Daiichi Sankyo’s “R&D Day 2015”

Tokyo, Japan (December 14, 2015) - Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) will hold its “R&D Day 2015” at its Tokyo headquarters at 3pm JST on Monday, December 14, 2015.

Dr. Glenn Gormley, Senior Executive Officer and Global R&D Head, will give a briefing about Daiichi Sankyo research and development activities to media, security analysts, and institutional investors. Topics will include an update on Daiichi Sankyo’s late stage innovative product pipeline and its R&D strategies for oncology.

Following the event, a video of “R&D Day 2015” will be available on the Daiichi Sankyo corporate website via the following link:
http://www.daiichisankyo.com/media_investors/investor_relations/ir_calendar/detail/005286.html

Attachment: presentation material
December 14 2015

Research and Development at Daiichi Sankyo

Glenn Gormley MD PhD
Senior Executive Officer, Global R&D Head
Daiichi Sankyo Co., Ltd.
Agenda

- Pipeline overview
- Pipeline update: Thrombosis, Diabetes and Pain
- Focus on Oncology
R&D Focus Therapeutic Areas

Priority Areas for Discovery*
- Oncology
- CV-M
- Pain

*Discovery: Research and Early Development up to Proof of Concept
# Major R&D pipeline

As of October 2015

<table>
<thead>
<tr>
<th>Therapeutic area</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardio vascular-Metabolics</strong></td>
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<td>(Nasal spray flu vaccine vaccine)</td>
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Targets for Approval and Launch

Japan
- Cravit® Injection
- Cravit® Tuberculosis
- Artist® Chronic AF

US
- CL108 Acute Pain & OINV
- Effient® Sickle Cell

Western Europe
- Lixiana® AF
- Lixiana® VTE

Other Regions
- Lixiana® AF & VTE (China·LTAM etc.)

FY2015
- Japan
- US
- Western Europe
- Other Regions

FY2016
- Japan
- US
- Western Europe
- Other Regions

FY2017
- Japan
- US
- Western Europe
- Other Regions

FY2018
- Japan
- US
- Western Europe
- Other Regions

> FY2019

Oncology
- Nimotuzumab
- Patritumab
- Pexidartinib
- Quizartinib (JPN)
- Zelboraf® (LCM)
- Ranmark® (BC adj)

CV-M
- CS-3150 (MRA)
- DS-8500 (GPR119)
- Effient® (LCM)
- Lixiana® (LCM)

Pain
- Mirogabalin

Other

Other Regions
- Lixiana® AF & VTE (China·LTAM etc.)
Agenda

• Pipeline overview

• **Pipeline update : Thrombosis, Diabetes and Pain**

• Focus on Oncology
Medical Management of Thrombosis

**Platelet aggregation**

- Platelet aggregation
- Anti-platelet agents: Prasugrel

**Blood coagulation**

- Blood coagulation pathway
- FXIIa / Kallikrein / HK
- FXI
- FIX
- FXa
- Thrombin

**Thrombus**

- Fibrin

**Fibrinolysis**

- Thrombin-activatable fibrinolysis inhibitor

**TAFIa inhibitor**

- TAFIa inhibitor (DS-1040)
- Fibrinolysis enhancer

**Plasmin**

- (α2-plasmin inhibitor)

**α2-PI inhibitor**

- α2-PI inhibitor (DS-9231)
- Fibrinolysis enhancer
Opportunity for a new fibrinolysis enhancer

Indicated Use of tPA in the treatment of Acute Ischemic Stroke

Onset of Stroke

0 hr

3 hr

8 hr

If No ICH (by CT)

Contraindicated: if ICH is present

Not Recommended: for minor neurological deficit / improving symptoms

Contraindicated

- Severe stroke or internal bleeding
- History of stroke or head trauma
- Treatment with warfarin or heparin

Global sales for alteplase: $1.1 B in 2014 (Source: EvaluatePharma)
**DS-8500 : GPR119 agonist**

