

A background image showing a male scientist in a white lab coat and glasses looking through a microscope, and a female scientist in a white lab coat looking down at a piece of paper. The image is overlaid with large, semi-transparent orange and blue circles.

Building Japan's Next Commercial Biotech

41st Annual J.P. Morgan Healthcare Conference

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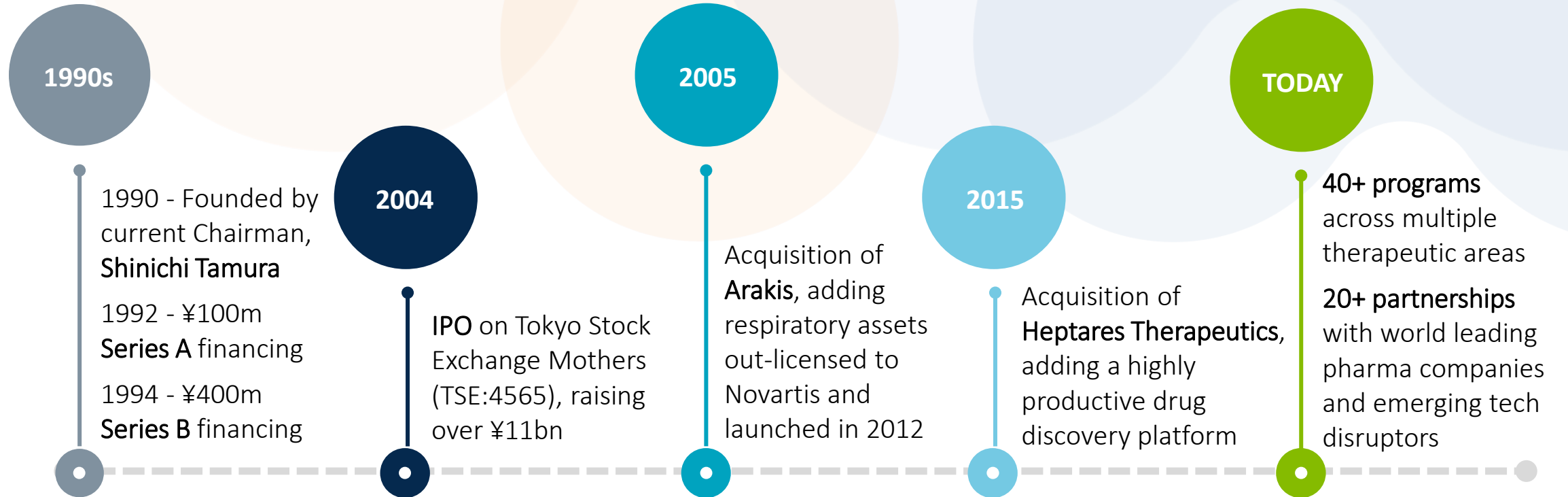
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References to "FY" in this presentation for periods prior to 1 January 2018 are to the 12-month periods commencing in each case on April 1 of the year indicated and ending on March 31 of the following year, and the 9 month period from April 1 2017 to December 31 2017. From January 1 2018 the Company changed its fiscal year to the 12-month period commencing in each case on January 1. References to "FY" in this presentation should be construed accordingly.

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From humble beginnings...



...to one of Japan's most innovative **science-led** biotech businesses

Proprietary StaR® membrane protein stabilization technology

Structure-based drug discovery platform, translational medicine and early clinical development capabilities in the UK

Japanese clinical development expertise

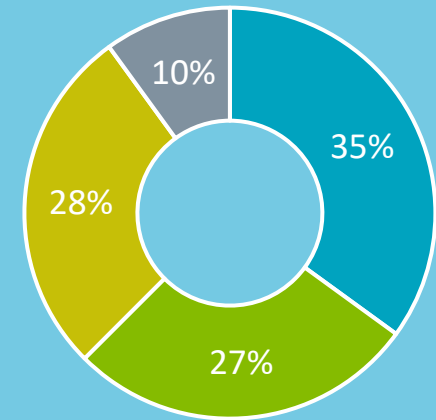
Listed on Tokyo Stock Exchange (4565-JP) with ~\$500m cash



EVOLVING WITH A SPECIALIST THERAPEUTIC FOCUS

Advancing a broad and deep pipeline of **40 partnered and in-house programs** across multiple therapeutic areas:

- Neurology
- Immunology
- Gastroenterology
- Other



200+
EMPLOYEES
WORLDWIDE



20+
WORLD-LEADING
PARTNERS



\$950M+
PARTNER REV.
RECEIVED TO DATE¹



500+
GLOBAL
PATENTS



25+
PRECLINICAL
CANDIDATES

¹ Includes upfront and milestone payments, royalties and R&D funding received from active, inactive and completed partnerships from 2005 to 2022.

Diversification of a big pharma, catalyst rich upside of a biotech

SELECTED PARTNERED

DISCOVERY

10+ PROGRAMS

Genentech
A Member of the Roche Group

Takeda

Lilly

abbvie

PRECLINICAL AND PHASE 1

2x programs

NEUROCRINE
BIOSCIENCES

2x programs

Pfizer

1x program

sanofi

1x program

GSK

PHASE 2

GLP-1 Ag



Pfizer

M4 Ag



NEUROCRINE
BIOSCIENCES

SELECTED IN-HOUSE

10+ PROGRAMS

EP4 Ant



sosei
HEPTARES
CANCER RESEARCH UK

GPR52 Ag



sosei
HEPTARES

EP4 Ag



sosei
HEPTARES

+ Multiple others

sosei
HEPTARES



To be discussed today

As a result of our strong focus on alliances, we have received **\$950+ million** to date¹ and are eligible to receive **\$5.6+ billion** total payments in the future²

¹ Includes upfront and milestone payments, royalties and R&D funding received from active, inactive and completed partnerships from 2005 to 2022.

² Includes development and commercial milestone payments from active partnerships as of 1 January 2023. Excludes royalties and R&D funding.

A differentiated business model that delivers

2022 MILESTONES

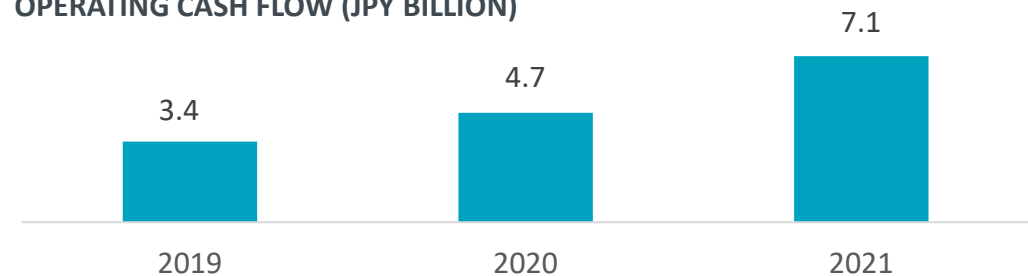
- ✓ New collaboration with **Cancer Research UK** for cancer immunotherapy
- ✓ New multi-target collaboration with **AbbVie** for neurology diseases
- ✓ M4 Ag Phase 2 IND acceptance by **Neurocrine Biosciences** for schizophrenia
- ✓ New multi-target collaboration with **Lilly** for diabetes and metabolic diseases
- ✓ GLP-1 Agonist Phase 2 clinical trial start by **Pfizer** for type 2 diabetes and obesity

