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FOR IMMEDIATE RELEASE

Tokyo, July 4, 2017

Documents presented at the Pharmaceutical Business Conference

Japan Tobacco Inc. (JT) (TSE: 2914) held a Pharmaceutical Business Conference today in Tokyo. Company Executives made presentations on the Group's overview, strategy, and the research and development of pharmaceutical Business.

Documents presented:

Document 1: Overview of Pharmaceutical Business at JT
Document 2: Research and Development at JT's Pharmaceutical Business

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Japan Tobacco Inc. is a leading international tobacco company. Its products are sold in over 120 countries and its globally recognized brands include Winston, Camel, Mevius, LD and Natural American Spirit. With diversified operations, JT is also actively present in pharmaceuticals and processed foods. The company's revenue was ¥2.143 trillion (US$19,703 million(*)) in the fiscal year ended December 31, 2016.

**Translated at the rate of ¥108.78 per $1*

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Document 1

Overview of Pharmaceutical Business at JT

July 4, 2017
Muneaki Fujimoto
President, Pharmaceutical Business

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FORWARD-LOOKING STATEMENTS

This presentation contains forward-looking statements. These statements appear in a number of places in this presentation and include statements regarding the intent, belief, or current and future expectations of our management with respect to our business, financial condition and results of operations. In some cases, you can identify forward-looking statements by terms such as “may”, “will”, “should”, “would”,“expect”, “intend”, “project”, “plan”, “aim”, “seek”, “target”, “anticipate”, “believe”, “estimate”, “predict”,“potential” or the negative of these terms or other similar terminology. These statements are not guarantees of future performance and are subject to various risks and uncertainties. Actual results, performance or achievements, or those of the industries in which we operate, may differ materially from any future results, performance or achievements expressed or implied by these forward-looking statements. In addition, these forward-looking statements are necessarily dependent upon assumptions, estimates and data that may be incorrect or imprecise and involve known and unknown risks and uncertainties. Forward-looking statements regarding operating results are particularly subject to a variety of assumptions, some or all of which may not be realized.

Risks, uncertainties or other factors that could cause actual results to differ materially from those expressed in any forward-looking statement include, without limitation:
(1)decrease in demand for tobacco products in key markets;
(2)restrictions on promoting, marketing, packaging, labeling and usage of tobacco products in markets in which we operate;
(3)increases in excise, consumption or other taxes on tobacco products in markets in which we operate;
(4)litigation around the world alleging adverse health and financial effects resulting from, or relating to, tobacco products ;
(5)our ability to realize anticipated results of our acquisition or other similar investments;
(6)competition in markets in which we operate or into which we seek to expand;
(7)deterioration in economic conditions in areas that matter to us;
(8)economic, regulatory and political changes, such as nationalization, terrorism, wars and civil unrest, in countries in which we operate;
(9)fluctuations in foreign exchange rates and the costs of raw materials; and
(10) catastrophes, including natural disasters.

History

1987	Jun.	Announced entry into the pharmaceutical business.
1988	Jul.	Established the pharmaceutical business division.
1993	Sep.	Opened the Central Pharmaceutical Research Institute. (Takatsuki, Osaka Pref.)
1998	Dec.	Acquired >50% open stock of Torii Pharmaceutical Co., Ltd.(Torii).
1999	Jan.	Founded Akros Pharma Inc.. (U.S.)
	Oct.	Formed a business tie-up with Torii. (Torii is in charge of manufacturing and sales while concentrating R&D activities at JT)