**Mechanism of Action**
- Amplify glucose-stimulated insulin secretion
- Improve β-cell function
- Stimulate GLP-1 secretion

**Intestine**
- L cell

**Pancreas**
- β cell
- cAMP

**GPR119 agonist (DS-8500)**

**Results of Phase 2a study are anticipated to be published in 1H 2016**

DPP-IV i: Dipeptidyl Peptidase-4 inhibitor  
GLP-1: Glucagon-Like Peptide-1  
PYY: Peptide YY
**DS-8500 : GPR119 agonist**

**Phase 2b: 12-week study has just started**

<table>
<thead>
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<th>Study timeline</th>
<th>Nov 2015 (FPI)〜 4Q FY2016 (TLR anticipated)</th>
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<tbody>
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<td>Region</td>
<td>Japan</td>
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<tr>
<td>Study endpoints</td>
<td>Primary endpoint: HbA1c</td>
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<td>Safety: adverse events, hypoglycemia</td>
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<td>Subject</td>
<td>T2DM patients</td>
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<tr>
<td>Study timeline</td>
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**Study endpoints**
- Primary endpoint: HbA1c
- Safety: adverse events, hypoglycemia

**Study timeline**
- Nov 2015 (FPI)〜 4Q FY2016 (TLR anticipated)

**Placebo**
- DS-8500 25mg
- DS-8500 50mg
- DS-8500 75 mg
- Sitagliptin 50 mg

**Run-in period**
- 2 wks

[Diagram showing randomization and study arms]

- Enroll T2DM
- Placebo
- Run-in period
- Placebo

**2-week Follow-Up**
- Around 70 patients per arm

**Follow-Up**
- 12 weeks

**http://www.clinicaltrials.jp/user/cteSearch_e.jsp** JapicCTI-153068
Pipeline for the Treatment of Pain

- **DS-1971**: Chronic pain
  - DPNP / PHN / FM
  - α2δ ligand

- **Mirogabalin**: DPNP / PHN / FM
  - Hydromorphone
  - μ opioid agonist

- **DS-7113**: Marketed
  - Loxonin
  - Loxoprofen
  - COX inhibitor

- **CL-108**: Pain relief while preventing or reducing OINV

- **Movantik**: OIC
  - peripheral
  - μ opioid antagonist

**Abbreviations**:
- **DPNP**: diabetic peripheral neuropathic pain
- **PHN**: post herpetic neuralgia
- **FM**: Fibromyalgia
- **OINV**: opioid induced nausea & vomiting
- **OIC**: opioid induced constipation
U.S. Pain Market Holds Great Opportunity

Large, Growing Market

U.S. Pain Market Gross Sales (US $ Billion)

2014: $27 Billion

Source: Symphony Health PHAST Audit, Encuity
Third Phase 3 study recently completed:

- Double-Blind, Active- and Placebo-Controlled study
- Population: 550 patients, with pain after bunionectomy surgery
- Results: co-primary endpoints were met:
  - Pain relief and prevention or reduction of OINV* (both p<0.001)
- Results are planned to be published in 2016

OINV: opioid-induced nausea and vomiting

NDA submission: anticipated 4Q FY2015
Mirogabalin: Phase 2, DB Study in DPNP

Primary Endpoint at Week 5

DPNP: Diabetic Peripheral Neuropathic Pain
PGB: Pregabalin

Average Daily Pain Score (ADPS)

- Placebo
- PGB 150mg BID
- 5mg QD
- 10mg QD
- 15mg QD
- 10mg BID
- 15mg BID

- 3 doses reached statistical significance versus placebo
  *: p<0.05, **: p<0.01
- 2 doses reached statistical significance versus pregabalin
  ¶: p<0.05

American Diabetes Association 74th Scientific Sessions; June 13-17, 2014; San Francisco, California.
West: Mirogabalin Phase 3 FM Study Design

