malignancy	Antibody utilizing ADC (target: CD37)				

ADC: Antibody-drug conjugate

*P2 for indication of endometriosis

Enzalutamide (XTANDI)

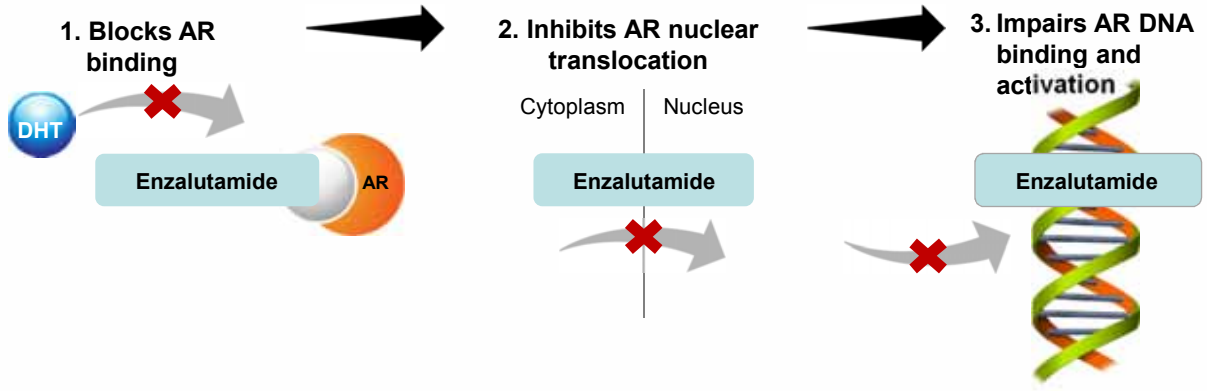
- Androgen receptor inhibitor
- Launched in 25 countries/areas for post-chemo mCRPC
- Label expansion ongoing

Xtandi (enzalutamide) capsules

mCRPC: metastatic castration-resistant prostate cancer

Androgen Receptor (AR) Inhibitor

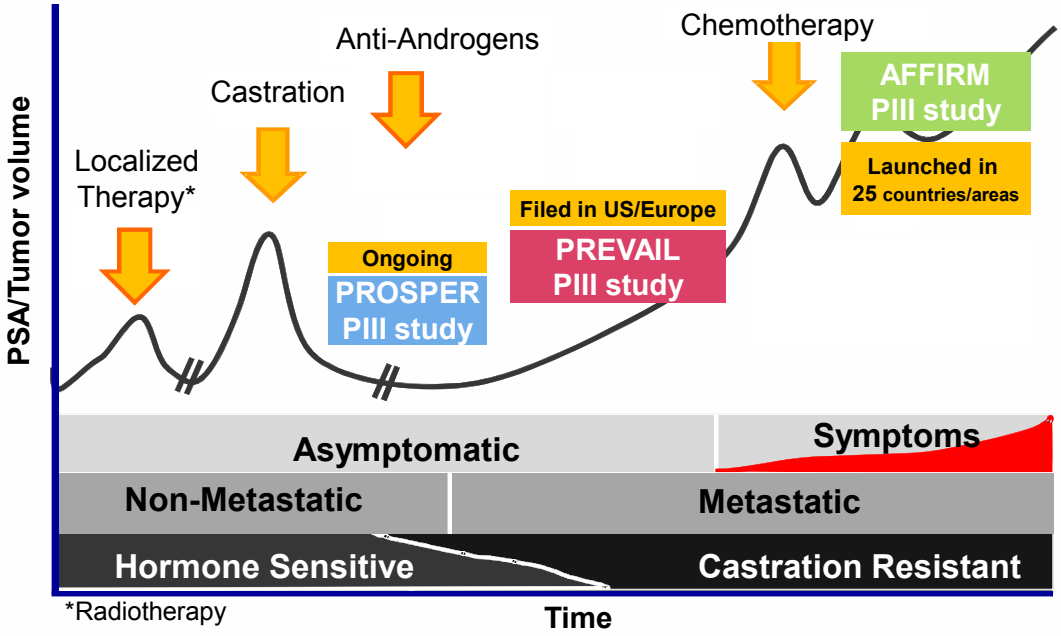
Enzalutamide is the first AR inhibitor that inhibits AR signalling in three distinct ways:[1,2]



DHT=dihydrotestosterone

1. Tran C, *et al. Science* 2009;324:787–90
2. Watson *et al. Proc Natl Acad Sci USA* 2010;107:16759–65

Maximizing the Value of Enzalutamide for Prostate Cancer Patients



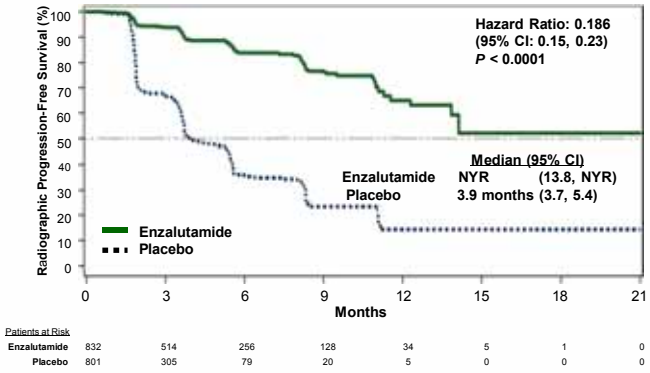
PSA: Prostate-specific antigen

P. Mulders *et al. EAU2012,* modified by Astellas

Prostate Cancer Development Progress

Study	Target	Design	PI	PII	PIII	Filed	Approved
PIII EU/US [AFFIRM study]	Post-chemo Metastatic castration-resistant prostate cancer (CRPC)	Placebo-controlled, n=1,199	Submitted in more than 70 countries Approved in more than 40 countries Launched in 25 countries/areas				
PIII EU/US/JP/Asia [PREVAIL study]	Pre-chemo Metastatic CRPC	Placebo-controlled, n=1,717	US: sNDA on Mar. 17, 2014 Priority review granted PDUFA date: Sep. 18, 2014 Europe: Variation to amend MAA on Apr. 2, 2014				
PIII EU/US/Asia [PROSPER study]	M0 CRPC Non-Metastatic CRPC	Placebo-controlled, n=1,500	First Patient In: Nov. 2013				
PII EU/US [TERRAIN study]	Pre-chemo Metastatic CRPC	To compare with bicalutamide, n=375	Completed enrollment: Jul. 2013				
PII US [STRIVE study]	Pre-chemo Metastatic or non-metastatic CRPC	To compare with bicalutamide, n=400	Completed enrollment: Mar. 2014				
PII US	Neoadjuvant therapy Undergoing prostatectomy	Monotherapy or combo with leuprolide or dutasteride, n=50	Last Patient Out: Nov. 2013				
PII EU	Hormone-naive Progressive prostate cancer	Open-label, n=67	Completed				