Source: ¹ FactSet as of 6 January 2023

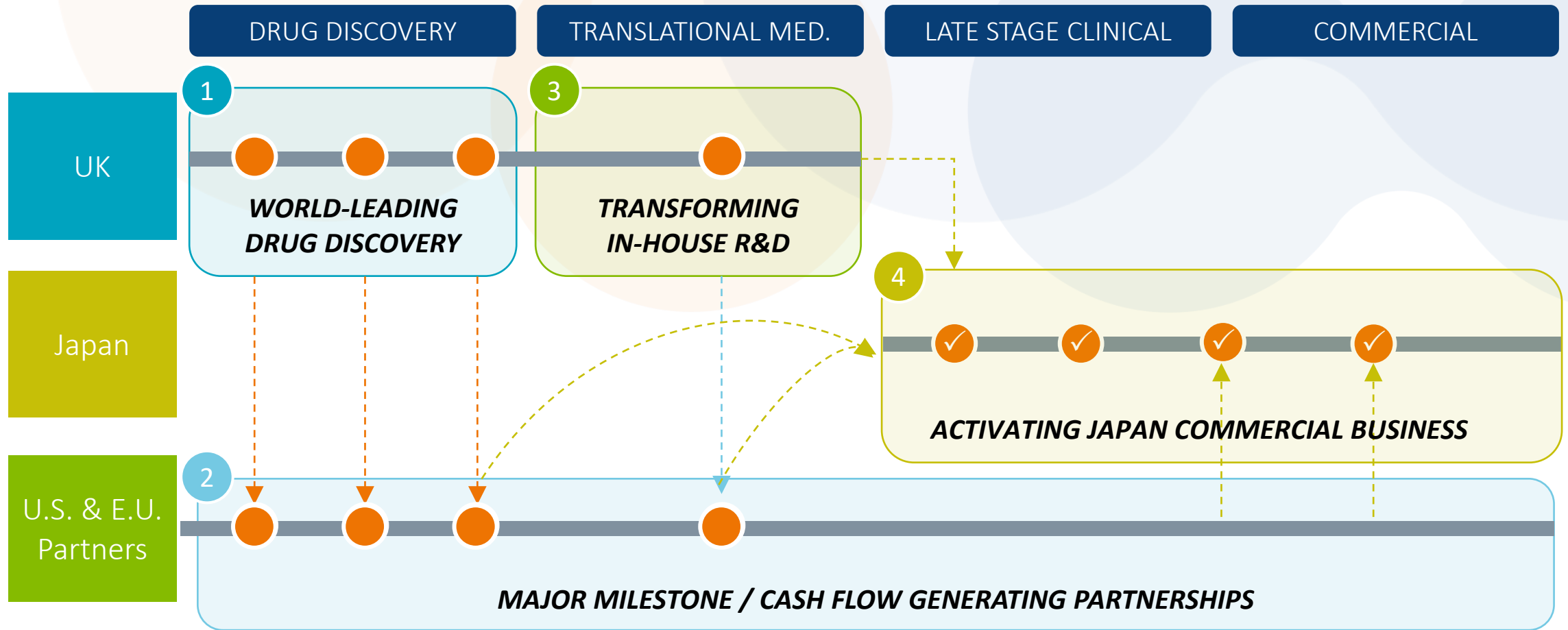
LTM RELATIVE SHARE PRICE PERFORMANCE¹



OPERATING CASH FLOW (JPY BILLION)



Clear strategy to drive the business forward



World-leading science. Life changing medicines

1 Why GPCRs? The 'second golden age' of GPCR discovery is here

~400
GPCR targets active in diseases²

~34%
of FDA approvals target GPCRs¹

27%
of global sales are GPCR drugs¹

NEUROLOGICAL DISORDERS

GASTROINTESTINAL DISEASES

IMMUNOLOGY/ONCOLOGY

METABOLIC DISORDERS

CARDIOVASCULAR

RESPIRATORY

“

Septerna emerges with \$100M to spark 'second golden age' of prolific drug target GPCR with pioneer as co-founder
By Kyle LaHucik · Jan 27, 2022 07:00am

Tectonic Therapeutic banks \$80M to shift GPCR drug discovery toward biologics
By Amirah Al Idrus · Apr 15, 2021 07:00am

With \$255M antibody biotech buy, AbbVie spies opportunity to take on tricky GPCRs
By James Waldron · Oct 20, 2022 12:40pm

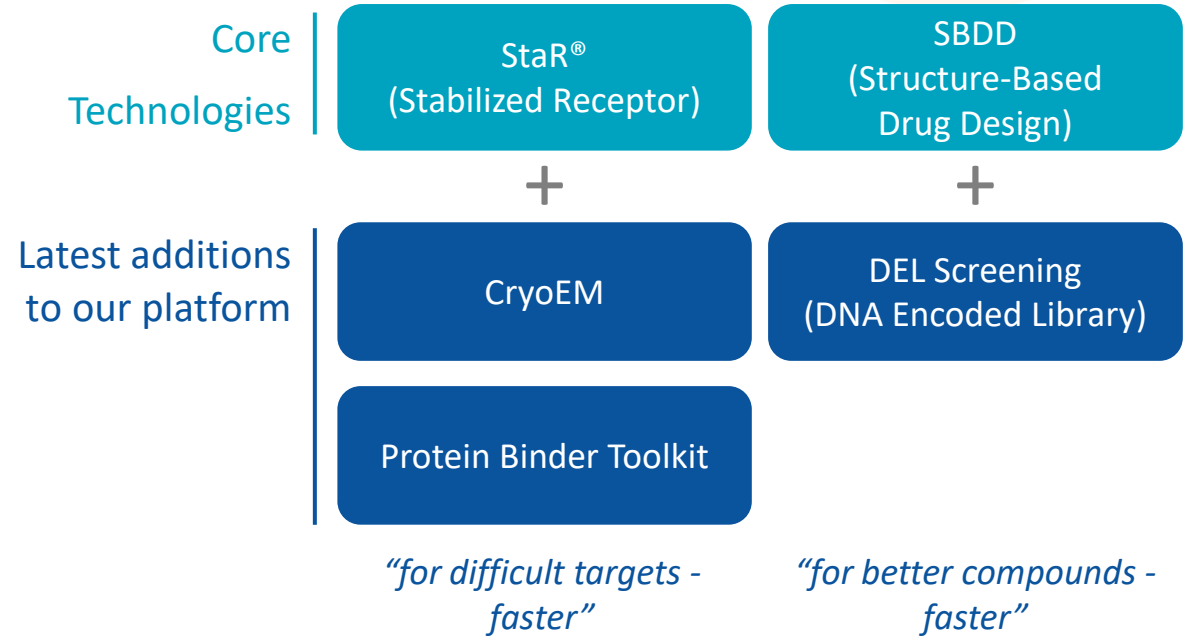
”

GPCRs are active in a wide range of disease areas, and offer broad therapeutic potential

GPCR research has led to more than 700 approved drugs over previous decades and is still ripe for development³

Sources: ¹ “Unexplored opportunities in the druggable human genome”, Nature Reviews, 2016 ; ² “Trends in GPCR in Drug Discovery – new agents, targets and indications”, Nature Reviews, 2017; ³ “Septerna emerges with \$100m to spark second golden age of prolific drug target GPCR with pioneer as co-founder” by Kyle LaHucik via Fierce Biotech, Jan 27 2022;

1 World-leaders choose our platform to prosecute complex GPCRs



Multi-target Discovery Collaborations

	Total Potential Milestones ¹
	\$1.8bn
	\$1.0bn
	\$1.2bn
	\$1.2bn
	\$730m

¹Potential option fees, development, regulatory and commercial milestone payments at time of signing. Sosei Heptares is also eligible to receive tiered royalties ranging from high single digit to mid-teen percentage on future net sales of any products developed under the partnerships