<Product history>

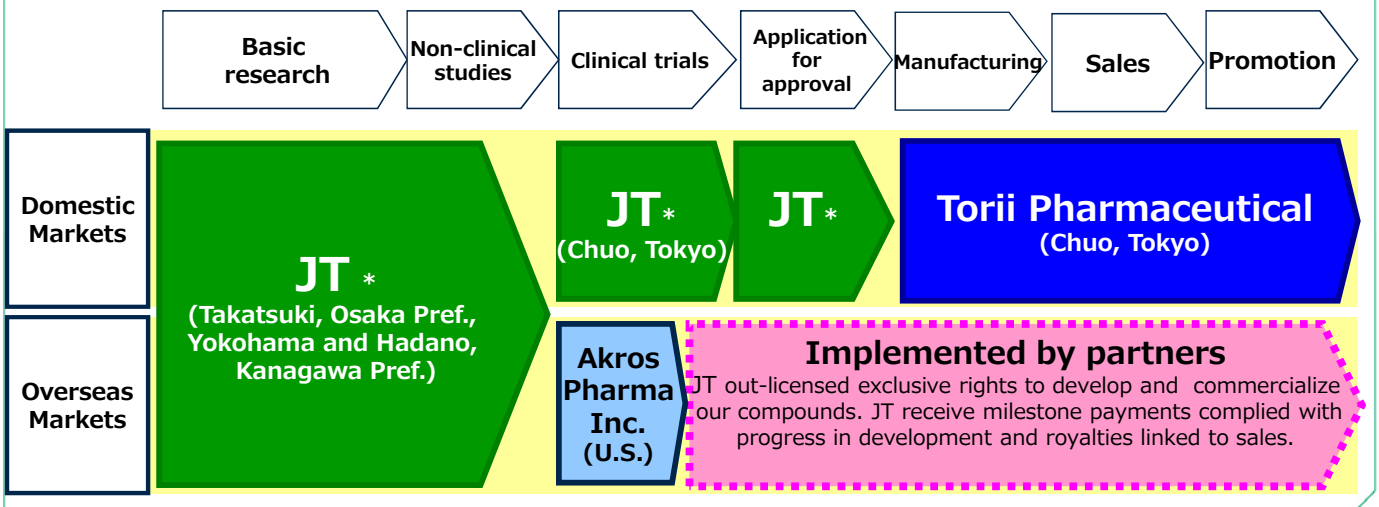
1998	Mar.	"Viracept Tablets", an anti-HIV drug : Approved in Japan.
2004	Mar.	"Viread Tablets", an anti-HIV drug (in-licensed from Gilead Sciences): Approved in Japan.
2005	Mar.	"Emtriva Capsules" and "Truvada Combination Tablets", an anti-HIV drug (in-licensed from Gilead Sciences) : Approved in Japan.
2009	Jan.	"REMITCH CAPSULES 2.5 μg", an oral antipruritus drug : Approved in Japan. Co-developed by Toray Industries, Inc.(Toray), Torii and JT.
2012	Aug.	"Stribild", an anti-HIV drug containing JTK-303(out-licensed to Gilead Sciences): Approved in U.S.. *A government office approved a new drug including JT's original compound for the first time.
2013	Mar.	"Stribild Combination Tablets", an anti-HIV drug containing JTK-303(out-licensed to Gilead Sciences): Approved in Japan.
	May	"Mekinist", an MEK inhibitor(out-licensed to GlaxoSmithKline): Approved in U.S.. *The rights to this drug has been held by Novartis since March 2015 due to a business transfer
2014	Jan.	"Riona Tablets", a therapeutic agent for Hyperphosphatemia (in-licensed from Keryx): Approved in Japan. Co-developed by JT and Torii.
		"CEDARTOLEN SUBLINGUAL DROP", a sublingual immunotherapy drug for Japanese cedar pollinosis: Approved in Japan. (developed by Torii)
2015	Sep.	"MITICURE House Dust Mite Sublingual Tablets", an allergen immunotherapy tablet for house dust mite allergy : Approved in Japan. (developed by Torii)
2016	Jun.	"Genvoya Combination Tablets", an anti-HIV drug containing JTK-303(out-licensed to Gilead Sciences): Approved in Japan.
	Dec.	"Descovy Combination Tablets LT/HT", anti-HIV drugs (in-licensed from Gilead Sciences): Approved in Japan.

Business model

Out-licensing

- Advantage: Cost efficiency / Good use of partner's expertise.
- Disadvantage: Time loss (We must stop development while we negotiate out-licensing agreement) / Profits must be shared with partners.

*Partially implemented by Torii(allergens, etc.)



Organization

Central Pharmaceutical Research Institute

- Pharmaceutical Frontier Research Laboratories
- Drug Metabolism & Pharmacokinetics Research Laboratories
- Chemical Research Laboratories
- Product Development Laboratories
- Biological/Pharmacological Research Laboratories
- Toxicology Research Laboratories



(Approx. 600)

R&D

Clinical development division

(Approx. 100)

Akros Pharma Inc.

(Approx. 50)

Clinical development



Torii Pharmaceutical

(Approx. 1,050 includes 500 MRs)

Manufacturing, sales and promotion

Approx. 1,800 of personnel

Approach to R&D focus area

- **Targeting diseases with strong Unmet Medical Needs**
- **Focusing First-In-Class(FIC) drugs**
- **Implementing a drug discovery strategy in view of a future paradigm shift in therapeutic method**
- **Specializing in small molecule compounds**

Current Focus Area

(i) Metabolic diseases

(ii) Autoimmune/Inflammatory diseases

(iii) Viral infection

(Reference) Torii's focus area and main products

① Renal diseases and hemodialysis
REMITCH CAPSULES, oral therapeutic agent for pruritus in hemodialysis patients; co-developed by JT, Torii and Toray
REMITCH OD Tablets, oral therapeutic agent for pruritus in hemodialysis patients; co-developed by JT, Torii and Toray
Riona Tablets, therapeutic agent for hyperphosphatemia; co-developed by JT and Torii

