NON-CONFIDENTIAL

H1 FY2021 Financial Results

Six-month period ended June 30, 2021

August 12, 2021 | Sosei Group Corporation (TSE:4565)

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References to "FY" in this presentation for periods prior to January 1, 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 nine-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.

Agenda

1. Overview of Financial Results
2. Operational Highlights
3. Muscarinic Agonist Programs
4. Q&A
5. Appendix

Note: This material was created to explain the details of our company and is not intended to be used for investment decisions. In addition, the contents reflect the views of our company at the time of the creation of the material, and the accuracy of the information is not guaranteed. Investments should be made based on the independent views of investors

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Overview of Financial Results

Chris Cargill, COO and CFO

Continued to execute on objectives and targeted investments

Summary Financial Highlights for the 6 months ended 30 June 2021

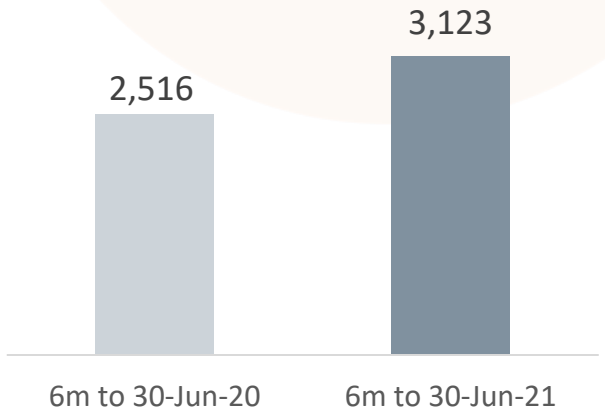
1. **Revenue of ¥3,123m** ($28.9m) vs. ¥2,516m ($23.2m) in H1 2020, driven by achievement of several progress-related milestone events and larger releases of deferred revenue from existing partners
2. **Cash Earnings Loss of ¥800m** ($7.4m) vs. loss of ¥181m ($1.7m) in H1 2020, as a result of planned increase in R&D investment (e.g., Muscarinic and prioritized in-house programs) and professional advisory fees
3. **Operating Loss of ¥1,849m** ($17.1m) vs. loss of ¥1,136m ($10.5m) in H1 2020 as a result of Oravi impairment and higher SBC[1] costs. Financing costs in the period largely offset by CC[2] and FX[3] gains
4. **Robust cash balance of ¥40.6bn,** an increase of ¥621m since the beginning of the year as a result of our balanced approach to investment and diversified partner base
5. **~¥10bn new growth capital raised after the period ended,** adding to our existing ~¥20.9bn funds earmarked to accelerate our strategic growth initiatives and investments

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

Notes: USD:JPY FX rates used - 2020 YTD average Rate: 108.25, 2021 YTD average rate; 108.11, 31 Dec 2020 spot rate: 103.52, 30 Jun 2021 spot rate: 110.54
1. SBC = Stock-Based Compensation 2. CC = Contingent Consideration 3. FX = Foreign Exchange

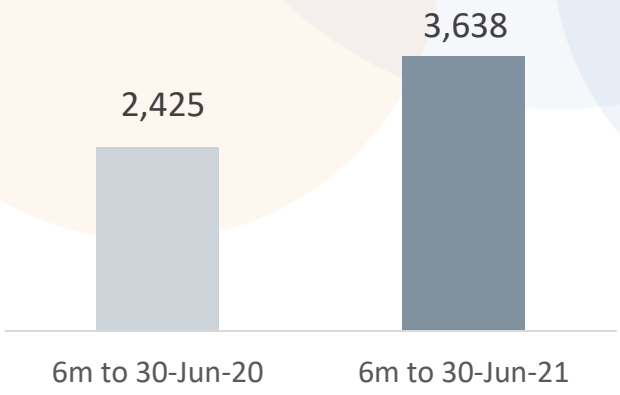
Encouraging revenue growth offset by planned increase in R&D (muscarinic and priority in-house programs) and non-cash costs

Revenue (JPY million)