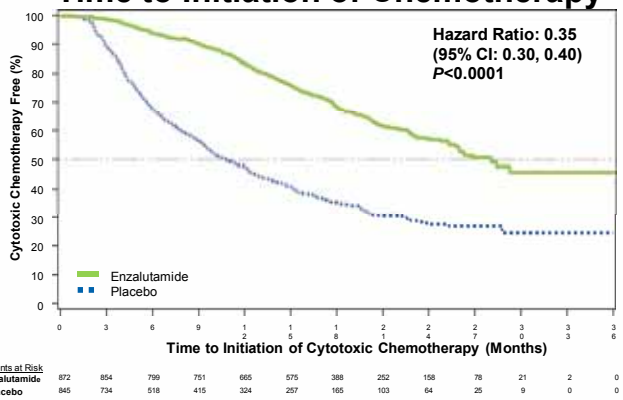
PREVAIL: Enzalutamide Prolonged Radiographic Progression-Free Survival and Time to Initiation of Chemotherapy



*12-month landmark for percentage of patients rPFS-free. CI = confidence interval; NYR = not yet reached.

Time to Radiographic Progression Free Survival

Time to Initiation of Chemotherapy



Enzalutamide delayed median time to initiation of chemotherapy by 17 months compared with placebo.

Beer TM, *et al. N Engl J Med* 2014; Epub ahead of print, DOI: 10.1056/NEJMoa1405095

PREVAIL: Enzalutamide Reduced Risk of Death

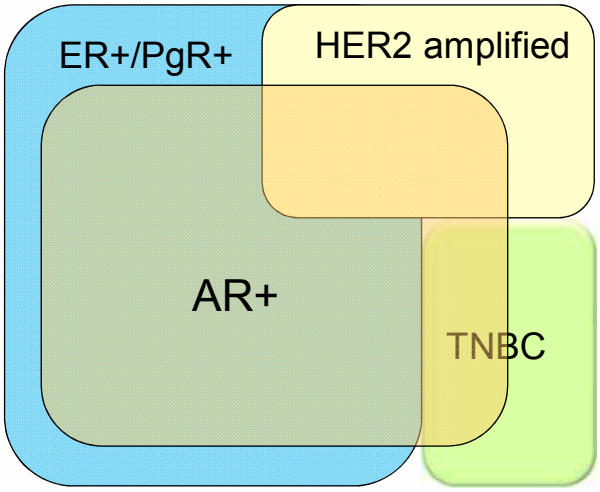
	XTANDI (N = 872)	Placebo (N = 845)
Primary survival analysis[a]		
Number of deaths	241 (27.6%)	299 (35.4%)
Median, months (95% CI)	32.4 (30.1, NR)	30.2 (28.0, NR)
Hazard ratio (95% CI)	0.71 (0.60, 0.84)	
Log-rank test p-value	< 0.0001	
Updated survival analysis[b]		
Number of deaths	299 (34.3%)	357 (42.2%)
Median, months (95% CI)	NR (31.7, NR)	31.0 (28.9, NR)
Hazard ratio (95% CI)	0.73 (0.63, 0.85)	

[a] The data cutoff date is 16 Sep 2013.
[b] The data cutoff date is 15 Jan 2014.
NR, not reached.

Beer TM, *et al. N Engl J Med* 2014; Epub ahead of print, DOI: 10.1056/NEJMoa1405095 and Supplementary Appendix

Androgen Receptor (AR) in Breast Cancer

Three major subsets of breast cancer



- Three subsets are currently managed with a distinct treatment paradigm
  - ~75% are positive for the ER/PgR receptors and are treated with hormones (initially)
  - ~15% have amplification of the growth factor receptor HER2 and are treated with anti-Her2 (throughout)
  - ~20% are triple negative for all of the above (TNBC) and are treated with cytotoxic agents
- ~70-85% of all breast cancers express AR (per literature)
  - >75% of ER+ express AR
  - 50-65% of HER2+ express AR
  - 10-30% of TNBC express AR

ER/PgR: Estrogen and/or progesterone, HER2: Human epidermal growth factor receptor 2
TNBC: Triple negative breast cancer

Collins L. *et al. Mod Pathol* 2011;24(7):924–931
Lehman B. *et al. J Pathol* 2014;232(2):142-50
Goldhirsch A. St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011

Breast Cancer Development Progress

Study	Target	Design	PI	PII	PIII	Filed
PII US/EU	Breast Cancer Advanced, androgen receptor-positive, triple-negative breast cancer	Open-label, n=80	First Patient In: Jun. 2013			
PII US/EU	Breast Cancer Advanced breast cancer that is estrogen receptor positive or progesterone receptor positive and human epidermal growth factor receptor 2 (HER2) normal	Placebo-controlled, in combination with exemestane, n=240	First Patient In: Dec. 2013			
PII US/EU	Breast Cancer Advanced, HER2 positive/ER negative breast cancer	Open-label, n=80	Planned First Patient In: 3Q/2014			

rilotumumab (AMG 102)

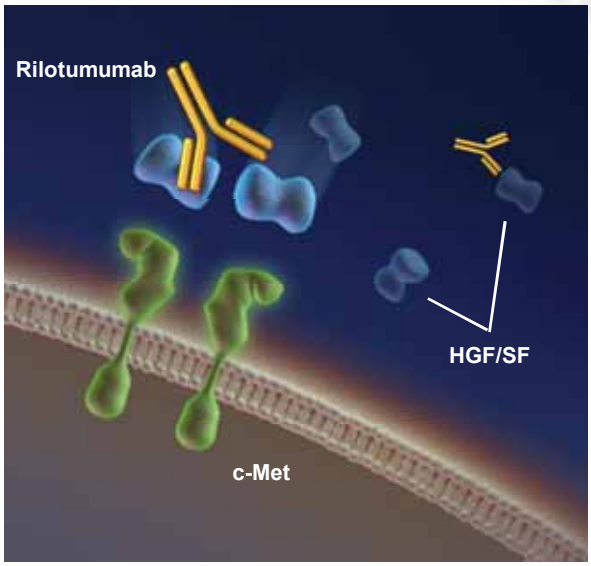
- Anti-HGF monoclonal antibody
- Gastric cancer
- Phase-III in Japan

[Territory of Astellas: Japan]

HGF: Hepatocyte growth factor

Selective Anti-HGF Monoclonal Antibody

- Rilotumumab is designed to selectively target HGF/SF, the only ligand of the c-Met receptor
- HGF and MET regulate multiple cellular functions including proliferation and survival
- MET expression is associated with poor prognosis in gastric cancer
- In preclinical models, the anti-HGF/SF antibody
  - blocked downstream signaling pathways
  - led to inhibition of HGF/SF-dependent tumor growth *in vivo*



Burgess T, *et al. Cancer Res.* 2006;66:1721-1729.