2

Clinical stage partnerships (Muscarinic Programs)

Phase II initiated '22

Neurocrine Biosciences Advancing Muscarinic Portfolio

Clinical studies, include:

- **Initiated Phase 2 placebo-controlled study** of NBI-1117568*, a selective M4 agonist, as a potential treatment for schizophrenia
 - ✓ NBI-1117568 offers the potential for an improved safety profile:
 - ❑ Without the need of combination therapy to minimize side effects
 - ❑ Avoids the need of cooperativity with acetylcholine when compared to non-selective muscarinic agonists and positive allosteric modulators in development
- **Phase 1 study** of a dual M1 / M4 agonist in 2023
- **Phase 1 study** of a selective M1 agonist in 2023



*In-licensed from Sosei Heptares. NBI-1117568 is investigational and not approved in any country

Sosei Heptares received
\$100m upfront, +\$30m @ Ph 2

Sosei Heptares to receive **ongoing R&D funding** and **up to \$2.6bn** in potential development, regulatory and commercial milestones, plus **tiered double digit percentage royalties** on net sales

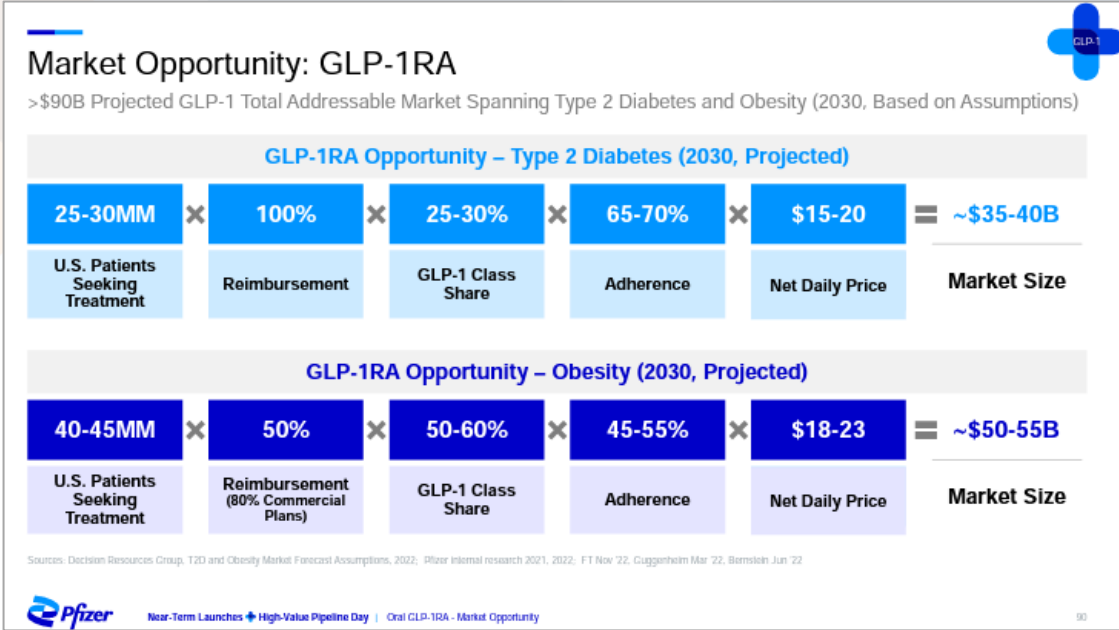
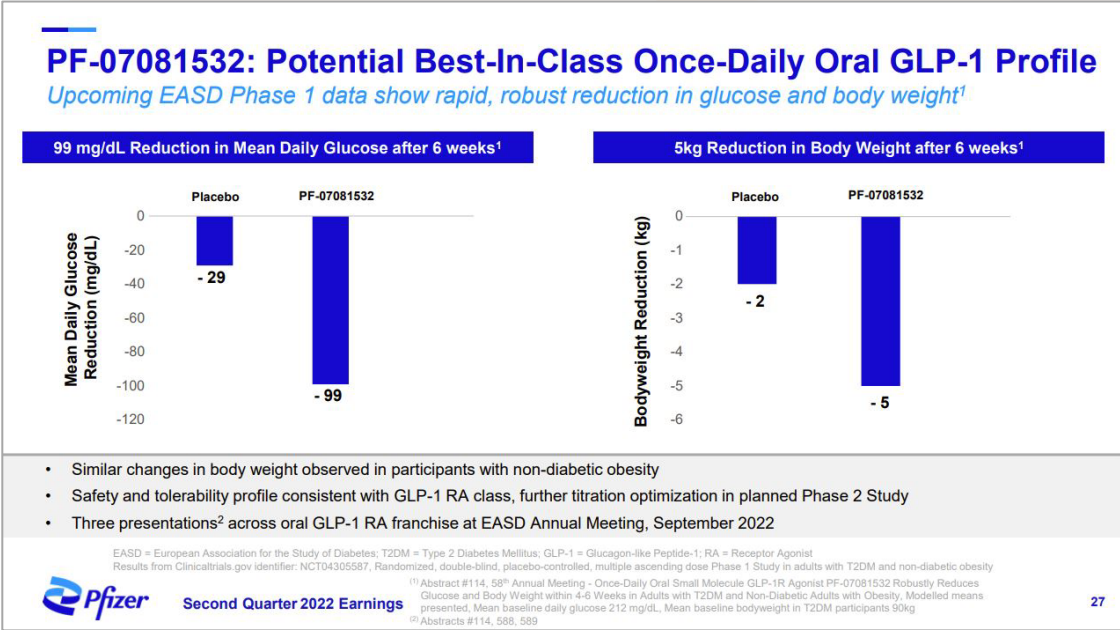
Sosei Heptares **retains rights to develop all M1 agonists in Japan in all indications**, with NBIX receiving co-development and profit share options

Developing novel muscarinic receptor agonists for schizophrenia and other neuropsychiatric disorders

Source: Neurocrine Biosciences Announces Conference Call and Webcast of Third Quarter 2022 Financial Results
<https://www.neurocrine.com/assets/2022/12/NBIX-Q3-2022-Earnings-Presentation-Final-10.31.22-1.pdf>

2 Clinical stage partnerships (Pfizer GLP-1 agonist for T2D and Obesity)

Phase II initiated '22



Orals projected to capture ~30% of GLP-1 market by 2032 due to strong patient preference

>60% of patients prefer BID oral vs. QW injections

\$25B GLP-1 market currently growing at +30% per year, projected to reach ~\$90B by 2030