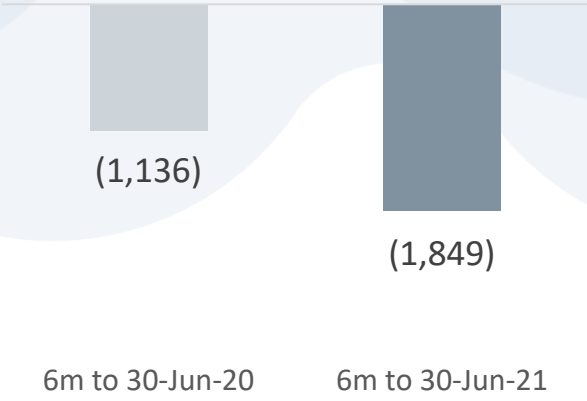
- Revenue +24% vs. H1 2020 due to progress milestones from existing partners:
  - Pfizer (MC4 Ph 1 start)
  - Biohaven (CGRP Ph 1 start)
  - Genentech (Delivery of StaRs®)
  - Deferred revenue releases on AbbVie and Genentech collaborations
- Royalties from Novartis were stable

Cash Operating Expenses[1,2] (JPY million)



- Increased R&D investment in muscarinic M_4R (HTL '878) and other prioritized high value creation in-house programs
- Strong interest from global partners for muscarinic programs
- H1 2020 spend lower than normal due to onset of pandemic in Mar-20, plus a large non-recurring supplier credit

Operating Loss (JPY million)



- Oravi impaired in the period – new distribution deal executed post period end expected to improve sales
- Higher SBC[1] costs from continued roll out of RSU[2] plans – aligning with shareholders
- Financing costs up from CB[3] issued in July 2020. H1 2020 result included realized RMF1[4] gain

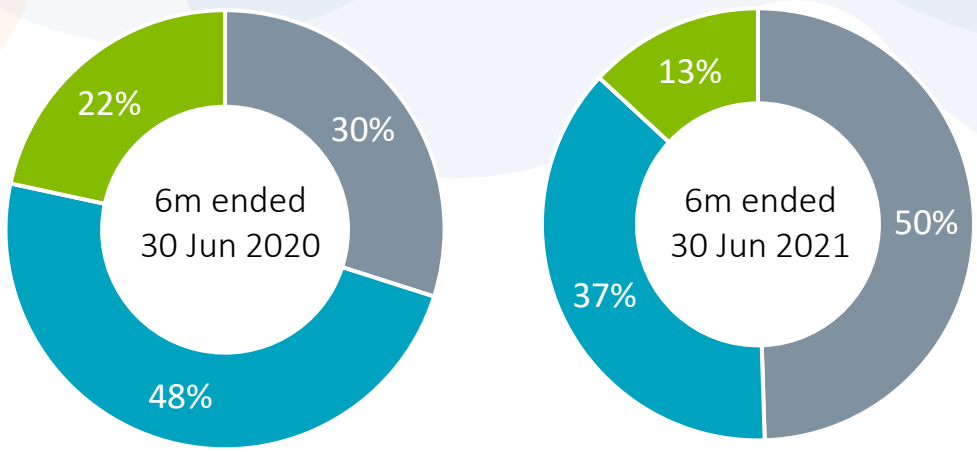
Notes: [1] Non-IFRS measure; [2] Cash Operating Expenses = Cash R&D + Cash G&A
1. SBC = Stock-Based Compensation 2. RSU = Restricted Stock Units 3. CB = Convertible Bond 4. RMF1 = Regenerative Medicine Fund 1

Encouraging revenue growth offset by planned increase in R&D (muscarinic and priority in-house programs) and non-cash costs (cont'd)