HGF/SF: Hepatocyte growth factor/scatter factor

Development Progress

	Study	Target	Design	Status
Asia	**PIII** [RILOMET-2 study] Japan/China/ Korea	First-line metastatic/locally advanced MET positive gastric or GEJ cancer	Placebo controlled, in combination with CX, n=450	Ongoing
	PI/Ib Japan	Advanced solid tumors or metastatic GEJ adenocarcinoma	Open label, PI part: monotherapy, PIb part: combination with CX, in Japanese subjects, n=21	Ongoing
US/EU	**PIII** [RILOMET-1 study]	First-line metastatic/locally advanced MET positive gastric or GEJ cancer	Placebo controlled, in combination with ECX, n=600	Ongoing
	PIb/II	Locally advanced or metastatic gastric or GEJ adenocarcinoma	PIb: open-label, dose de-escalation, in combination with ECX, n=9 PII: placebo-controlled, in combination with ECX, n=121	Completed in 2013

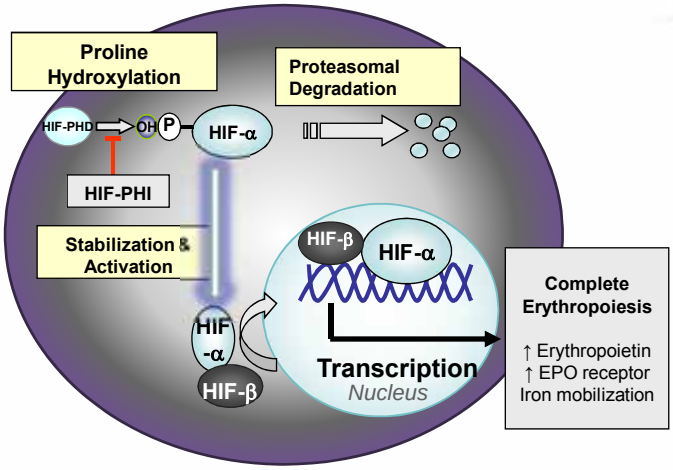
GEJ: Gastroesophageal junction
CX: Cisplatin and capecitabine
ECX: Epirubicin, cisplatin and capecitabine

Roxadustat (ASP1517/FG-4592)

- Hypoxia-inducible factor prolyl-hydroxylase inhibitor (HIF-PHI)
- Anemia associated with chronic kidney disease in patients not on dialysis and on dialysis
- Europe Phase-III
  Japan Phase-II
  [Territory of Astellas: Europe and Japan]

A New Therapy for Anemia in CKD

- Novel mechanism-of-action
- Oral Administration
- Phase-II demonstrated:
  - anemia correction and maintenance in dialysis and non-dialysis patients with CKD
- Phase-II suggests the following:
  - effective without IV iron
  - transient elevation of EPO within physiologic range thereby reducing ESA side effects *e.g.* blood pressure

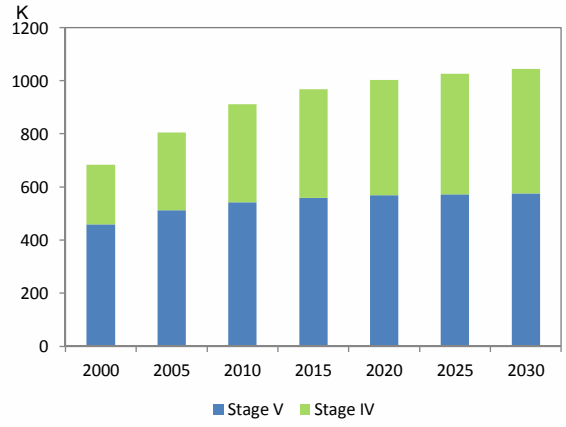


Ivan *et al. Science* 2001, 292:464-8
Jaakkola *et al. Science* 2001, 292:468-7

CKD: Chronic kidney disease; IV: Intravenous,
EPO: Erythropoietin, ESA: Erythropoietin stimulating agent

Unmet Medical Need

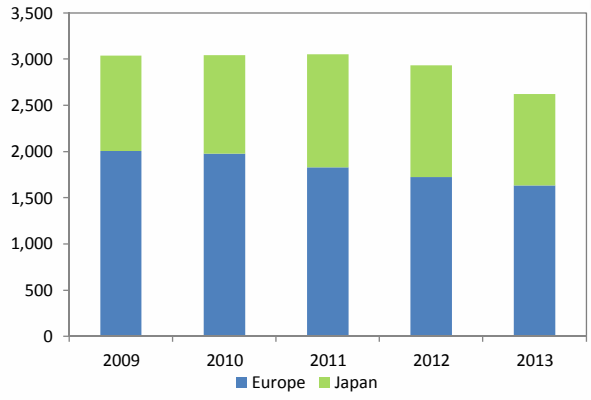
EU5 - CKD Patient Numbers
Large specialist market with growth projected to continue



Steady growth in CKD patients in EU5
- Large specialist market

Source: Epi Database® (Synix Inc. / Kantar Health)

Erythropoetin Stimulating Agents
EU5 & JAPAN (USD 000's)



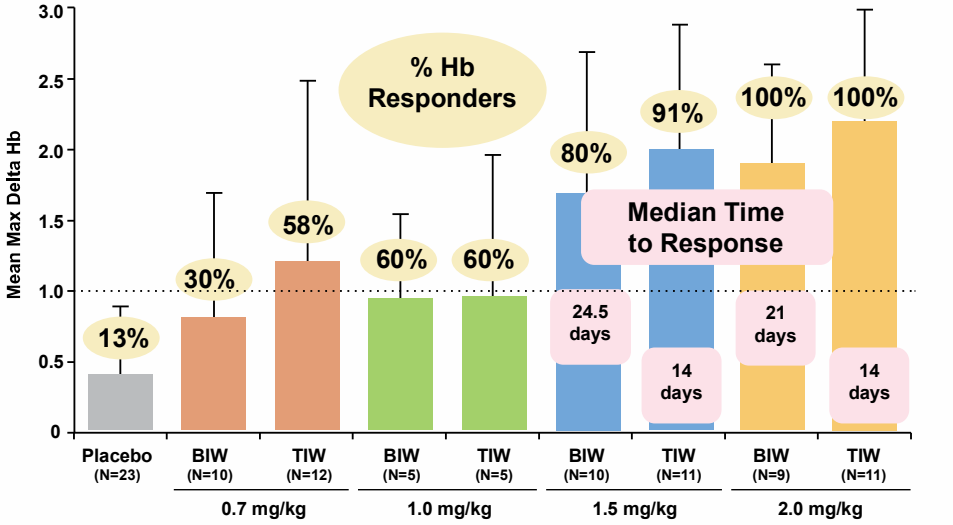
Steady decrease in ESA sales in EU & Japan
- Lower dosing due to cardiovascular safety concerns

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Calculated based on MIDAS 2009-2013 MAT

EU5 = Germany, France, UK, Italy, Spain.