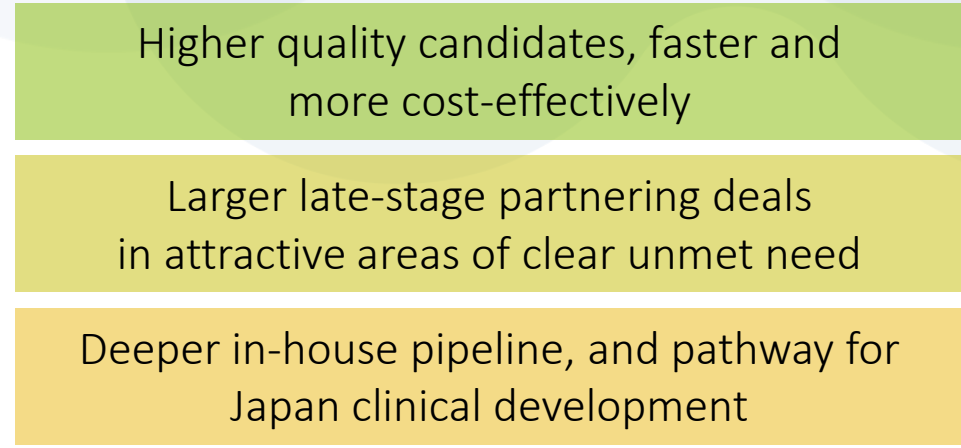
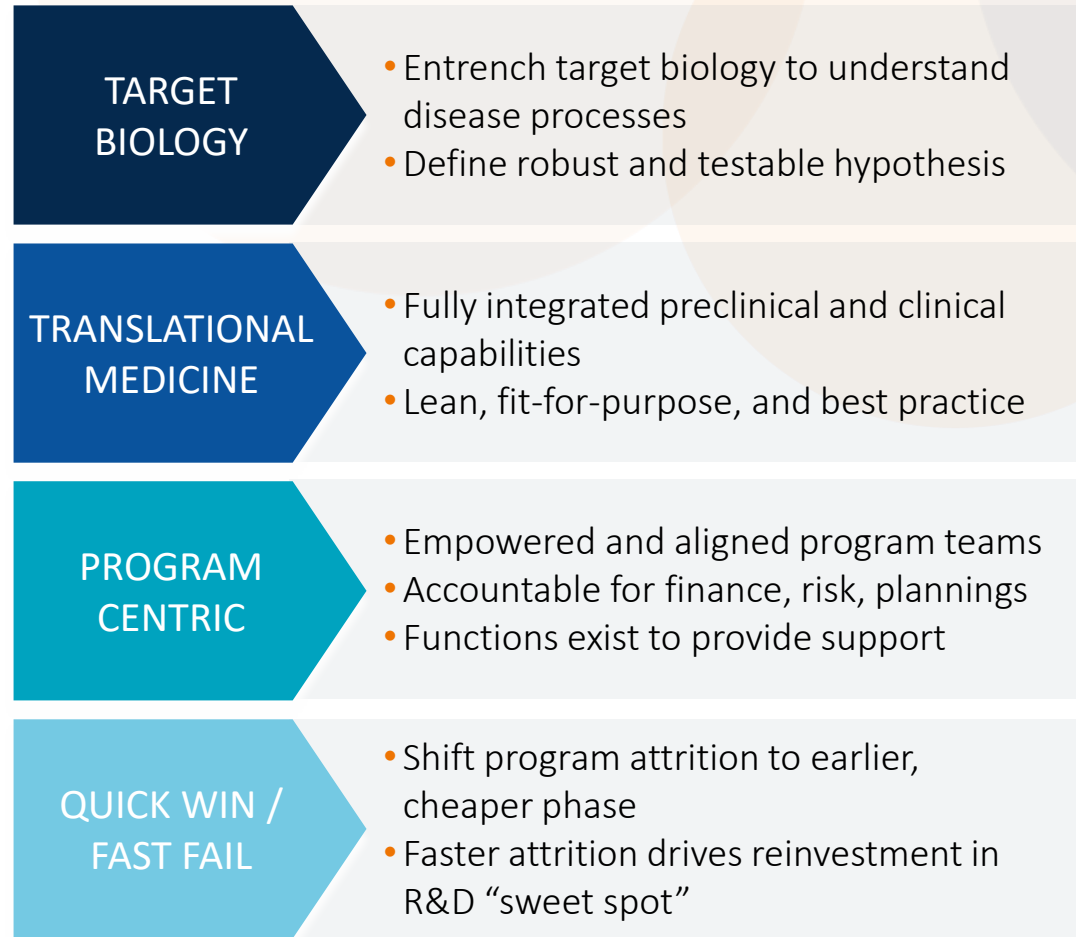
Well-positioned to compete on efficacy, tolerability and simplicity of administration vs. other oral therapies

Source: Pfizer Quarterly Corporate Performance – Second Quarter 2022 presentation
https://s28.q4cdn.com/781576035/files/doc_financials/2022/q2/Q2-2022-Earnings-Charts-FINAL.pdf







3

Doing R&D differently to enhance productivity, value and success



Complementing our world-leading science with operational best practice to increase efficiency, PoS, & ROI

3 Multiple wholly-owned assets to begin clinical studies next 12 months

Indication and target	 <p>Immunosuppression in solid tumors</p>	 <p>Schizophrenia and Psychosis</p>	 <p>Inflammatory Bowel Disease</p>
	<p>EP4 antagonist</p>	<p>GPR52 agonist</p>	<p>EP4 agonist</p>
Target Product Profile	<ul style="list-style-type: none"> Once daily oral small molecule To be used in combo with checkpoint inhibitors Collaboration with Cancer Research UK 	<ul style="list-style-type: none"> Once daily oral small molecule 24hr target engagement 	<ul style="list-style-type: none"> Oral GI restricted Good potency and selectivity Minimal GI systemic exposure
Clinical start target	<p>H1 2023 </p>	<p>H1 2023</p>	<p>H2 2023</p>

4 Huge opportunity to create a disruptive pharma business in Japan



Second largest pharma market (excl. China)

Large, ageing population

Universal health care system

FOCUS: underserved, specialty TA/DAs

ADOPT: lean, rational development and commercial model

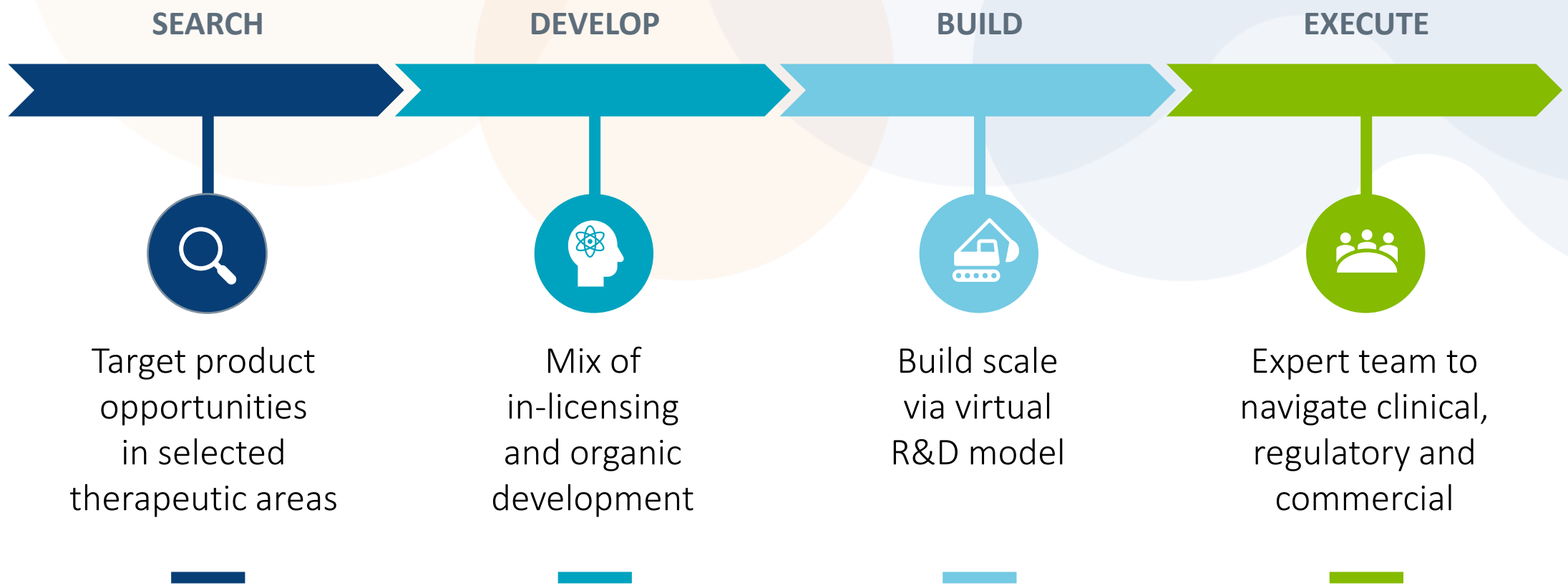
BUILD: Japan as lynchpin market, APAC for expansion