Double-Blind Treatment
(300 patients per arm)

- Mirogabalin 15 mg QD
- Mirogabalin 15 mg QD
- Mirogabalin 15 mg QD
- Mirogabalin 15 mg BID
- Placebo
- Placebo
- Pregabalin 75 mg BID
- Pregabalin 150 mg BID

- **Primary outcome:** change from baseline in the ADPS at week 13

> Titration (1 week)  
> Maintenance (12 weeks)

ADPS: Average Daily Pain Score  
FM: Fibromyalgia

**Top Line Results anticipated in 1H 2017**
Asia: Peripheral Neuropathic Pain (PNP) Phase 3 Study Design

Double-Blind Treatment
(150 patients per Mirogabalin arm, 300 patients in placebo arm)

- **5 mg** QD
- **10 mg** QD
- **15 mg** QD
- **5 mg** BID
- **10 mg** BID
- **15 mg** BID
- Placebo

**Titration** (1-2 weeks)  **Maintenance** (12 weeks)

- Primary outcome: change from baseline in the ADPS at week 14

ADPS: Average Daily Pain Score  
PNP: DPNP+PHN  
DPNP: Diabetic Peripheral Neuropathic Pain  
PHN: Post Herpetic Neuralgia

Top Line Results anticipated in 1H 2017
Agenda

- Pipeline overview
- Pipeline update: Thrombosis, Diabetes and Pain
- Focus on Oncology
Daiichi Sankyo Oncology Strategy

• Focus on FIC opportunities
• Develop Personalized medicine based therapies
• Maintain strong academic partnerships
  • National Cancer Center of Japan
  • UCSF
  • Max Planck
• Partner with innovative biotech companies
  • ArQule
• Strategic acquisitions
  • Plexxikon
  • Ambit
# Oncology Clinical Pipeline

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<th>Growth Survival Receptors</th>
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<tbody>
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ADC: Antibody Drug Conjugate  
ADCC: Antibody Dependent Cellular Cytotoxicity
DS-8201: Phase 1

Innovative anti-HER2 antibody drug conjugate (ADC)

- **DS-8201 compared to T-DM1**
  
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<th>T-DM1</th>
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<td>Antibody</td>
<td>HER2 Ab</td>
<td>Trastuzumab</td>
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<td>Conjugated toxin</td>
<td>Topoisomerase I inhibitor</td>
<td>Tubulin inhibitor</td>
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<td>DAR*</td>
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  *DAR: Drug to Antibody Ratio

- **Differentiation from T-DM1**
  - Different conjugated toxin
  - Original ADC technology
  - Higher drug to antibody ratio

- **Mechanism of action**
  - Ab binds HER2 receptor and is internalized
  - Conjugated toxin is released inside cell
  - Toxin causes targeted cell death

- **Patient-derived tumor xenograft models**
  
  - **Gastric cancer (T-DM1 insensitive)**
  - **Breast cancer (HER2 weakly +)**

  DS-8201 demonstrated potent anti-tumor efficacy against:
  - T-DM1 insensitive model
  - HER2 weakly-positive model
Next Generation of DS Oncology Portfolio

**Immune-oncology**
- Immune checkpoint inhibitors
- Cell therapy

**Epigenetics**
- IDH1 mutant inhibitor
- EZH 1/2 inhibitor
IDH1 mutant inhibitor and EZH1/2 dual inhibitor

- IDH1 mutant inhibitor decreases 2-hydroxyglutarate (2-HG) and improve transcriptional abnormality
- EZH 1/2 inhibitor decreases histone methylation and increases transcription of tumor suppressor genes
- Clinical studies of both inhibitors planned for 2016
Focus on Late Stage Oncology Projects

Four novel compounds targeting unique pathways in Phase 2/3 registration trials

- **Quizartinib (Ph3)**
  - Acute myeloid leukemia (AML)