Dose-Dependent Increase in Hb Concentration in Phase-II Study

Mean ± SD Maximal △Hb g/dL (Efficacy Evaluable Population, n=96)



Hb response defined as an increase >=1 g/dL from BL at any time from wk 3-6

Hb: Hemoglobin, BL: Baseline

Besarab A *et al.* (Oral presentation at ASN 2010): FG-4592, a novel oral HIF-PHI, elevates Hb in anemic stage 3-4 CKD patients

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FIBROGEN

Development Progress

	Study name	Population	Comparator	Patients N	Status	Sponsor
US/ Europe **PIII**	Andes	Non Dialysis	Placebo	450-600	Recruiting	FibroGen
	Alps	Non Dialysis	Placebo	450-600	Recruiting	Astellas
	Dolomites	Non Dialysis	Darbepoetin alfa	570	Recruiting	Astellas
	Himalayas	Incident Dialysis	Epoetin alfa	750	Recruiting	FibroGen
	Sierras	Stable Dialysis	Epoetin alfa	600-750	In Preparation	FibroGen
	Pyrenees	Stable Dialysis	Darbepoetin alfa & Epoetin alfa	750	In Preparation	Astellas
Japan **PII**		Non Dialysis	Placebo	100	Recruiting	Astellas
		Stable Dialysis	Darbepoetin Alfa	120	Ongoing	Astellas

A total of 6 Phase III studies will support filings in Europe in both non-dialysis and dialysis indications.

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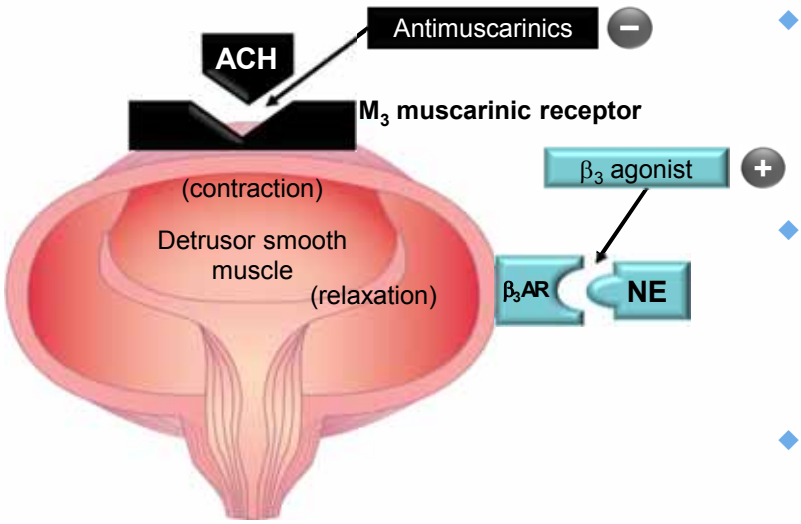
FIBROGEN

solifenacin/mirabegron (EB178)

- Concomitant use of solifenacin and mirabegron
- Overactive bladder (OAB)
- Europe/US/Asia Phase-III

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Complementary Receptor Pathways Offering Opportunity for Combination Therapy



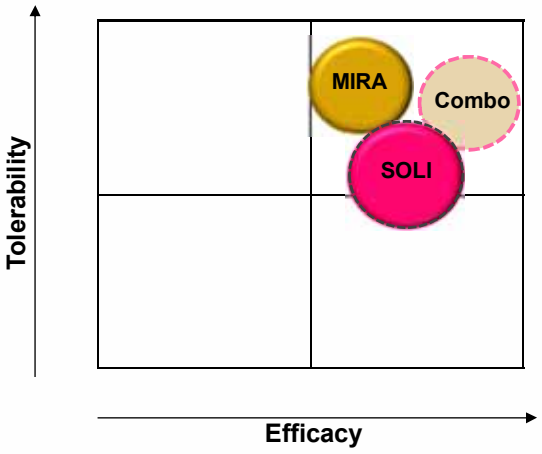
Takeda M, *et al. J Pharmacol Sci.* 2010;2110:121-127.
Fowler CJ, *et al. Nat Rev Neurosci.* 2008;8:453-466.

- Muscarinic and β_3 adrenergic receptors represent two different targets for pharmacologic therapy of OAB
- When acetylcholine binds to the muscarinic receptor, the detrusor smooth muscle contracts and voiding occurs
- When norepinephrine binds to the β_3 adrenergic receptor, the detrusor smooth muscle relaxes and the bladder fills

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ACH: Acetylcholine, NE: Norepinephrine

Unmet Medical Need in OAB

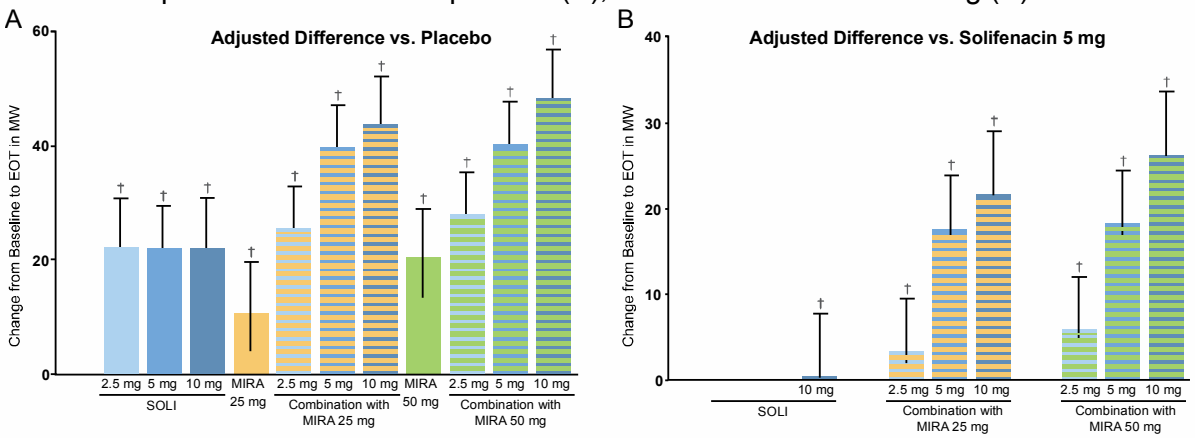


- Co-Administration use (and/or FDC tablet) fills the need that exists for patients requiring greater efficacy without an increase in antimuscarinic side effects
- If successful, the inclusion of combination data in the mirabegron label may potentially help guide clinicians in their use of combination therapy for OAB
- To date, no other oral, OAB agent includes combination data in their label