Stable, pro-innovation market

Relatively weak incumbents

Attractive market for disruptors

4 Our plan for Japan



Over \$500 million capital available to in-license approved and/or post POC assets from pharma / biotech originators

Strategy to enhance our success



Key initiatives over the next 3 years aimed at increasing corporate value

Our 2030 vision



Novel medicines on the market globally, through our collaborations with partners

Commercial business in Japan, based on in-licensed and in time, own products

Broad, deep and sustainable pipeline of programs with significant potential

Rapidly growing sales, cash flow and profits

Leading biotech in Japan driving innovative medicines to patients



Appendix 1
Additional information

Board and Leadership team

Board of Directors

	Shinichi Tamura Chairman of the Board	 
	Chris Cargill Representative Executive Officer, President and CEO	 
	Tomohiro Toyama External Independent Director	
	Miwa Seki External Independent Director	   
	Kuniaki Kaga External Independent Director	 
	Dr. David Roblin External Independent Director	    
	Noriaki Nagai External Independent Director	 
	Rolf Soderstrom External Independent Director	       

Executive Management

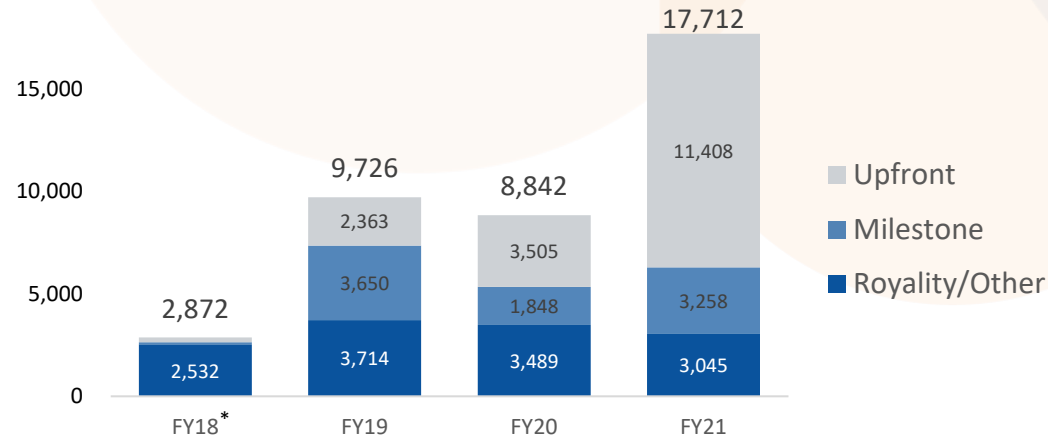
	Chris Cargill Representative Executive Officer, President and CEO	 
	Hironoshin Nomura Chief Financial Officer	 
	Dr. Matt Barnes President, Heptares Therapeutics, Head of UK R&D	 
	Tadayoshi Yasui Representative Director President, Sosei Co.Ltd.	 
	Kieran Johnson Chief Accounting Officer	 
	Kazuhiko Yoshizumi Chief Compliance Officer	

Senior R&D Leadership

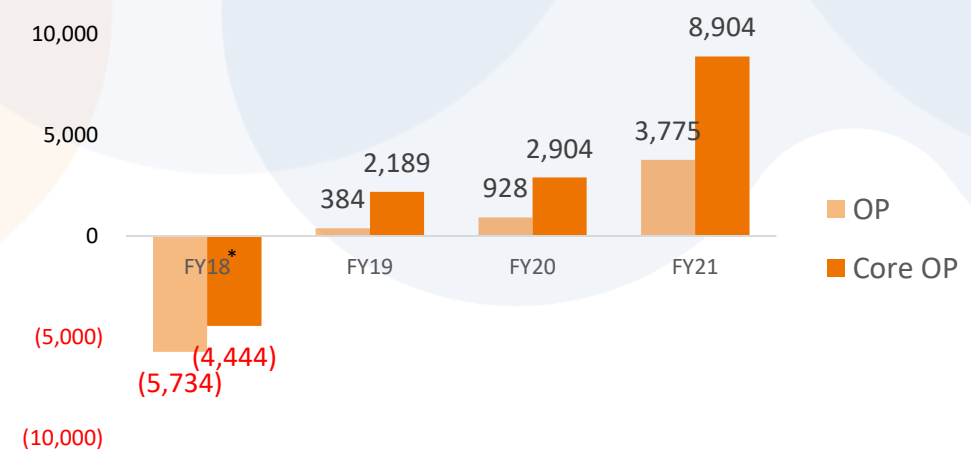
	Dr. Alastair Brown Senior Vice President, Translational Medicine	 
	Dr. David Howe Vice President, Non-CNS Development & Experimental Medicine	  
	Dr. Marcus Messenger Vice President, Business Development	  
	Dr. Barry Kenny Senior Business Advisor	   
	Dr. Stacey Southall Senior Director, Biophysics	 
	Dr. Nigel Swain Senior Director, Medicinal Chemistry	
	Dr. Chris de Graaf Senior Director, Computational Chemistry	 
	Dr. Rie Suzuki Senior Director, Translational Medicine	
	Dr. Wendy Winchester Senior Director, Translational Medicine	 

Our unique and balanced business model continues to support a sustainable financial profile

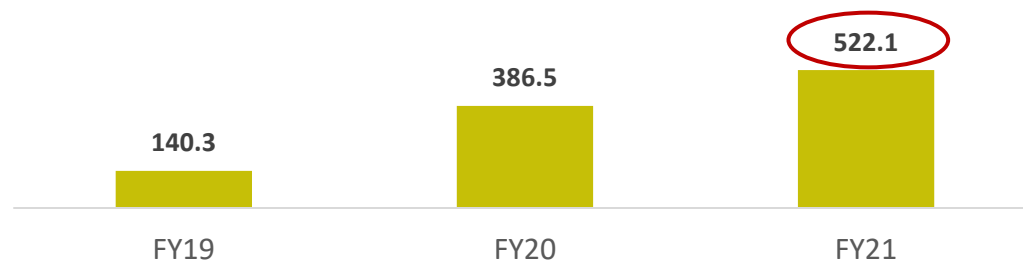
REVENUE (JPY million)



OPERATING PROFIT (JPY million)



CASH AT BANK (USD million)



















FY2021

- **~¥10bn new growth capital raised**, adding funds earmarked to accelerate our strategic growth initiatives and investments
- **Net cash inflow** of ¥20bn (\$136m), resulting in a **robust cash balance** of ¥60bn (\$522m) at year end
- Capital to be deployed domestically in Japan to facilitate **in-licensing, acquisitions and co-investments**