	JPY million		USD million	
	6m ended 30 Jun 2020	6m ended 30 Jun 2021	6m ended 30 Jun 2020	6m ended 30 Jun 2021
Revenue	2,516	3,123	23.2	28.9
Cash Cost of Sales	(304)	(366)	(2.8)	(3.4)
Cash R&D	(1,500)	(2,382)	(13.9)	(22.0)
Cash G&A	(925)	(1,256)	(8.5)	(11.6)
Other Cash Income	32	81	0.3	0.7
Cash Earnings Loss	**(181)**	**(800)**	**(1.7)**	**(7.4)**
Non-Cash Costs	(955)	(1,049)	(8.8)	(9.7)
Operating Loss	**(1,136)**	**(1,849)**	**(10.5)**	**(17.1)**
Net Finance Costs	46	(32)	0.4	(0.3)
Equity Accounted Investments	(180)	488	(1.6)	4.5
Net Profit before income tax	**(1,270)**	**(1,393)**	**(11.7)**	**(12.9)**
Net Profit	**(2,117)**	**(2,297)**	**(19.6)**	**(21.2)**

Notes: USD:JPY FX rates used – 2020 YTD average rate: 108.25, 2021 YTD average rate: 108.11

Revenue by Type



	6m ended 30 Jun 2020		6m ended 30 Jun 2021	
Milestone	¥753m	$7.0m	¥1,546m	$14.3m
Royalty	¥1,219m	$11.2m	¥1,167m	$10.8m
Other	¥544m	$5.0m	¥410m	$3.8m

Sustainability of business model and corporate strategy is reflected in our robust and well capitalized balance sheet

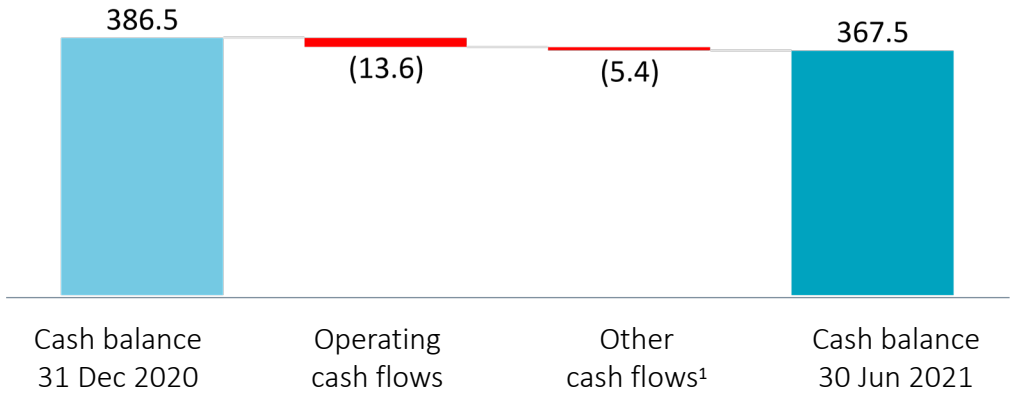
	JPY million		USD million	
	As of 31 Dec 2020	As of 30 Jun 2021	As of 31 Dec 2020	As of 30 Jun 2021
Goodwill & intangibles	25,936	27,412	250.5	248.0
Property, plant & equip.	3,824	3,915	36.9	35.4
Cash at hand	40,008	40,629	386.5	367.5
Equity Acc. investments	3,087	3,666	29.8	33.2
Other financial assets	1,593	3,519	15.4	31.8
Other assets	2,017	2,207	19.5	20.0
Total Assets	**76,465**	**81,348**	**738.6**	**735.9**
Convertible Bonds	14,789	14,918	142.9	135.0
Other liabilities	9,295	10,674	89.7	96.5
Total Liabilities	**24,084**	**25,592**	**232.6**	**231.5**
Net Assets	**52,381**	**55,756**	**506.0**	**504.4**

Notes: USD:JPY FX rates used – 31 Dec 2020 spot rate: 103.52, 30 Jun 2021 spot rate: 110.54
1. Includes Investing, financing and FX related movements

Commentary

1. ✓ Small cash inflow when balances are aggregated in JPY, however weaker JPY in H1 2021 drove a reduction in total cash balance when aggregated in USD
2. ✓ Increase due to positive revaluation of several investment securities, including significant increase in value of our new Centessa Pharma holding following its IPO