MIRA: Mirabegron, SOLI: Solifenacin
Combo: Combination, FDC: Fixed dose combination

Results of Phase-II Symphony Study

Changes from baseline to EOT in mean voided volume per micturition versus placebo (A), and versus solifenacin 5 mg (B)



Duration: 12 weeks, Number of subjects: 1,306, Primary endpoint: Change from baseline to EOT in mean volume voided per micturition, Key secondary endpoints: Change from baseline to EOT in mean number of micturitions/24 hours, Change from baseline to EOT in mean number of incontinence episodes/24 hours

Abrams P, *Eur Urol.* 2014 Feb 19. pii: S0302-2838(14)00131-6. doi: 10.1016/j.eururo.2014.02.012. [Epub ahead of print]

- **Phase-III is ongoing**

Mirabegron combination therapy with solifenacin demonstrated greater efficacy than solifenacin alone on change from baseline to EOT in mean volume voided per micturition.

EOT: End of treatment

Isavuconazole

- Azole antifungal
- Invasive Aspergillosis, Mucormycosis, Candidemia/Invasive Candidiasis
- Phase-III in US

[Territory of Astellas: US and Canada]

New Broad Spectrum Antifungal Agent

- Convenient formulation
  - Water soluble prodrug
  - Rapidly converted to active moiety isavuconazole by esterases
  - 98% oral bioavailability
  - Long $t_{1/2}$
  - Reduced risk of drug-drug interactions
  - No need for cyclodextrin in IV formulation, avoids renal impairment restriction
- Characteristics
  - Broad antifungal spectrum of *in vitro* and *in vivo* activity including *Aspergillus spp., Candida spp.,* and Mucorales

Unmet Medical Need

Invasive Aspergillosis

- Fungal infection predominantly occurring in immunocompromised patients
- Untreated mortality ≈100%
- With treatment ≈20% 6-week mortality
- Voriconazole is the standard of care

Invasive Mucormycosis

- Rare angioinvasive fungal infection predominantly occurring in immunocompromised patients and patients with uncontrolled diabetes
- Untreated mortality ≈100%
- With treatment ≈35-65% mortality
- Amphotericin is the standard of care

- For both indications, FDA granted isavuconazole
  - Orphan status – 7 years exclusivity
  - QIDP status – Priority review; 5 additional years exclusivity

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All-Cause Mortality in Phase-III SECURE Study

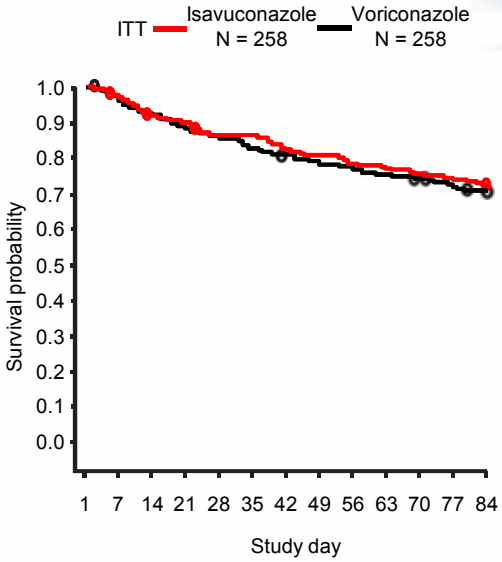
All-cause mortality through Day 42 (ITT population)

	Isavuconazole N = 258	Voriconazole N = 258
All-cause mortality, n (%) [a]	48 (18.6)	52 (20.2)
Adjusted treatment difference, % (95% CI) [b]	–1.0 (–7.8, 5.7)	

[a] 5 Patients with unknown survival status were counted as deaths

[b] Isavuconazole–voriconazole; calculated by a stratified Cochran–Mantel–Haenszel method (strata: Geographic region, Allogeneic BMT/HSCT, and Uncontrolled malignancy status)

Study design:
-Isavuconazole: IV 200 mg TID (Days 1 & 2); IV or oral 200 mg QD (Day 3 onwards)
-Voriconazole: IV 6 mg/kg BID (Day 1); IV 4 mg/kg BID (Day 2); IV 4 mg/kg or oral 200 mg BID (Day 3 onwards)
-Treatment duration: 84 days
-Primary endpoint: Day 42 All-cause Mortality in the intent-to-treat (ITT) population



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Safety and tolerability

10 most frequent TEAEs by System Organ Class

System Organ Class	Isavuconazole N = 257	Voriconazole N = 259	p-value
Overall, n (%)	247 (96.1)	255 (98.5)	
Gastrointestinal disorders	174 (67.7%)	180 (69.5%)	
Infections and infestations	152 (59.1%)	158 (61.0%)	
General disorders & admin. site conditions	148 (57.6%)	144 (55.6%)	
Respiratory, thoracic & mediastinal disorders	143 (55.6%)	147 (56.8%)	
Metabolism and nutrition disorders	108 (42.0%)	121 (46.7%)	
Nervous system disorders	95 (37.0%)	89 (34.4%)	
Skin and subcutaneous tissue disorders	**86 (33.5%)**	**110 (42.5%)**	**0.037**
Investigations (abnormal laboratory tests)	85 (33.1%)	96 (37.1%)	
Blood and lymphatic system disorders	77 (30.0%)	82 (31.7%)	
Psychiatric disorders	70 (27.2%)	86 (33.2%)	
Eye disorders	**39 (15.2%)**	**69 (26.6%)**	**0.002**
Hepatobiliary disorders	**23 (8.9%)**	**42 (16.2%)**	**0.016**

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ASP015K

- JAK inhibitor
- Rheumatoid arthritis
- Japan Phase-III Preparation (Western Phase-II*)

*A license agreement was executed with Janssen Biotech, Inc. for the development and commercialization worldwide except for Japan. Phase-IIb studies were completed by Astellas.