② Skin diseases
ANTEBATE, topical corticosteroid

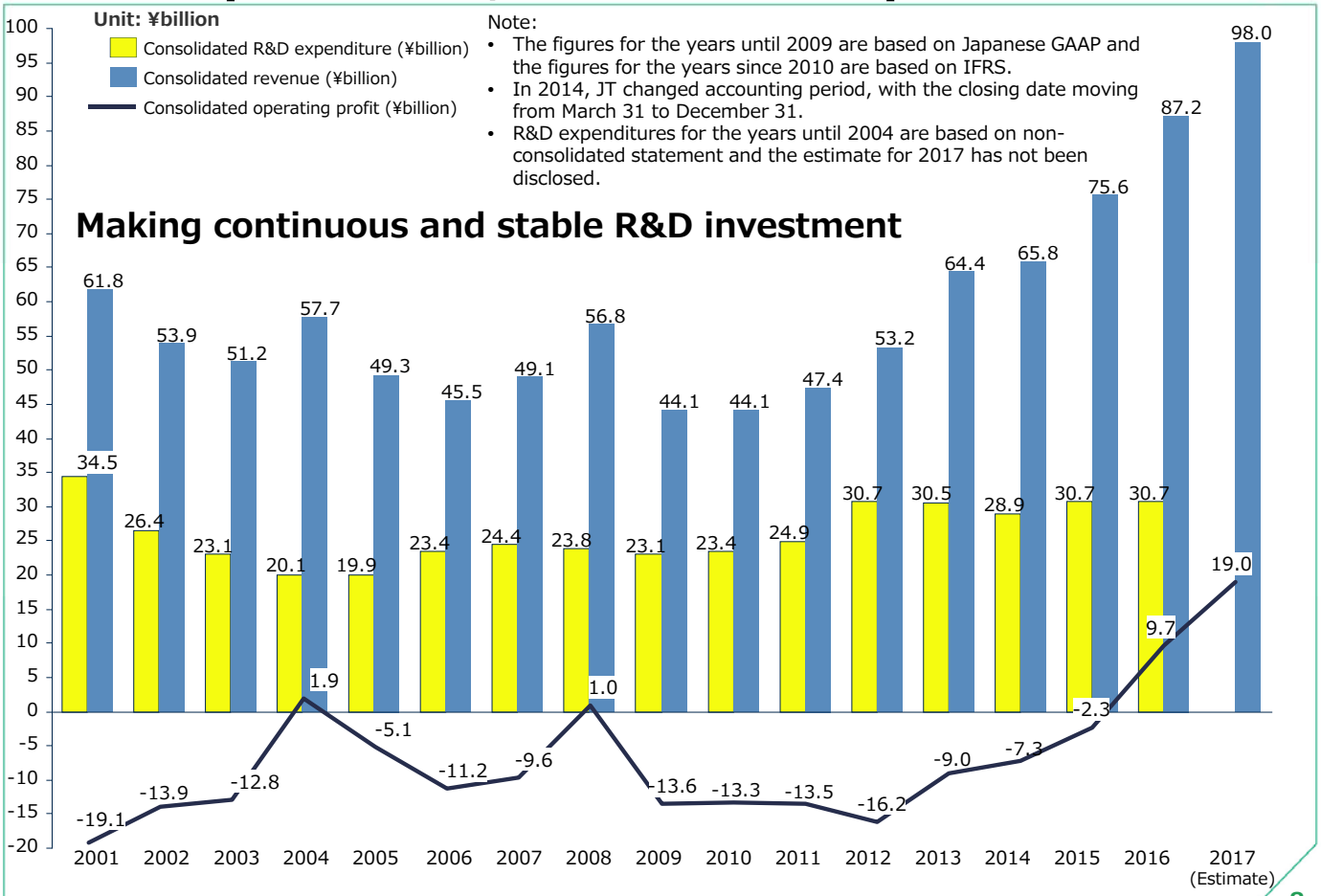
③ Allergens
CEDARTOLEN SUBLINGUAL DROP, allergen immunotherapy drugs
MITICURE House Dust Mite Sublingual Tablets, allergen immunotherapy tablet

④ HIV infection
Truvada Combination Tablets, **Stribild Combination Tablets**, **Genvoya Combination Tablets** and **Descovy Combination Tablets**

Torii is working in close cooperation with JT to search and develop new in-licensed compounds, and also devotes efforts to develop new dosage form and additional indication of existing products, and R&D in allergens.

<<Status of clinical development (as of the end of June 2017)>>
- **JTT-751** (Riona Tablets), iron-deficiency anemia (Oral)- Phase 2 (co-developed by JT and Torii)
- **TO-203**, house dust mite induced allergic asthma (Allergen Immunotherapy)(Sublingual tablets)- Phase 2/3 completed
- **TO-203**, house dust mite induced allergic rhinitis in children (Allergen Immunotherapy) (Sublingual tablets) -Application
- **TO-206**, Japanese cedar pollinosis (Allergen Immunotherapy)(Sublingual Tablets)- Application

R&D expenditure, revenue and profit



Profit growth drivers

■ Progress in R&D/market launch



- ➢ Reaping the fruits of past R&D activities
- ➢ Steadily launching new drugs

● Major products recently launched

Stribild Combination Tablets (antiviral agent for HIV)
- ・Overseas Out-licensed to Gilead Sciences FDA approval in Aug. 2012
- ・Japan Sold by Torii MHLW approval in Mar. 2013

Genvoya Combination Tablets (antiviral agent for HIV)
- ・Overseas Out-licensed to Gilead Sciences FDA approval in Nov. 2015
- ・Japan Sold by Torii MHLW approval in Jun. 2016

Mekinist (MEK inhibitor)
- ・Worldwide Out-licensed to GlaxoSmithKline and Novartis* FDA approval in May. 2013

*The rights to this drug has been held by Novartis since March 2015 due to a business transfer

Riona Tablets (therapeutic agent for hyperphosphatemia)
- ・Japan Sold by Torii MHLW approval in May. 2014

■ Revenue

- ➢ Growing sales of out-licensed products
  Increased royalty revenue from out-licensed products / Milestone revenue related to the progress in drug development
- ➢ Driving growth of domestic revenue with recent launch of anti-HIV drugs, Riona Tablets, etc.