Cash Flow Bridge (6m ended 30 Jun 2021)



Unchanged FY2021 financial guidance (12m to 31-Dec-21)

Guidance (Dec-21)

Cash R&D expenses	Cash G&A expenses
¥4,000 to 5,000m	**¥1,800 to 2,300m**
✓ Increased investment in HTL'878 selective M_4R agonist program – valuable opportunity to secure a new major partnership ✓ Accelerate new and prioritized in-house programs with strong value creation potential	✓ Continued global implementation of Oracle Netsuite Enterprise Resourcing Planning (ERP) system ✓ Continued build-out of Compliance and Governance capabilities

Investing today to drive growth tomorrow

Successful international offering and buyback of existing bonds completed after the period ended

Net proceeds of ¥29.8bn from Euro-Yen denominated convertible bonds due 2026

- ✓ Largest mid-cap convertible bond raise in Asia Pacific region since 2015
- ✓ Highly successful liability management exercise, with strong 98% investor take-up
- ✓ Lowered Group's funding cost, extended maturity of debt and potentially reduced dilution upon conversion

Use of proceeds:

- Approximately ¥18.9bn to be allocated towards the **repurchase of existing convertible bonds – completed**
- New ¥10bn net proceeds to be added to existing ¥20.9bn capital and allocated to **strategic growth initiatives** (acquisitions and/or investments)
- Approximately ¥0.9bn to be allocated towards **R&D of new pipeline programs** and working capital

We continue to evaluate strategic growth ideas and are well capitalized to execute when a potential opportunity presents itself

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2

Operational Highlights

Shinichi Tamura, Chairman and CEO

Excellent progress expanding our drug discovery business

Summary Operational Highlights for the 6 months ended 30 June 2021

- **New strategic technology collaborations** with PharmEnable and InveniAI* for AI-driven drug discovery, and Metrion Biosciences to explore SBDD approaches for ion channels
- **Excellent progress across partnered programs** including MC4 antagonist (partnered with Pfizer) and CGRP antagonist (partnered with Biohaven) both entered Phase 1 clinical trials, and StaR® proteins delivery to Genentech, all triggering development milestone payments
- **Spin-off company Orexia Therapeutics merged into Centessa Pharmaceuticals**, a new asset-centric company, which completed its $380m raise / $1.7bn market cap. NASDAQ IPO in June 2021
- **Potential clinical candidate for SARS-CoV-2 MPro program have now been identified** and suitable for further development as an oral treatment of COVID-19

World-leading platform for identifying and exploiting new druggable targets, and a corporate strategy designed to deliver value creation for all stakeholders

* Executed in July 2021 (event occurred post period close)

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10 drug candidates generated from our SBDD platform have been successfully advanced into clinical trials

LAST 12 YEARS (StaR® / SBDD GENERATED)

DRUG DISCOVERY | DEVELOPMENT

Identified	Generated	Produced
36	24	10
optimized leads	preclinical candidates	clinical candidates

New

TODAY

LEAD OP	PRECLINICAL	CLINICAL
5 compounds	11 candidates	10 candidates

MEDIUM TERM OUTLOOK

TECHNOLOGY | DRUG DISCOVERY

Deliver at least	Generate on average
4	2
new programs to lead optimization stage every 2 years	new preclinical candidates every year

One of THE most productive drug discovery teams in the world over the past 12 years