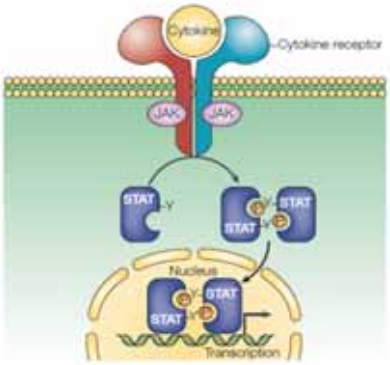
JAK: Janus Kinase

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Selective JAK inhibitor

- Oral JAK inhibitor
- More selective for JAK1/3, vs JAK2/2
- Once daily dosing
- Strong data package to advance Phase-III program in patients with RA in Japan
  - Positive PIIb (Dose Finding Study) in Japan
  - Further safety and efficacy evidence from western PIIb studies
  - No DDI with MTX
  - 52 weeks toxicology study completed

JAK Signal Transduction



Nat Rev Immunol. 2003;3(11):900-11

Inhibitory effect on Cell Proliferation

Cells	IC50, nmol/L
T-Cell [1)]	18
TF-1 [2)]	248
Ratio (TF-1/T-Cell)	14

1) IL-2 induced T-cell proliferation assay
2) EPO induced TF-1 (Human Erythroleukemia Cell line) proliferation assay

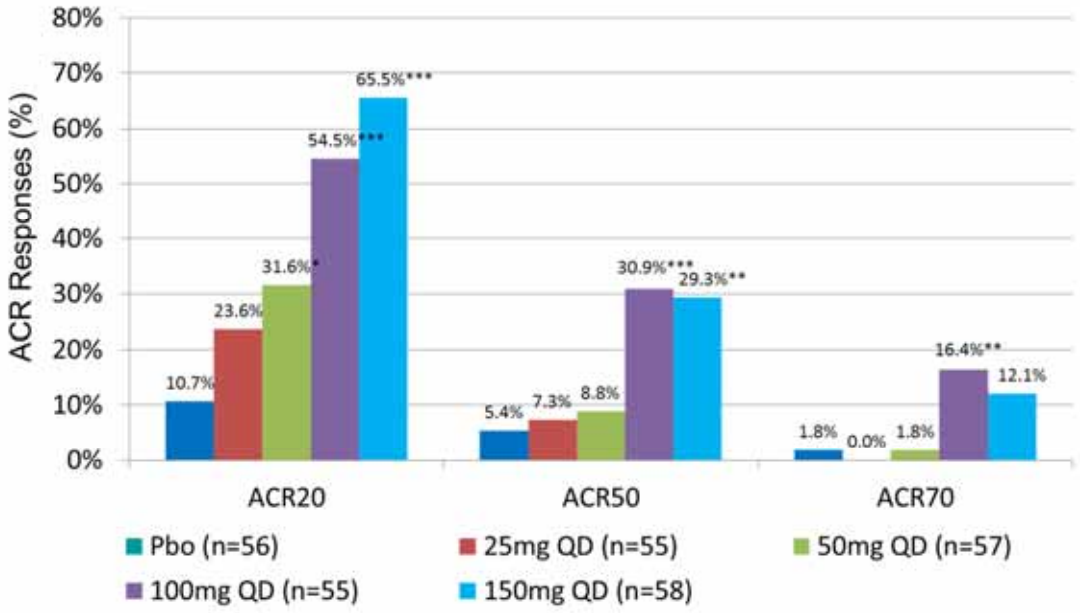
RA: Rheumatoid arthritis,
DDI: Drug-drug interaction, MTX: Methotrexate

Development Progress

Region	Phase	Target / Design	Status
JP	PIIb	Moderate-Severe RA Monotherapy ASP015K 25, 50, 100, 150 mg QD vs placebo 12 week treatment, n=281	Completed
	PII (OLE)	Patients who completed P2b study	Ongoing
Western	PIIb	Moderate-Severe RA with MTX ASP015K 25, 50, 100, 150 mg QD vs placebo 12 week treatment, n=379	Completed
	PIIb	Moderate-Severe RA without MTX ASP015K 25, 50, 100, 150 mg QD vs placebo 12 week treatment, n=289	Completed
	PII (OLE)	Patients who completed P2b study	Ongoing

OLE: Open label extension

Japan Phase-IIb Study Result - ACR Response Rates at Week 12



*P<0.05; **P<0.01; ***P<0.001; P values vs placebo; LOCF imputation

ACR: American College of Rheumatology

Takeuchi *et al. EULAR 2014*

Japan Phase-IIb Study Result - Safety Summary

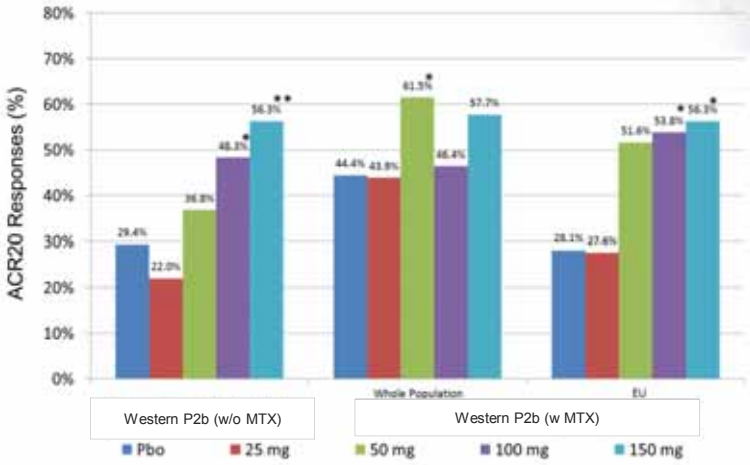
	Placebo (N=56)	25mg QD (N=55)	50mg QD (N=57)	100mg QD (N=55)	150mg QD (N=58)
TEAE, %	**36 (64.3%)**	**39 (70.9%)**	**37 (64.9%)**	**29 (52.7%)**	**39 (67.2%)**
Discontinuations due to TEAE, %*	**10 (17.9%)**	**7 (12.7%)**	**5 (8.8%)**	**6 (10.9%)**	**4 (6.9%)**
Infections and infestations, %**	**12 (21.4%)**	**18 (32.7%)**	**14 (24.6%)**	**7 (12.7%)**	**17 (29.3%)**
GI disorders, %⁺	**3 (5.4%)**	**8 (14.5%)**	**11 (19.3%)**	**6 (10.9%)**	**10 (17.2%)**
Death, %¥	**0 (0.0%)**	**0 (0.0%)**	**1 (1.8%)¥**	**0 (0.0%)**	**0 (0.0%)**
SAE, %	**1 (1.8%)**	**1 (1.8%)**	**2 (3.5%)**	**3 (5.5%)**	**0 (0.0%)**

*TEAE leading to discontinuation was mainly RA aggravation (21 out of a total 32 cases)
**Nasopharyngitis was the most common infection. No serious infection was observed.
⁺Diarrhea was the most common GI disorder
¥ Death was reported for one patient with suspect of intracerebral haemorrhage and considered unrelated to study drug.