Pipeline (as of the end of June 2017)

Code/*development phase (Generic name)		Potential Indication/ Dosage form	Mechanism	In-house/licensing	Supplementary explanation
JTZ-951	Japan: Phase 2 Overseas: Phase 1	Anemia associated with chronic kidney disease /Oral	HIF-PH inhibitor	In-house *Out-licensed to JW	(Competing candidates) Roxadustat: Global Ph3 Daprodustat: Global Ph3
JTE-052	Japan: Phase 3	Autoimmune/ allergic diseases /Oral, Topical	JAK inhibitor	In-house Co-development with Torii *Out-licensed to LEO	Most advanced clinical study is for atopic dermatitis in Japan
JTE-051	Overseas: Phase 2	Autoimmune/ allergic diseases /Oral	Interleukin-2 inducible T cell kinase (ITK) inhibitor	In-house	No program in clinical stage is reported from any companies
JTT-251	Overseas: Phase 1	Type 2 diabetes mellitus /Oral	PDHK inhibitor	In-house	No program in clinical stage is reported from any companies
JTK-351	Japan: Phase 1	HIV infection /Oral	HIV integrase inhibitor	In-house	—
JTE-451	Overseas: Phase 1	Autoimmune/ allergic diseases /Oral	RORγ antagonist	In-house	While competition to develop RORγ antagonist drugs is intense, JT is not lagging behind competitors.
JTT-751 (ferric citrate)	Japan: Phase 2	Iron-deficiency anemia/Oral	Oral iron replacement	In-license (Keryx Biopharmaceuticals) Co-development with Torii	*Additional indication

Notes:
- The clinical trial phases presented above are based on the first dose.
- Out-licensed to JW Pharmaceutical (South Korea) under a license agreement for exclusive rights to development and commercialization in South Korea for application to oral medication.
- Out-licensed to LEO Pharma (Denmark) under a license agreement for exclusive rights to development and commercialization in the world outside Japan for topical use in dermatological indications.

For the future

- **R&D investment**
  - Continuous and stable R&D investment independent from revenue fluctuations
- **Open innovation**
  - Creation of FIC new drugs that fulfill Unmet Medical Needs.
    - New drug targets
    - Drug Efficacy / Development technologies
    - Advancing into cutting-edge fields (leading to future drug creation)
  - Active engagement in partnering and licensing rather than public invitation programs.
    - Building mutual trust and respect
    - Dispatching researchers

    *Reference
    Public invitation programs: a[3], COCKPI-T FINDS, TaNeDS, PRISM
    Comprehensive partnerships: AK Project, TK Project
- **Enhancement of in-licensing** (expansion of the domestic pipeline)
  - Group-wide in-licensing activity in co-operation with JT and Torii
  - Participating in BIO conferences / Organizing partnering conferences (overseas)

Conclusion

- **With the entire group working together to deliver new drugs to patients as soon as possible.**

  - **3 Key Principles**
    - Carrying on full effort for the patients
    - Targeting FIC, small molecule compounds
    - Continuous and stable R&D investment

  - **4 Key Strategies**
    - Continue to out-license our New Molecule Entities globally
    - Put more emphasis on in-licensing for the Japanese Market
    - Determine indications and clinical development plan with both global licensing and domestic sales franchise in mind
    - Contribute to JT Group profit through R&D for products of next generation and maximizing the value of existing products

Document 2

Research and Development at JT's Pharmaceutical Business

July 4, 2017
Shigenori Ohkawa, Ph.D.
Head of Central Pharmaceutical Research Institute

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R&D Strategy

➢ The mission of JT's pharmaceutical business

- Development of world-class, unique R&D capabilities
- Reinforcement of the market presence through the development of innovative new drugs

➢ Basic strategy

- Drug discovery focused on patients' needs
- R&D aiming at First-In-Class drugs
- Focus on development of small molecule compounds
- Setting of R&D focus area based on Unmet Medical Needs
- Out-licensing to partners for global development
- Active open innovation

Locations of R&D facilities



Akros Pharma Inc.
(New Jersey, USA)



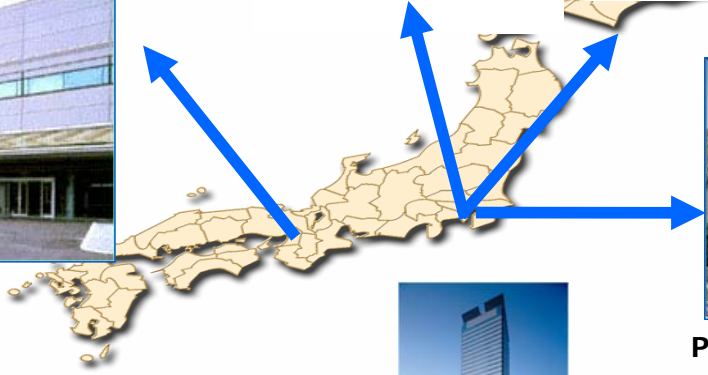
Toxicology Research Laboratories
(Hadano, Kanagawa)



Pharmaceutical Frontier Research Laboratories
(Yokohama, Kanagawa)



Central Pharmaceutical Research Institute
(Takatsuki, Osaka)





JT's headquarters
(Minato, Tokyo)



Pharmaceutical division
Torii Pharmaceutical's headquarters
(Chuo, Tokyo)