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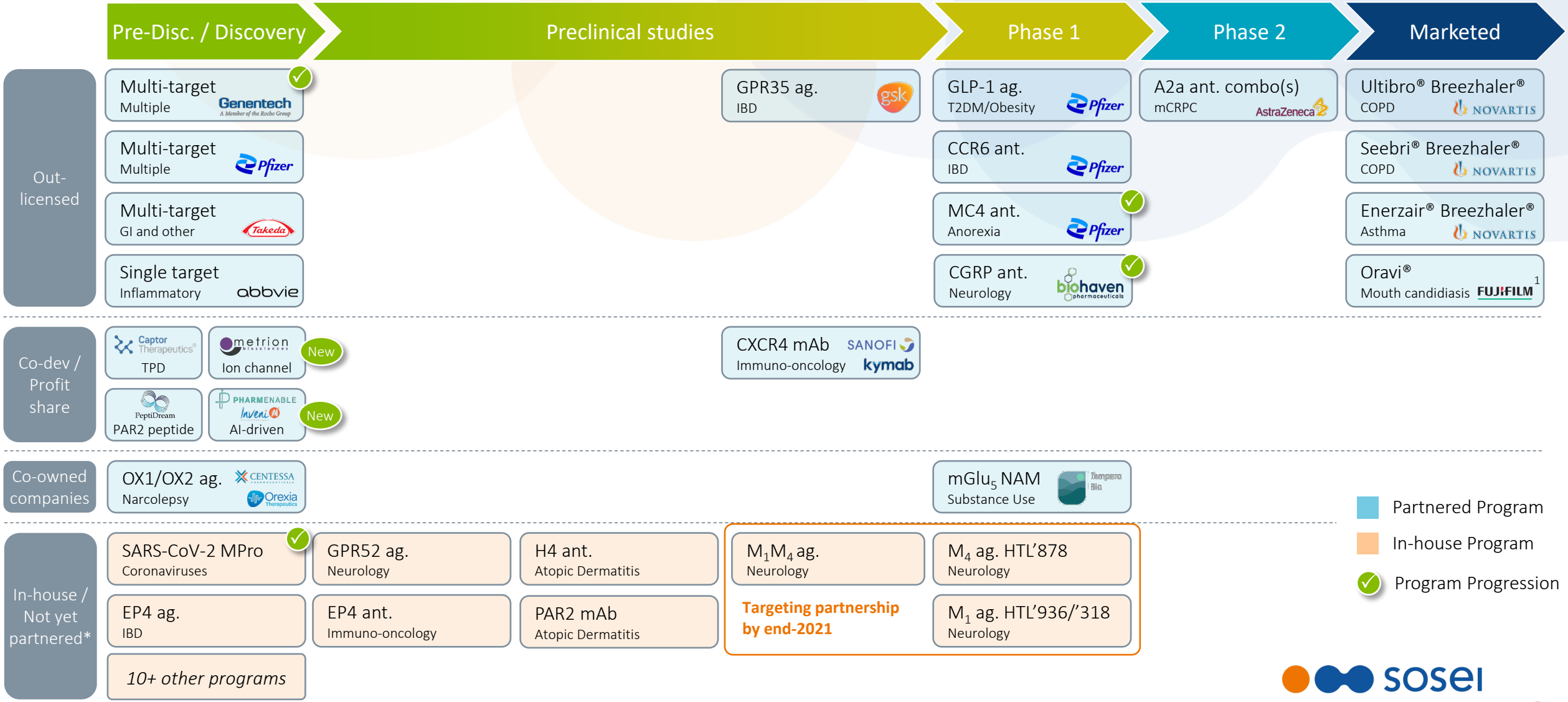
We saw excellent progress across our deep pipeline and added multiple new technology collaborations



Note: Seebri®, Ultibro®, Enerzair® and Breezhaler® are registered trademarks of Novartis AG. [1] New distribution deal executed with new distribution partner to commence on 1 November 2021. Fujifilm responsible for distribution until 31 October 2021.
* The in-house pipeline displayed above includes fully funded programs only and excludes back-up programs and similar indication programs for one target. For example – A2a ant, SSTR5 ag, GLP-1 ant, GLP-2 ant, M1 and M4 backup programs (list not exhaustive).