Note: FY18 is 9 month from April 2018 to December 2018

Partnered pipeline programs

Compound	Target / Mechanism of Action	Modality	Indication	Partner	Disc.	PreClin	Ph1	Ph2	Ph3	App	Mkt
Partnered											
Seebri® Breezhaler®	LAMA	SME	COPD	 NOVARTIS	█	█	█	█	█	█	█
Ultibro® Breezhaler®	LAMA+LABA	SME	COPD	 NOVARTIS	█	█	█	█	█	█	█
Energair® Breezhaler®	LAMA+LABA+ICS	SME	Asthma	 NOVARTIS	█	█	█	█	█	█	█
ORAVI®	Antifungal agent miconazole	SME	Oropharyngeal candidiasis	 Hisamitsu	█	█	█	█	█	█	█
NBI'568	Muscarinic M4 agonist	SME	Schizophrenia	 NEUROCRINE BIOSCIENCES	█	█	█	█	█	█	█
Not disclosed	Muscarinic M1 agonist	SME	Neurology diseases	 NEUROCRINE BIOSCIENCES	█	█	█	█	█	█	█
Not disclosed	Muscarinic M1/M4 agonist	SME	Neurology diseases	 NEUROCRINE BIOSCIENCES	█	█	█	█	█	█	█
PF-07081532	GLP-1 agonist	SME	T2DM / Obesity	 Pfizer	█	█	█	█	█	█	█
PF-07054894	CCR6 antagonist	SME	Inflammatory bowel disease	 Pfizer	█	█	█	█	█	█	█
PF-07258669	MC4 antagonist	SME	Anorexia	 Pfizer	█	█	█	█	█	█	█
Not disclosed	CGRP antagonist	SME	Neurology diseases	 Pfizer	█	█	█	█	█	█	█
Not disclosed	GPR35 agonist	SME	Inflammatory bowel disease	 GSK	█	█	█	█	█	█	█
Not disclosed	Multi target	SME/LME	Multiple indications	 Genentech <small>A Member of the Roche Group</small>	█	█	█	█	█	█	█
Not disclosed	Multi target	SME/LME	Gastrointestinal and other	 Takeda	█	█	█	█	█	█	█
Not disclosed	Multi target	SME	Inflammatory / Neurology	 abbvie	█	█	█	█	█	█	█
Not disclosed	Multi target	SME	Diabetes / Metabolic	 Lilly	█	█	█	█	█	█	█





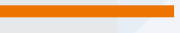

















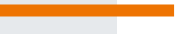




Notes: SME = small molecule, LME = large molecule, mAb = monoclonal antibody. Seebri®, Ultibro®, Energair® and Breezhaler® are registered trademarks of Novartis AG.

Partnered pipeline programs (cont'd)

Compound	Target / Mechanism of Action	Modality	Indication	Partner	Disc.	PreClin	Ph1	Ph2	Ph3	App	Mkt
Co-development											
KY1051	CXCR4 mAb	mAb	Immuno-oncology		████████████████████						
Not disclosed	PAR-2	Peptide	Inflammatory diseases		████████████████						
Not disclosed	Targeted Protein Degradation	SME	Gastrointestinal disorders		██████████████						
Not disclosed	AI-Augmented Drug Discovery	SME	Neurology diseases		██████████████						
Not disclosed	Ion Channel Drug Discovery	SME	Neurology diseases		██████████████						
Not disclosed	Multi target AI-powered	SME/LME	Immune diseases		██████████████						
Not disclosed	Antibody Discovery	mAb	Disease-relevant GPCR targets		██████████████						
Not disclosed	Multi target AI-powered	SME/LME	Immune diseases		██████████████						
Not disclosed	Gut-brain axis drug discovery	SME	Gastrointestinal disorders		██████████████						
Co-owned companies											
TMP301	mGlu5 NAM	SME	Substance use disorders		██						
Not disclosed	OX2 agonist (Oral)	SME	Narcolepsy	 	██████████████						

Notes: SME = small molecule, LME = large molecule, mAb = monoclonal antibody

In-house pipeline programs

Compound	Target / Mechanism	Modality	Indication	Originator	Disc.	PreClin	Ph1	Ph2	Ph3	App	Mkt
In-house Programs											
Not disclosed	H4 antagonist	SME	Atopic Dermatitis								
HTL0039732	EP4 antagonist	SME	Immuno-oncology	 							
Not disclosed	GPR52 agonist	SME	Neurology diseases								
Not disclosed	EP4 agonist	SME	Inflammatory bowel disease								
Not disclosed	PAR-2 mAb	mAb	Atopic Dermatitis								
Not disclosed	SARS CoV-2 Mpro	SME	Coronaviruses								
Multiple programs	Not disclosed	SME/LME	Neurology diseases								
Multiple programs	Not disclosed	SME/LME	GI and Inflammatory diseases								
Multiple programs	Not disclosed	SME/LME	Immunology diseases								
In-house Programs (No longer internally funded. Targeting academic / industrial partnership)											
HTL'310	SSTR5 agonist	Peptide	Hypoglycaemic disorders								
HTL'097	GLP-1 antagonist	Peptide	Hypoglycaemic disorders								
HTL'023	Dual GLP-2/GLP-1 agonist	Peptide	Intestinal failure / NASH								
Not disclosed	Apelin agonist	Peptide	Pulmonary Arterial Hypertension								

Notes: SME = small molecule, LME = large molecule, mAb = monoclonal antibody



Appendix 2

*Summary of wholly-owned
programs targeting FTIH in 2023*

EP4 Antagonist

Background & Executive Summary

Target & Disease indication(s)

- EP4 mediating PGE₂ immunosuppression
- Combination with checkpoint inhibitors (CPI's) in cancers with high expression of PGE2

Rationale

- Tumour derived PGE2 induces profound immunosuppression in the tumour microenvironment (TME), primarily acting via EP4
- EP4 antagonism will relieve PGE₂-mediated immunosuppression and switch the TME from tumour tolerant to tumour aware. **Phase 1 data with competitor EP4 antagonist, E7046 supports this hypothesis**

Target Product/Molecule Profile

- Once daily oral small molecule EP4 antagonist for the treatment of PGE2 high cancers in combination with CPI's