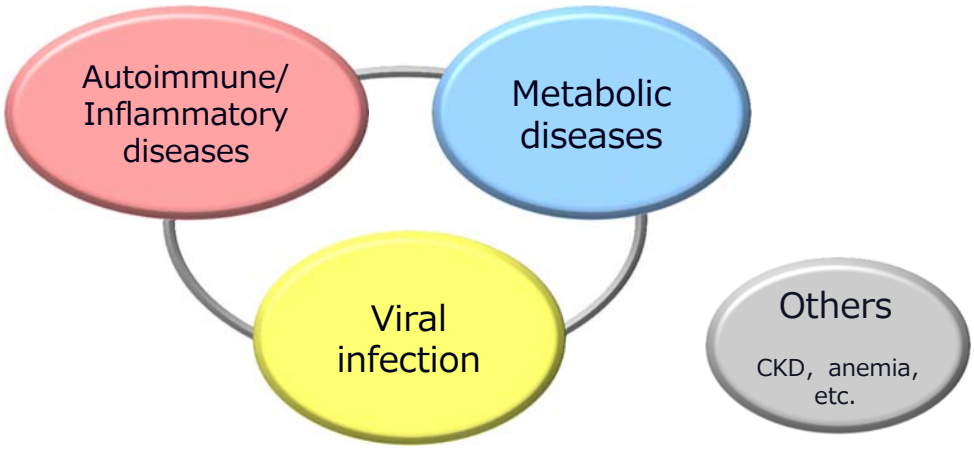
New Drugs Approved in Recent Years

Drug and indication	Year of approval
Stribild Combination Tablets **HIV infections** HIV integrase inhibitor, elvitegravir (+ cobicistat, FTC and TDF)	**Overseas (2012)/Japan (2013)** Overseas: Out-licensed to Gilead Sciences
Genvoya Combination Tablets **HIV infections** HIV integrase inhibitor, elvitegravir (+ cobicistat, FTC and TAF)	**Overseas (2015)/Japan (2016)** Overseas: Out-licensed to Gilead Sciences
Mekinist Tablets **BRAF mutation-positive melanoma** MEK inhibitor, trametinib	**Overseas (2013)/Japan (2016)** Worldwide: Out-licensed to GlaxoSmithKline (transferred to Novartis since 2015)
Riona Tablets **Hyperphosphatemia in chronic renal diseases** Ferric citrate	**Japan (2014)**



Current Focus Area

Focusing on major three therapeutic areas



- Conducting R&D on diseases having strong Unmet Medical Needs based on the future treatment paradigm (to be explained later).
- New drug targets:
  - ✓ Selecting new drug targets based on deep understanding of pathology of target diseases.
  - ✓ Setting target product profiles (TPPs) focused on differentiation from existing therapies.
  - ✓ Pursuing best practices by utilizing all available resources.

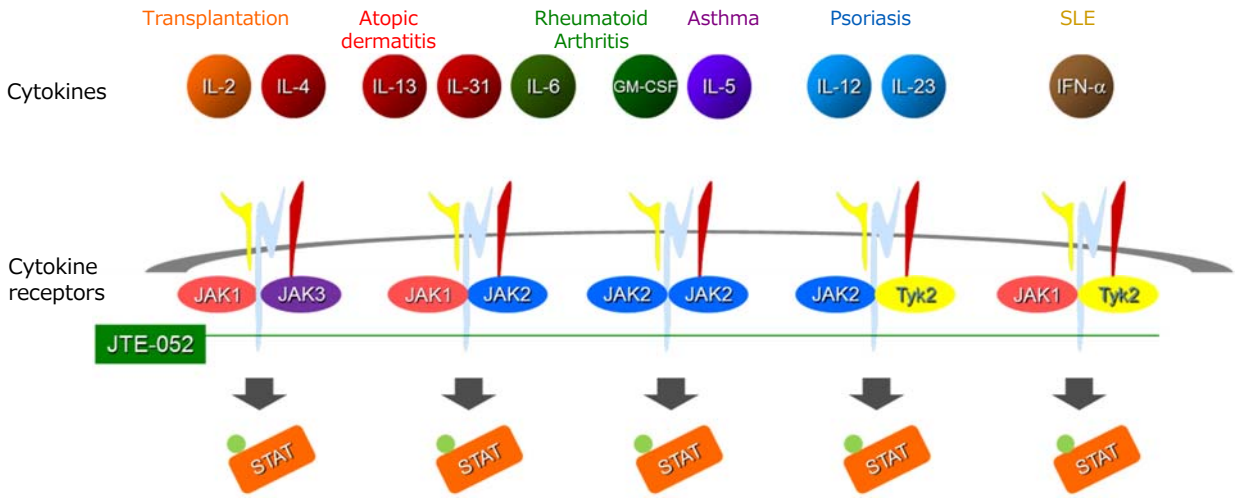
R&D Pipeline

Area	Code	Mechanism	Discovery / Preclinical	Phase 1	Phase 2	Phase 3	NDA
Autoimmune/ inflammatory diseases	JTE-052	JAK inhibitor					Japan:Ph3 Overseas:LEO
	JTE-051	ITK inhibitor				Overseas	
	JTE-451	RORγ antagonist			Overseas		
	Early programs						
Metabolic diseases	JTT-251	PDHK inhibitor			Overseas		
	Early programs						
Viral infection	JTK-351	HIV Integrase inhibitor			Japan		
	Early programs						
Others	JTT-751	Oral iron replacement				Japan	
	JTZ-951	HIF-PH inhibitor				Japan:Ph2 Overseas:Ph1	
	Early programs						