Takeuchi *et al. EULAR 2014*

Topline Result of Western Phase-IIb Studies

- **PIIb study without MTX**
  - ACR 20 response statistically significantly higher in the 100 and 150 mg dose groups
- **PIIb study with MTX**
  - ACR 20 response statistically significant only in the 50 mg dose group.
  - Unexpectedly high placebo response rate in ACR20 (44%).
  - Secondary analyses (e.g. DAS-28 CRP, ESR, CRP) and Sub-group analyses (by region) supported efficacy consistent with other P2b study results.



These efficacy and safety results provide a robust data package supporting advancement of the Japan Phase III clinical program

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evolocumab (AMG 145)

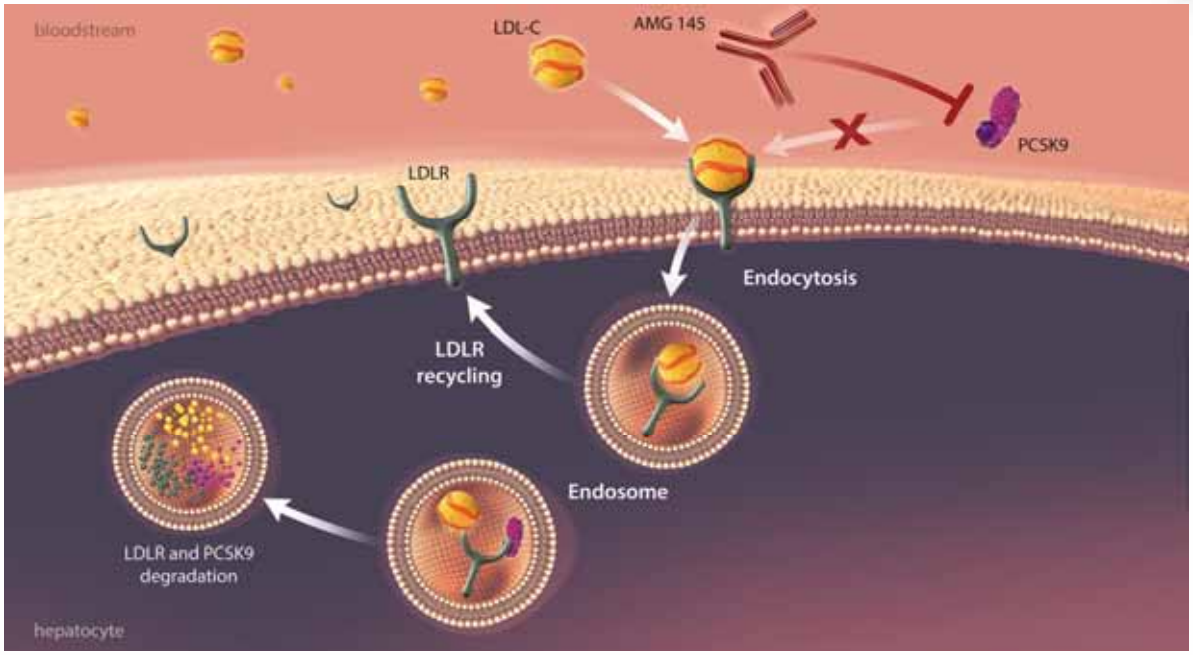
- Anti-PCSK-9 monoclonal antibody
- Hyperlipidemia
- Phase-III in Japan

astellas
Leading Light for Life

PCSK9: Proprotein convertase subtilisin/kexin type 9

astellas AMGEN BioPharma

A Human Monoclonal Antibody Inhibiting PCSK9



PCSK9: Proprotein convertase subtilisin/kexin type 9,
LDL: Low-density lipoprotein, LDL-R: LDL receptor

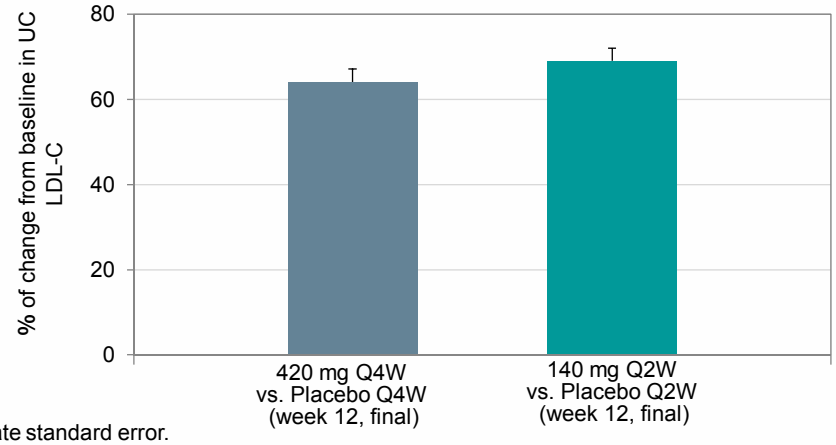
Development Progress

Region	Study	Description	Design	Status
Global (incl. Japan)	**PII** OSLER	Open-label extension, (Long-term safety study)	Open-label, n=1,324	Ongoing
	PIII OSLER-2	Open-label extension (Long-term safety study)	Open-label, n=3,515	Ongoing
	PIII TAUSSIG	Homozygous familial hypercholesterolemia	Open-label, n=310	Ongoing
	PIII FOURIER	Secondary prevention (Outcome study on cardiovascular events)	Double blind, placebo-controlled, n=22,500	Ongoing
Japan	**PII** YUKAWA	Combination therapy with stable statin	Double blind, placebo-controlled, n=310	Completed
	PIII YUKAWA-2	Combination therapy with stable statin	Double blind, placebo-controlled, n=300	Ongoing

YUKAWA-2, Japanese Phase 3, is expected to complete in 2014.

Phase-II YUKAWA Study in Japan

Mean percentage reduction in UC LDL-C versus placebo at Week 12



Error bars indicate standard error.
Graph created by Astellas based on Hirayama *et al. Circ J* 2014; 78: 1073-82

The occurrence of adverse events (AEs) was generally balanced across treatment groups. The three most common AEs were nasopharyngitis, increased creatine phosphokinase and arthralgia. There was no correlation of AEs with evolocumab dose levels or administration intervals.