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Next wave of COVID-19 therapies – SARS-CoV-2 protease inhibitors – are starting to show promise

	Pfizer	SHIONOGI	sosei HEPTARES
Overview	PF-07321332 – small molecule oral antiviral treatment; twice a day dosing at first sign of infection / first awareness of an exposure	S-217622 – small molecule oral antiviral treatment; once a day dosing.	SH-879 – small molecule oral antiviral treatment; once or twice daily dosing immediately after a positive test result and for up to 2 weeks after
Phase	Phase 2/3 trial initiated in July 2021 for PF-07321332/ritonavir combo	Japanese Phase 1 trial initiated in July 2021	Potential clinical candidate identified suitable for further development
Key data findings	• Exhibits potent *in vitro* antiviral activity against SARS-CoV-2 • Robust preclinical antiviral effect and good preclinical safety profile, • Good tolerability, no safety findings up to 500mg dose 2x daily with ritonavir/10 days in healthy volunteers • Requirement for ritonavir combination boost exposure	• Animal studies showed ability to decrease the viral load quickly and significantly • No safety concerns reported so far	• Comparable antiviral activity to Pfizer's PF-07321332 against SARS-CoV-2 in cell based assays • Low *in vitro* clearance, superior *in vivo* clearance and high plasma exposure from oral dosing • Does not likely require co-dosing with ritonavir for PK boosting in human clinical trials, unlike Pfizer's PF-07321332

Source: Company announcements; Company websites

Our M^{Pro} inhibitor SH-879 represents an excellent opportunity for further development as an oral drug for the treatment of COVID-19

TARGET PRODUCT PROFILE

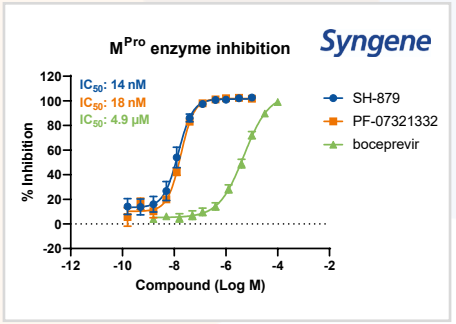
Once or twice daily oral agent for treatment of SARS-CoV-2 viral infection dosed immediately after a positive test result and for up to 2 weeks thereafter, with potential for broader application for intervention of associated human coronavirus infections

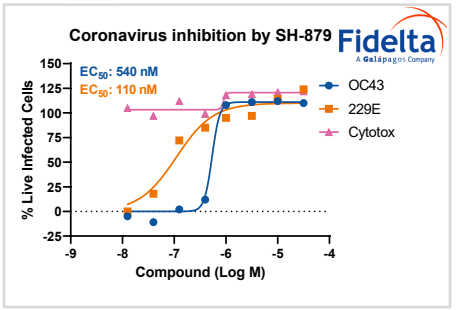
PROGRAM STAGE

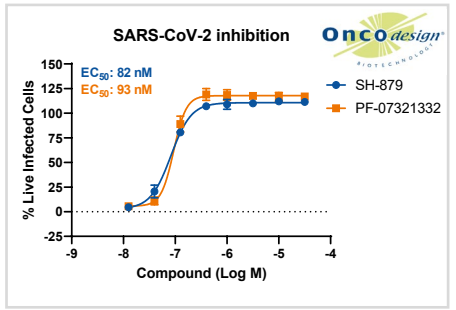
Excellent progress has been made in >1 chemical series of inhibitors since project initiation Apr-20

Potential clinical candidates have now been identified, suitable for further development

Promising PK results from SH-879, our most advanced asset (see adjacent charts for cell-based antiviral assay data)







NEXT STEPS

- Proactively seeking funding via charitable organizations and trusts / other philanthropic sources of funding, to rapidly progress our molecules
- Program is available for global partnering to accelerate progress to human clinical trials Significant inbound interest received and under assessment
- Program remains a core ESG project – We will not profit/receive economics from sales to Least Developed Countries*. For all other countries, we will reinvest a portion of any profits received towards our Group's ESG initiatives

* Regardless of pandemic/endemic status. List of LDCs as defined by the United Nations.