JTE-052

■ JAK inhibitor

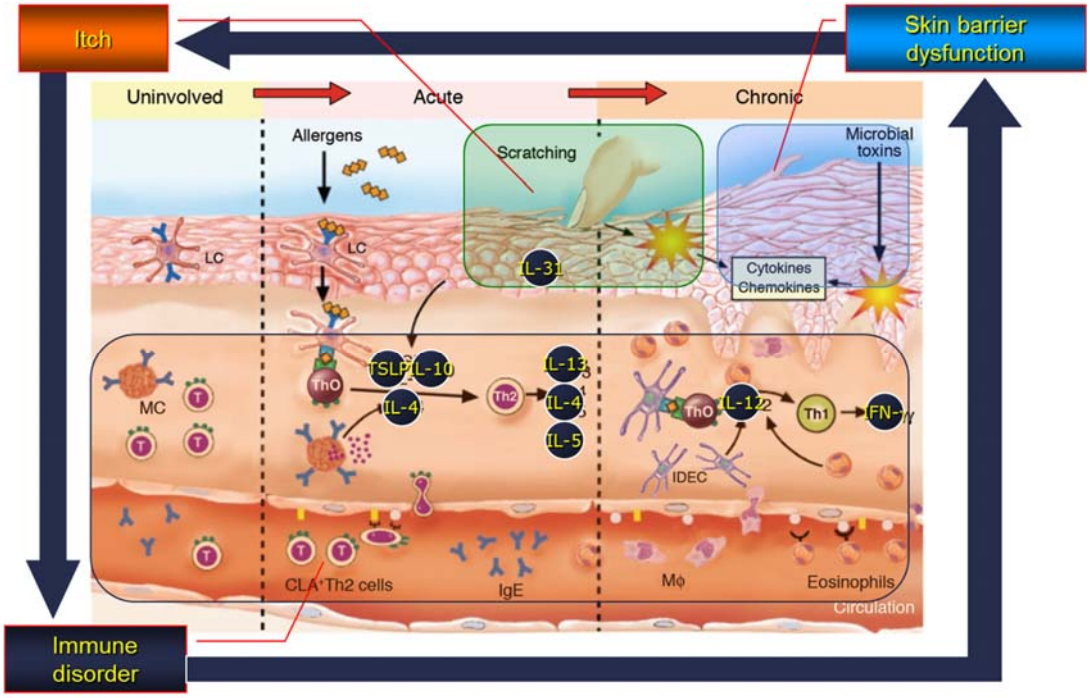
Cytokines trigger a variety of pathological conditions by activating the JAK-STAT pathway.



JTE-052 is expected to be effective as treatment for a variety of allergic and autoimmune diseases such as atopic dermatitis.

Pathological Conditions of Atopic Dermatitis

Three major factors aggravate and escalate pathological conditions by creating a vicious circle via cytokines.



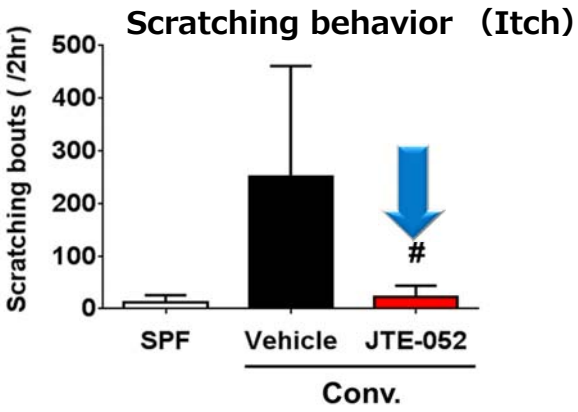
Clinical Expectations for JTE-052 in Treatment of Atopic Dermatitis

- JTE-052 showed significant effects on three major pathological factors in atopic dermatitis models
  - Amelioration of skin inflammation
    Clinical score ↓, Cytokine production ↓, Inflammatory cell infiltration ↓
  - Improvement of skin barrier function
    Transepidermal water loss ↓, Natural moisturizing factor ↑
    Filaggrin ↑ (cultured human keratinocytes)
  - Attenuation of scratching behavior
    Scratching bouts ↓

Vehicle **JTE-052**



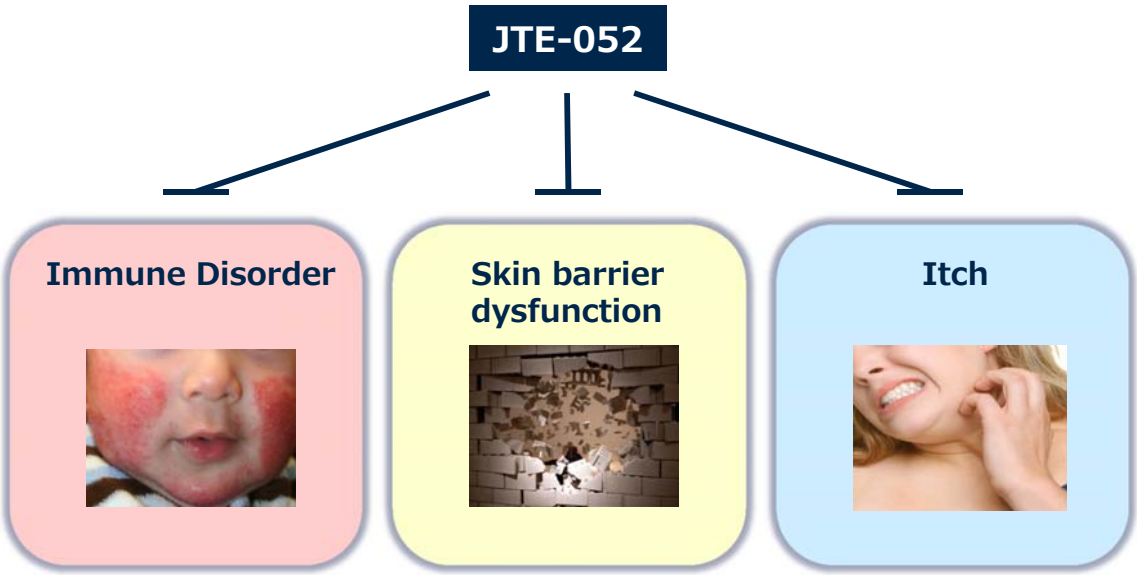
Efficacy in atopic dermatitis mouse (NC/Nga mouse)