The study showed robust, dose-dependent LDL-C changes with evolocumab and beneficial changes in other lipid parameters in patients already on a stable statin

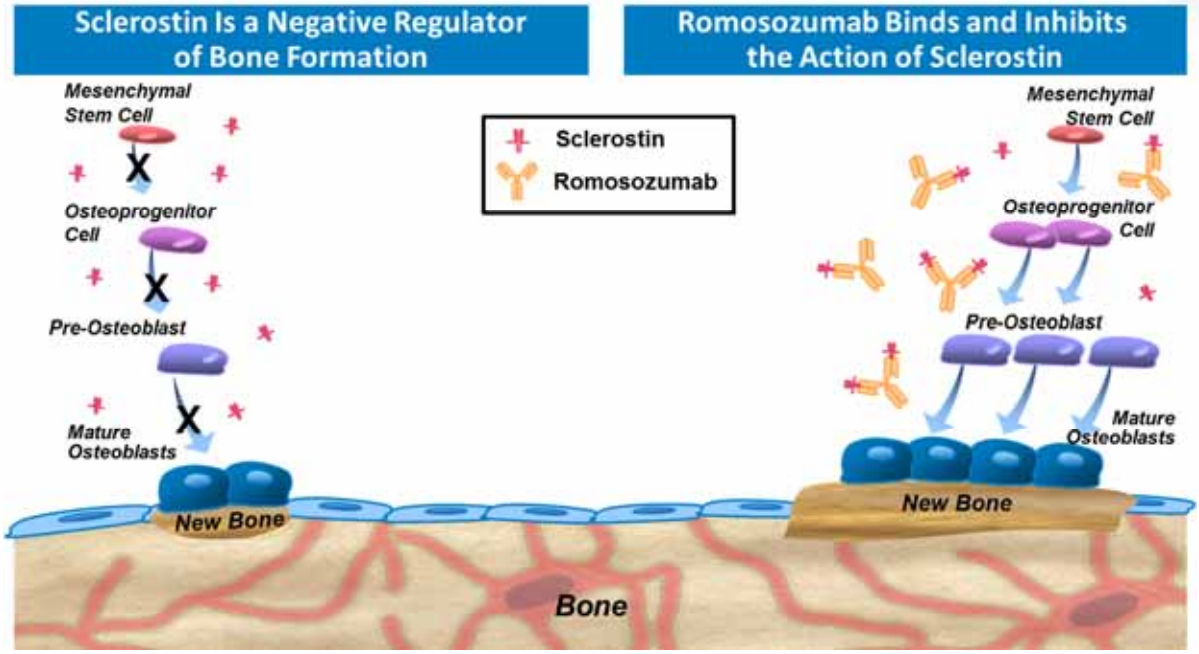
UC: Ultracentrifugation,
LDL-C: Low-density lipoprotein cholesterol
Q2W: Every 2 weeks, Q4W: Monthly

romosozumab (AMG 785)

- Anti-Sclerostin monoclonal antibody
- Osteoporosis
- Phase-III in Japan

JAPAN DEVELOPMENT

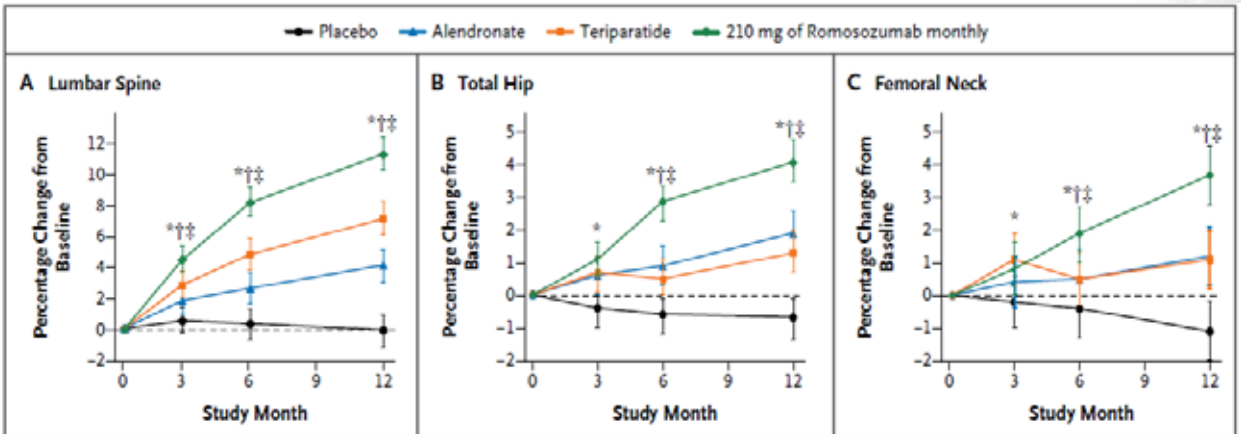
Inhibiting Sclerostin to Increase Osteoblast Mediated Bone Formation



JAPAN DEVELOPMENT

Data from Global Phase-II Study

Percentage Change from Baseline in Bone Mineral Density



Data are least-squares means, and I bars indicate 95% confidence intervals. The asterisk indicates P<0.05 for the comparison of the 210-mg monthly dose of romosozumab with placebo, the dagger P<0.02 for the comparison of the 210-mg monthly dose with alendronate, and the double dagger P<0.02 for the comparison of the 210-mg monthly dose with teriparatide.
Alendronate and teriparatide were administered open label.

- Adverse events were similar across groups, except for mild, generally non-recurring injection site reactions observed more frequently with romosozumab compared to placebo, but with no observed dose-related relationship.
- Most common adverse events included mild upper respiratory tract infection, pain in the back and joints, and headache

210mg Romosozumab given monthly resulted in greater BMD increases than teriparatide at months 6 and 12*.

*Exploratory analyses

McClung MR, *et al. N Engl J Med* 2014;370(5):412-20.

Development Progress - Major Clinical Studies

Region	Study	Target	Design	Status
Global (incl. Japan)	**PIII** FRAME study	Postmenopausal women with osteoporosis	Double-blind, placebo-controlled study, n=7,180	Ongoing
	PIII BRIDGE study	Men with osteoporosis	Double-blind, placebo-controlled study, n=225	Ongoing
Japan	**PII**	Postmenopausal women with osteoporosis	Double-blind, placebo-controlled, dose-finding study, n=252	Ongoing

Summary

Bringing Innovative Therapeutics to Patients

Maximize Value of New Products

mirabegron , EB178*, Vesomni (Urology GCL)**
Enzalutamide (XTANDI) (Oncology GCL)

Enhance Innovation

ASP015K
ASP1517/FG-4592 [roxadustat]
AMG102 [rilotumumab]
AMG145 [evolocumab]
AMG785 [romosozumab]
Isavuconazole
ASP0113
ASP7374

Pursue Operational Excellence

Multi-Track R&D process
Leveraging preferred vendors
TA-aligned decision making

* mirabegron & solifenacin combo
** solifenacin & tamsulosin combo

TA: Therapeutic Area