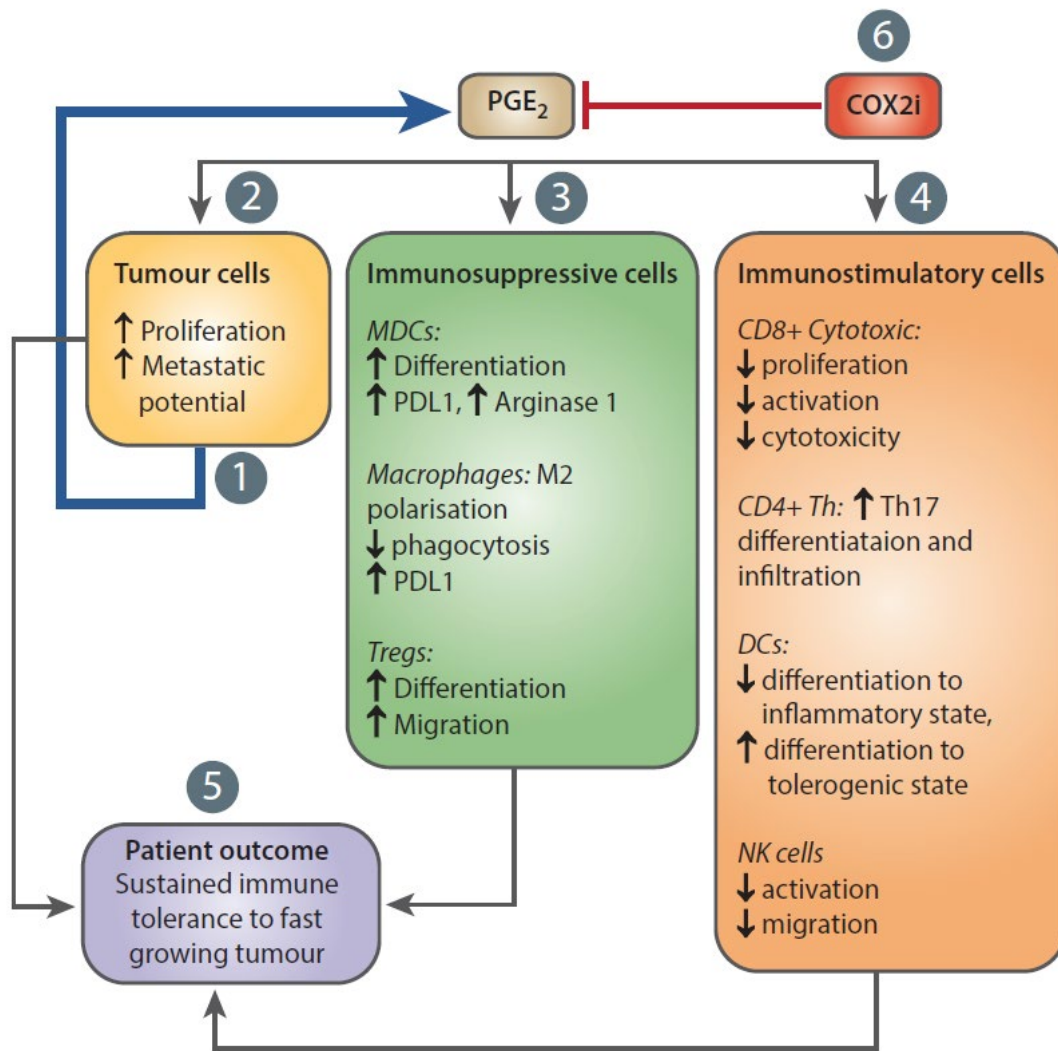
Current Status & Next Milestone

- Preclinical studies and clinical manufacture completed
- Clinical studies starting H1 2023

Executive Summary

- Proprietary StaR® technology used to identify highly potent and selective antagonists of the EP4 receptor
- Candidate is a class-matching, selective, potent, orally-bioavailable molecule; once daily, low dose, human administration is predicted to deliver target suppression throughout dosing period
- Positive anti-tumour data in mouse syngeneic model of colorectal cancer (CT26) in combination with CPI
- Blockade of EP4 represents a promising therapeutic opportunity to remove PGE2 mediated immunosuppression
- Working with CRUK to test compound in the clinic alone and in combination with CPI's which is expected to confer efficacy in previously CPI unresponsive cancer patient populations

EP4 Antagonist in Oncology – Proposed Mechanistic Hypotheses



1. Epithelial tumour cells secrete large quantities of PGE₂ into the TME.
2. PGE₂ increases proliferation of some tumours and thereby increases their metastatic potential.
3. PGE₂ propagates an immunosuppressive TME; stimulates MDSC differentiation, M2 polarisation and T_{reg} migration.
4. PGE₂ propagates an immunosuppressive TME; reduces CD8 activity and killing, increases Th17 rather than Th1 differentiation, supports DC maturation towards a tolerogenic state, decreases NK cell migration and activation.
5. Together these effects combine to make the patient tolerant to their growing tumour.
6. Multiple licensed pharmacological agents can reduce PGE₂ generation through COX1/2 suppression. We hypothesise that clinically relevant regimens of these agents fail to effectively suppress TME PGE₂.
7. Reducing immunosuppression in the TME in combinations with CPI's will improve response rates in specific cancer patient populations.

GPR52 Agonist

Background & Executive Summary

Target & Disease indication(s)

- Oral small molecule GPR52 agonist
- Schizophrenia
- Psychosis and/or cognitive decline in dementias

Rationale

- G_s coupled Orphan GPCR
- Co-located with D2 receptors in medium spiny neurons (MSN) and with D1 in prefrontal cortex (PFC)
- GPR52 activation will afford a D2 antagonist-like effect in D2 MSNs and a D1 agonist like effect in PFC
 - *i.e. an antipsychotic and pro-cognitive profile*
- Novel mechanism to treat both positive, negative and cognitive symptoms of schizophrenia

Target Product/Molecule Profile

- Once daily oral small molecule

Current Status & Next Milestone

- Candidate status
- FTIH starting H1 2023

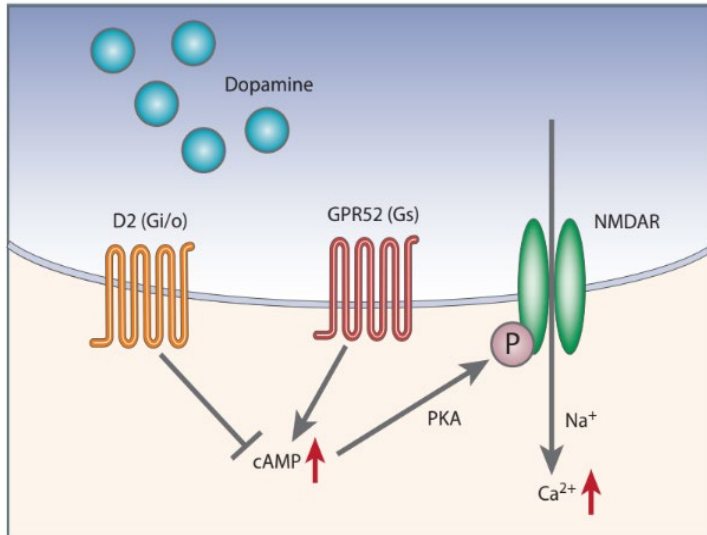
Executive Summary

- Therapy to address positive symptoms, negative symptoms and cognitive impairment in schizophrenia, without adverse effects typically associated with antipsychotics
- Potential for other patient settings (e.g. cognition and/or psychosis in dementias)
- High quality molecule (HTL'149) in preclinical development
 - Excellent pharmacology and DMPK profile
 - In vivo activity in efficacy models
 - Rodent and dog MTD/DRFs completed;
 - Route/process development completed; GMP manufacture ongoing
 - FTIH start 2Q23
- Back-up molecules identified in other series
- Biomarker validation ongoing

GPR52 Agonist Target Rationale

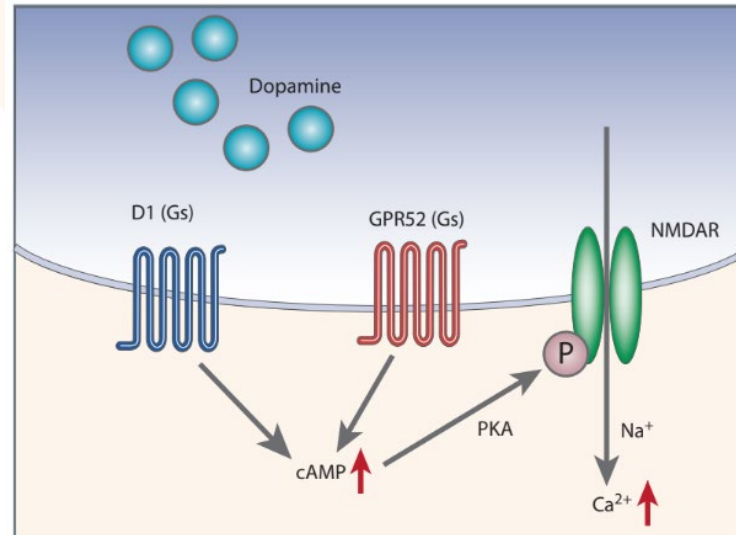
Treatment of positive symptoms and cognitive dysfunction in Schizophrenia