- **Pexidartinib (Ph3)**
  - Tenosynovial giant cell tumor (TGCT)

- **Tivantinib (Ph3)**
  - Hepatocellular carcinoma (HCC) in partnership with ArQule

- **Patritumab (Ph2/3)**
  - Non-small cell lung cancer (NSCLC)
Quizartinib

Investigational FLT3 Inhibitor

Acute Myeloid Leukemia (AML)

Granted Orphan Drug Designation by the FDA and EMA

Granted Fast Track Status by the FDA
Quizartinib: a Selective Inhibitor of ITD mutated FLT3 receptor

Reference:

Reference:

Reference:
Acute Myeloid Leukemia

Epidemiology in US

<table>
<thead>
<tr>
<th>Estimated New Cases in 2015</th>
<th>20,830</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of All New Cancer Cases</td>
<td>1.3%</td>
</tr>
<tr>
<td>Estimated Deaths in 2015</td>
<td>10,460</td>
</tr>
<tr>
<td>% of All Cancer Deaths</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

FLT3-ITD mutation: 23% of AML survival rate lower than patients without this mutation

Overall Survival for AML Patients ≤ 60 y.o.
Paradigm for the Treatment of AML

**Newly diagnosed AML**

- **Induction therapy**
  - **Failure**
    - **HSCT**
      - Hematopoietic stem cell transplantation
    - **Relapse**
      - **Salvage therapy**
  - **Complete remission**
    - **Consolidation chemotherapy**

*First-line treatment*

*Target for QuANTUM-R*
Quizartinib: Effect in FLT3-ITD(+) AML

Observed Response Rate for specific and non-specific FLT3 Inhibitors Administered as a Single Agent in FLT3-ITD(+) AML

Patients (%) Achieving CRc

QUIZARTINIB’S DIFFERENTIATION
- Potency
- Selectivity
- Favorable Pharmacokinetics
- Continuous FLT3 inhibition

Modified from Ambit Presentation & Knapper, S., 2011 and ASCO 2015
Quizartinib: QuANTUM-R Phase 3 Study

Endpoints:
- primary: OS
- secondary: EFS

Randomized:

- AML FLT3-ITD (+) (Refractory or Relapse within 6 months) N = 326

Quizartinib

Follow-Up

Low-dose Cytarabine

Follow-Up

MEC* or FLAG-IDA*

Follow-Up

TLR anticipated in 1H 2017

MEC: mitoxantrone, etoposide, and intermediate-dose cytarabine
FLAG-IDA: fludarabine, cytarabine, and granulocyte colony stimulating factor (G-CSF) with idarubicin

https://clinicaltrials.gov/show/NCT02039726
Plans to Maximize Value of Quizartinib

Ongoing program
QuANTUM-R (US, EU, Asia)
NDA Approval

Planning Phase
JP study
1st line therapy

FY2014 FY2015 FY2016 FY2017 FY2018 FY2019 FY2020 -
Summary of Quizartinib

Highly Selective Treatment for Relapsed Refractory AML

• Targeted therapy against ITD mutated FLT3 receptor
• Once daily oral dosing
• Well tolerated outpatient treatment
• Overall survival in Phase 2: 6 months
Pexidartinib : PLX3397
Investigational CSF-1R Inhibitor
Tenosynovial Giant Cell Tumor (TGCT)

Granted Orphan Drug Designation by the FDA and EMA
Granted Breakthrough Therapy designation by FDA
No Approved Systemic Therapies for TGCT

Diffuse TGCT: a rare disease that affects larger joints such as knee, hip, ankle, shoulder, elbow

75% of diffuse cases involve the knee

Recurrent, diffuse TGCT may require multiple surgeries and even amputation

Early Results in Treatment of TGCT

Walking with cane
Unable to straighten knee
Narcotics for pain
Unable to work
Amputation considered

Walking unassisted
Improved range of motion
Off narcotics
Back to work

Tap et al, ASCO 2014
Efficacy Evaluation by RECIST 1.1 Criteria

PR = 45% (95% CI: 27–64%)