J Allergy Clin Immunol. 2015;136:667-677
Society for Investigative Dermatology (SID) 75th Annual Meeting etc

Efficacy of JTE-052 on major three pathological factors

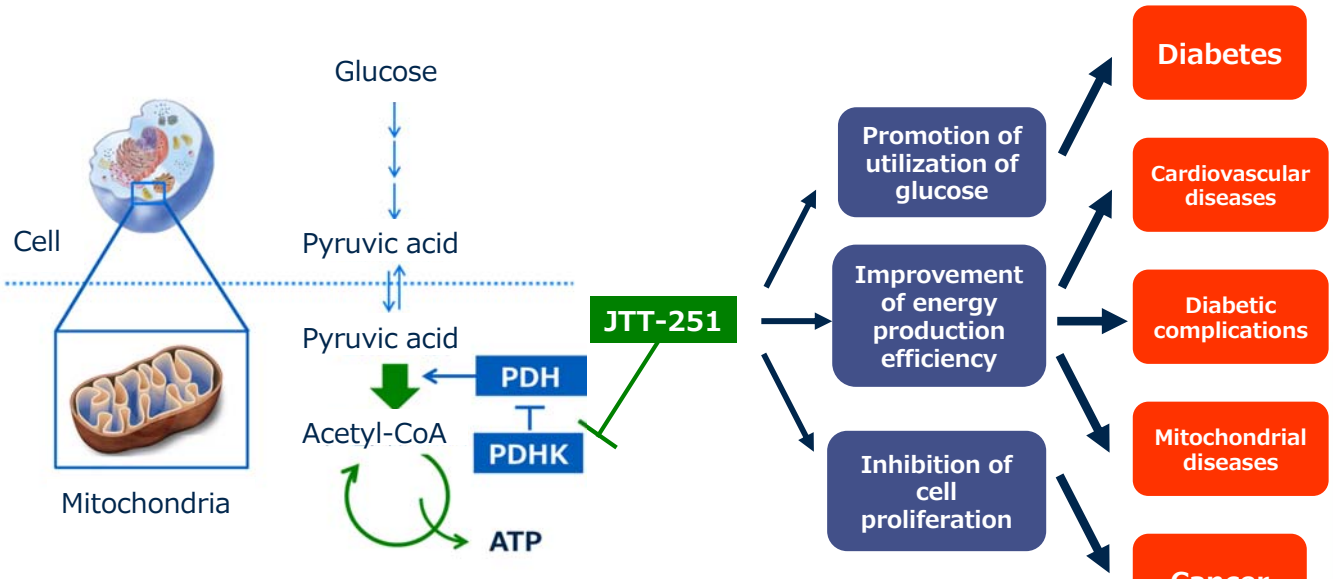
Expectations as a drug differentiated from existing treatments (Steroid/Tacrolimus)



JTT-251

■ PDHK* inhibitor

✓ PDH controls energy production from glucose in mitochondria.
✓ JTT-251 promotes the utilization of glucose by activating PDH.



*PDHK: Pyruvate Dehydrogenase Kinase

Potentials of Small Molecule Drugs

- Enable to select various drug discovery targets compared with biologics.
- Lead to discovery of entirely new mechanisms through forward pharmacology.*
- Create new value through repositioning.
- Small molecule drugs, along with cell therapy, are essential in the field of regenerative medicine.
- Enable to affect multiple targets as required for CNS drugs and so on.

- Can be administered in various dosage forms, including an oral agent.
- A patent is acquired on a compound-by-compound basis in principle.
- Can be manufactured at low cost compared with biologics.
- Ensure a high level of stability and easy quality control.
- Usually have no immunogenicity.

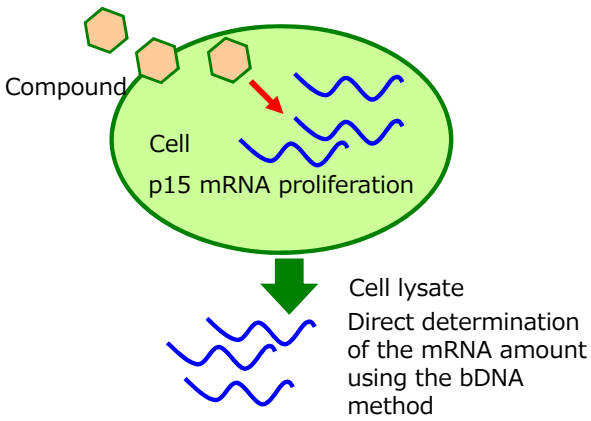
* : Approach based on the process of:
phenotypic assay → discovery of active compounds → search for drug targets

Potentials of Small Molecule Drugs – Forward Pharmacology

- Assay for a lead compound for the MEK inhibitor Trametinib

Selecting compounds that induce the activity of $p15^{INK4b}$ from the chemical library through high-throughput screening (HTS).