Striatopallidal neurons



Proposed GPR52 signal transduction. GPR52 activation counteracts Gi/o-coupled D2 receptors in striatopallidal neurons

Prefrontal cortical neurons



Potentiates NMDA activity through phosphorylation of the NMDA receptor via cAMP/PKA, as seen in D1 receptor-NMDA signal transduction

Rationale

- GPR52 receptors principally co-located with D2 and D1 receptors
 - D2 in Medium Spiny Neurons
 - D1 in Prefrontal Cortex
- GPR52 Activation \uparrow cAMP
 - D2 Antagonist-like effect in Medium Spiny Neurons
 - Psychosis
 - D1 Agonist-like effect in Prefrontal Cortex
 - Cognition & negative symptoms
- No side effects associated with antipsychotics due to blockade of other D2 receptor populations
- Potential for other indications / disease settings e.g. psychosis / cognition in dementia)

Source: Novel Therapeutic GPCRs for Psychiatric Disorders: Komatsu, Int. J. Mol. Sci. 2015, 16, 14109; doi:10.3390/ijms160614109

GI restricted EP4 Agonist for the treatment of IBD

Background & Executive Summary

Target & Disease indication

- Inflammatory bowel disease (IBD)

Target Rationale

- IBD genetic risk association
- PGE2 has well documented mucosal protective roles – key role in maintaining gut homeostasis and promoting mucosal repair.
- Through combined anti-inflammatory and barrier protecting effects, EP4 agonists are expected to bring benefits in IBD and promote mucosal healing

Target Molecule Profile

- Oral GI restricted EP4 agonist with good potency and selectivity. GI targeting strategy with minimal systemic exposure.

Current Status & next milestone

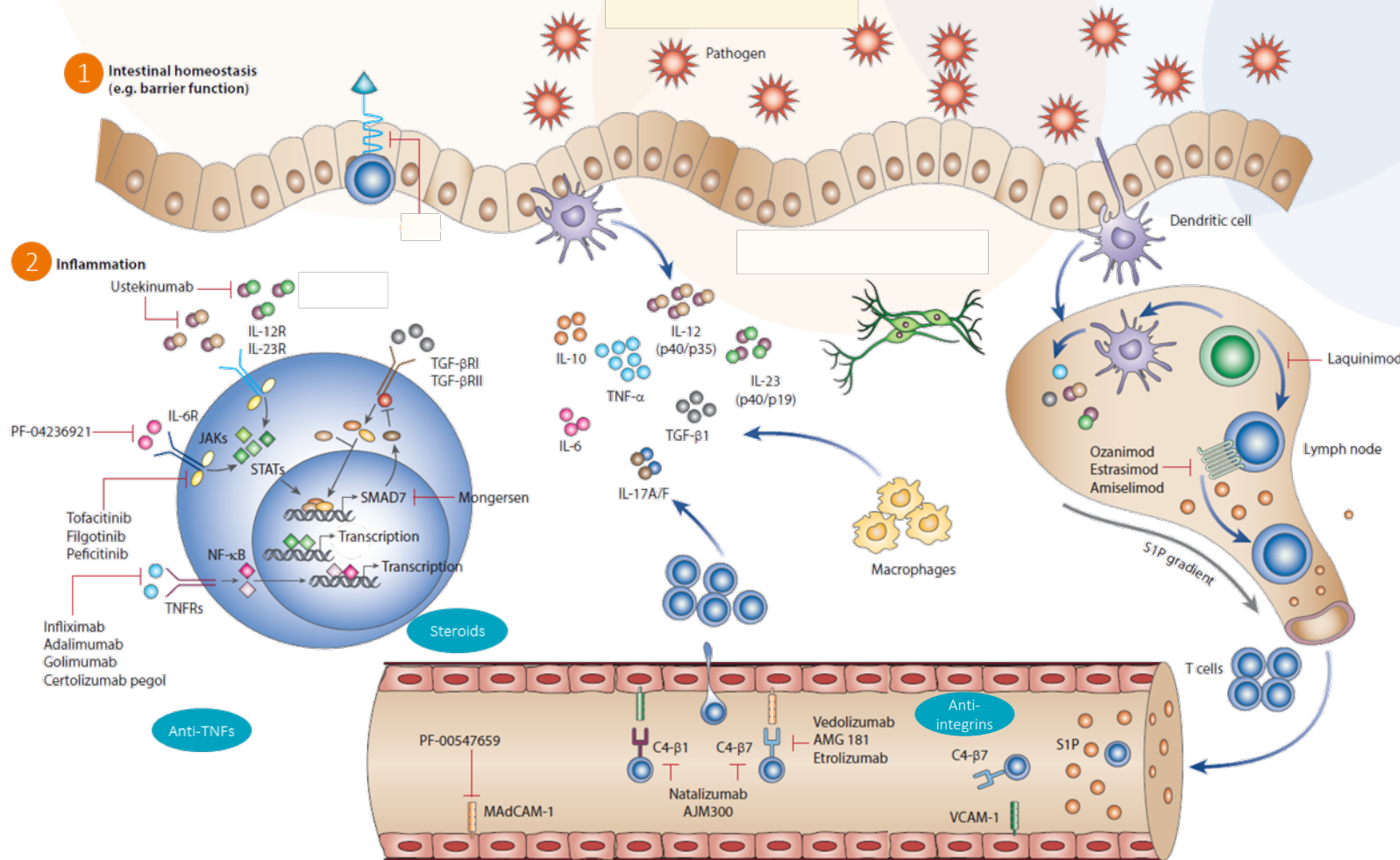
- Status: Candidate Nomination
- Next Milestone: Candidate Selection

Executive Summary

- **EP4 represents an attractive target for the treatment of IBD**
 - Strong mechanistic rationale in IBD supported by human genetic evidence.
 - Strong commercial opportunity for novel oral agents that can promote mucosal healing to induce long term remission & reduce risk of surgery.
 - Current therapeutic strategies primarily target immune pathways: but only 20-40% achieve long term remission with existing biologic therapies
- **Sosei Heptares is developing an oral GI restricted EP4 agonist molecule with minimal systemic exposure for the treatment of IBD**
 - Successful application of SBDD to design molecules with excellent GI restricted properties
 - Lead molecule has completed candidate nomination package and is being transitioned to full preclinical development.
 - High potent EP4 agonist with low oral bioavailability in preclinical species
 - Robust efficacy demonstrated in rodent colitis models.
 - Good in vitro safety profile and early toxicology studies completed.
- **FIC opportunity for an oral gut restricted agent** to promote regeneration and mucosal repair via a differentiated MOA on the epithelial axis

Oral GI restricted EP4 agonist for the treatment of IBD

Proposed Mechanistic Hypotheses



Proposed benefits of EP4 agonist

- 1 Intestinal homeostasis – EP4** accelerates mucosal healing via promoting regeneration and repair of damaged epithelial mucosa. EP4 agonists promote barrier function via direct action on gut epithelial cells.
- 2 Immune cell function– EP4** is expressed in gut immune cells and regulates Th1 cytokine release. EP4 signalling promotes differentiation of proresolving macrophages.

Source: Adapted from (Weissshof et al 2018)

Key: Current IBD therapies (SOC)

Locations

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