PR: Partial Response

Tap et al, NEJM 2015
Pending symptomatic TGCT

**Endpoints:**

- **Primary:** Response rate at week 25

**Study Design**

- **Part 1:** Placebo controlled (24 weeks)
- **Part 2:** Open-label extension (up to 2.5 years)

**TLR anticipated in 1H 2018**

https://clinicaltrials.gov/show/NCT02371369
• Treatable patients in the US, EU and Japan are estimated to be around 38,000
  • Often under-diagnosed
  • Affected patients have normal life expectancy

• High unmet need
  • High morbidity
  • No systemic therapies approved
Further Investigations of Pexidartinib

Collaboration with Merck:

Pexidartinib in combination with anti-PD-1 therapy for advanced melanoma and multiple other solid tumors

Other potential indications:

Glioblastoma
Ovarian cancer
Breast cancer
Sarcomas
Pexidartinib in Combination with anti-PD-1 Therapy for Advanced Solid Tumors

T CELL

PD-1 mAb Pembrolizumab

PD-1

PD-L1

T-Cell-Mediated Killing

Myeloid Suppressor Cell

CSF1R

CSF1

Pexidartinib

CANCER CELL
# Combination study of Pexidartinib and Pembrolizumab

## Phase 1 / 2a study outline

<table>
<thead>
<tr>
<th></th>
<th>Part 1: Dose-escalation phase</th>
<th>Part 2: Expansion phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>Pexidartinib: dose escalation + Pembrolizumab: 200 mg every 3wks</td>
<td>Pexidartinib: RP2D + Pembrolizumab: 200 mg every 3wks</td>
</tr>
<tr>
<td><strong>Target patients for enrollment</strong></td>
<td>Advanced solid tumors N=24</td>
<td>Advanced melanoma (+ other Solid tumors) N=376</td>
</tr>
<tr>
<td><strong>Outcome measures</strong></td>
<td>Primary: Safety during 1 year treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Secondary: Objective response rate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(rate of a complete response or partial response relative to historical control)</td>
<td></td>
</tr>
</tbody>
</table>

**TLR for part 2 anticipated in 2H 2019**

RP2D=Recommended phase 2 Dose

[https://clinicaltrials.gov/show/NCT02452424](https://clinicaltrials.gov/show/NCT02452424)
Tivantinib

Investigational MET Inhibitor for treatment of Hepatocellular Carcinoma (HCC)
Liver and Intrahepatic Bile Duct Cancer

- Epidemiology in US\(^1\)

> Estimated New Cases in 2015: 35,660
> % of All New Cancer Cases: 2.2%
> Estimated Deaths in 2015: 24,550
> % of All Cancer Deaths: 4.2%

![Graph showing New Cases and Deaths from 1992 to 2012](http://seer.cancer.gov/statfacts/html/livibd.html)

Percent Surviving 5 Years: 17.2% (2005-2011)

---

Tivantinib: Selective, oral MET inhibitor

Role of MET in HCC

- MET is the only receptor for hepatocyte-growth factor (HGF) leading to:
  - Cell survival
  - Cell invasion
  - Cell proliferation

- MET expression is correlated with poor prognosis in patients with HCC
Tivantinib: Phase 2 Study in 2\textsuperscript{nd} line HCC

Patients with Advanced HCC\*  

HCC\*: Hepatocellular carcinoma

Endpoints:
- primary: TTP
- secondary: PFS, OS, ORR
- tertiary: TTP, PFS, OS in subgroups by MET Diagnostic status (high vs low levels)

Tivantinib PO BID (N=71)

Placebo PO BID (N=36)

Crossover AFTER Rx PD

Lancet Oncol 2013;14:55-63
Successful Results of the Phase 2 Study

- Treatment with Tivantinib met the primary endpoint of the study, with a 56% improvement in TTP (data not shown here)
  - **TTP:** HR = 0.64  \( p = 0.04 \)