Branched DNA (bDNA) method



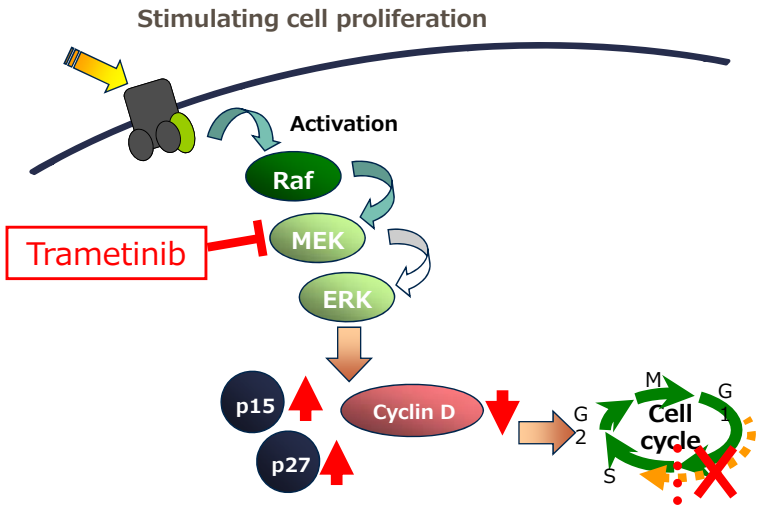
- Add a compound to normal cells.
- Dissolve cells and directly determine the amount of p15 mRNA contained in the cell lysate.
- Raise the signal sensitivity through the amplified probe technique based on the bDNA method because the amount of mRNA contained in cells is low.

Potentials of Small Molecule Drugs

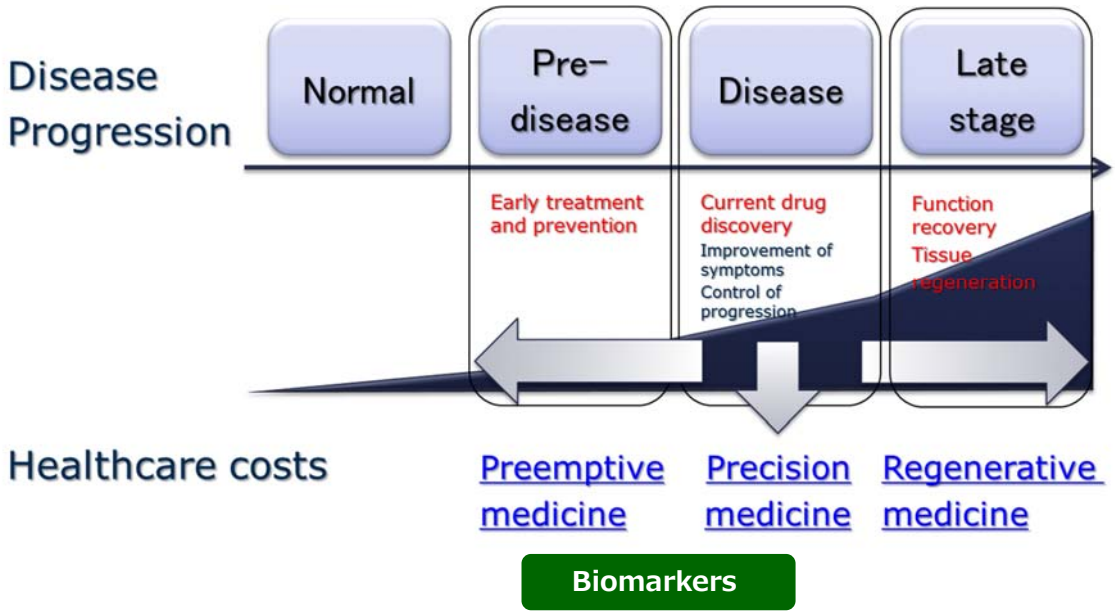
■ Search for target molecules for Trametinib through chemical biology

The target molecule for Trametinib was identified as MEK through the chemical biology method.

- ✓ Inhibit the phosphorylation of MEK by binding to unphosphorylated MEK (IC_{50} 6.7 nM).
- ✓ Inhibit the phosphorylation of ERK in the downstream by binding to phosphorylated MEK (IC_{50} 290 nM).



R&D Activities based on Future Treatment Paradigm



- ✓ Selection of drugs suited to individual patients' conditions
- ✓ Preparation for a paradigm shift in therapies toward the upstream and the downstream
- ✓ Positioning of drugs in a wide selection of therapeutic options

Open Innovation

Look outside research institutions and companies for missing pieces that cannot be internally obtained for development of First-In-Class drugs that satisfy Unmet Medical Needs.

Target discovery	Leading generation/ optimization	Preclinical
● Cause of diseases ● New drug targets etc.	● HTS ● Chemical library ● *in vitro/in vivo* assays ● Unique animal models etc.	● Biomarkers ● Repositioning etc.



- Own search for partners
- Dispatch of researchers for collaborative research
- Buildup of trust and respect

The number of joint research programs has tripled in recent years (between 2013 and 2017).

R&D Strategy

➢ The mission of JT's pharmaceutical business

- Development of world-class, unique R&D capabilities
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➢ Basic strategy

- Drug discovery focused on patients' needs
- R&D aiming at First-In-Class drugs
- Focus on development of small molecule compounds
- Setting of R&D focus area based on Unmet Medical Needs
- Out-licensing to partners for global development
- Active open innovation