- Pronounced benefit was observed in patients with high expression of MET
  - **TTP:** HR = 0.43  \( p = 0.03 \)
  - **OS:** HR = 0.38  \( p = 0.01 \)

- These are the first randomized data in HCC showing OS advantage with a MET inhibitor and identifying a subgroup responding to a targeted therapy
Tivantinib: METIV·HCC Phase 3 design

Patients with MET-high inoperable hepatocellular carcinoma (HCC) treated with one prior systemic therapy (N ≈303)

Randomized

Tivantinib
120mg PO BID (N=202)

Placebo
PO BID (N=101)

Endpoints:
primary:  OS
secondary: PFS, safety

TLR anticipated in 1H 2017

https://clinicaltrials.gov/show/NCT01755767
Patritumab

Investigational Anti-HER3 Monoclonal Antibody
Non-Small Cell Lung Cancer (NSCLC)
Head and Neck Cancer (H&N)
Lung and Bronchial Cancer

Epidemiology in US\(^1\)

<table>
<thead>
<tr>
<th>Estimated New Cases in 2015</th>
<th>221,200</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of All New Cancer Cases</td>
<td>13.3%</td>
</tr>
<tr>
<td>Estimated Deaths in 2015</td>
<td>158,040</td>
</tr>
<tr>
<td>% of All Cancer Deaths</td>
<td>26.8%</td>
</tr>
</tbody>
</table>

The HER Family
(human epidermal growth factor receptors)

- Erbitux® (anti-HER1 mAb)
- Herceptin® (anti-HER2 mAb)
- Patritumab (anti-HER3 mAb)
Unique Property of HER3: Escape from Growth Inhibition associated with Current Treatments

HER3 is activated through dimerization with HER1 and HER2 receptors

Heregulin binding to HER3 enhances tumor growth
Phase 2: HERALD Study Design

Subjects with Advanced NSCLC Who Have Progressed on at Least One Prior Chemotherapy

- **Biomarker Hypothesis**: Patritumab will have the greatest benefit in patients with high expression of the HER3 ligand heregulin

Endpoints:
- **Primary**: PFS
- **Secondary**: OS, ORR

NSCLC stratified by histology subtype

Randomized allocation:
- Erlotinib + Patritumab (high dose) (N=70)
- Erlotinib + Patritumab (low dose) (N=71)
- Erlotinib + Placebo (N=71)
HERALD: PFS in patients with High levels of Heregulin

Biomarker positive group showed significant improvement in PFS

Joachim von Pawel et al. ASCO Annual Meeting 2014
Patritumab: HER3 Lung Trial

2 Part Phase 2b / 3 Study

Part A

- Erlotinib + Patritumab (n=20)
- Erlotinib + Placebo (n=20)

Part B

- Erlotinib + Patritumab (n=300)
- Erlotinib + Placebo (n=300)

Low expression of HRG

High expression of HRG

Primary End Point
PFS

Primary End Point
OS

- Confirm safety and efficacy
- Define HRG cut-off for part B
- 1H FY2016 (Part A)

TLR (Part B) anticipated in 2H 2018
Patritumab: Head & Neck Cancer Indication

**Phase 1b (n=15):**
- Patients: R/M Head and Neck Cancer 1\(^{st}\) Line
- Cetuximab + Platinum chemo + Patritumab
- Enrollment completed
- Results will be published in 1H 2016

**Phase 2 (n=105):**
- Enrollment to begin December 2015
- 2:1 randomization: high vs low HRG

Follow up PFS

https://clinicaltrials.gov/show/NCT02350712
Launch Timeline of DS Pipeline in Oncology

Oncology pipeline is a key driver for DS future growth

- FY2014
- FY2015
- FY2016
- FY2017
- FY2018
- FY2019
- FY2020 -
Thank you
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