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Organic growth plan driving our world-leading GPCR drug discovery

Continuing to build a broad pipeline of high-value creating programs, partnerships and co-investments

Strategic growth plan driving corporate value expansion

STRATEGIC GROWTH PLAN

OBJECTIVE

Capital raise completed to pursue revenue focused deals in 2021

Seek out revenue-generating opportunities

Invest / collaborate in novel technologies

OBJECTIVE

Add new technology capabilities to our SBDD platform

✓ PHARMENABLE ✓ Inveni AI

OBJECTIVE

Take steps to expand beyond core GPCR specialty

✓ metrion biosciences

Expand drug target classes beyond GPCRs

In-license late-stage programs for Japan

OBJECTIVE

Bring international medicines to Japanese patients in areas of unmet need

Seeking to add new revenues, access new technologies, and expand and future-proof our capabilities

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3

Muscarinic Agonist Programs – A neuroscience pipeline with a multi-blockbuster profile

Dr. Tim Tasker, CMO

Recapping the status and progress of our Muscarinic programs

- Patented StaR® technology enabled SBDD approach to identify novel **highly selective muscarinic M_4R, M_1R and dual M_1R/M_4R orthosteric agonists**
- Muscarinic M_4R and M_1R represent **clinically validated targets** for the treatment of psychosis and cognition, precedented by non-selective muscarinic agonists (e.g. xanomeline) in short term clinical studies (5 weeks) in schizophrenia ("SZ") and mild-moderate Alzheimer's disease ("AD") (6 months)
- **Multi-blockbuster commercial opportunity** for orally dosed novel mechanisms targeting control of positive symptoms and with an improved safety profile over current Standard of Care. Further improvement in efficacy an upside
- **Increased investment in M_4R agonist program** this year (following reversion in early 2021), with **program nearing Phase 2 readiness for SZ** with a back-up compound which is Phase 1 ready
- New **M_1R agonist and a dual M_1R/ M_4R agonist IND ready** in 2022, utilizing Proof of Mechanism data in AD from pathfinder compound to accelerate early development

Lead M_4R orthosteric agonist (HTL'878) Ph 2 ready in the near term, and a first-in-class M_1R orthosteric agonist compound IND ready in 2022 whilst maintaining a broad muscarinic portfolio

Our Muscarinic programs represent a ready-made neuroscience pipeline with multiple blockbuster opportunities

Program	Compound	Indication	Discovery	Preclinical	Phase 1	Phase 2	Next Milestone 12-18 months
M_4R ortho agonist	HTL'878	Schizophrenia	■	■	■	▨	Phase 2 ready
	Not disclosed	Schizophrenia	■	■	▨		Completion of Phase 1 SAD
M_1R/M_4R dual ortho agonist	Not disclosed	Schizophrenia & Alzheimer's cognition & psychosis	■	■	▨		IND ready
M_1R ortho agonist pathfinders	HTL'318	Alzheimer's Dementia Lewy Bodies	■	■	■		Regulatory consultation
	HTL'936	Alzheimer's Dementia Lewy Bodies	■	■	■		Clinical PK
M_1R ortho agonist	Not disclosed	Alzheimer's Dementia Lewy Bodies	■	■	▨		IND ready

Negotiations progressing well with multiple potential global development/co-development partners. Current intention remains to partner all programs in order to aggressively accelerate their development

Key: Full box = completed phase. Striped box = next milestone

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4th-gen candidates aim to be effective treatments for SZ with fewer side effects

HTL'878

					Efficacy			Safety	
					Positive symptoms	Negative symptom	Cognitive impairment	Extrapyramidal symptoms**	Weight gain
	MoA	Typical medicine	Peak sales example	Generation	Number of patients 20M*	Number of patients 11.5M*	Number of patients 16M*	-	-
Typical antipsychotic	D2 Ant	Haldol	(Historic data unavailable)	1st	+++	-	-	++++	+
Atypical antipsychotics	D2 Ant + 5-HT Regulator	Zyprexa Risperdal Latuda	Zyprexa $5,000M+ (2010)	2nd	+++	+	+	++	++++
	D2 partial Ag + 5-HT Regulator	Abilify REXULTI Vraylar	Abilify $6,100M+ (2013)	3rd	+++	+	+	+	+
	M_4R Agonist***	KarXT CVL-231 **HTL'878**	-	4th	+++	++	++	-	-

Following reversion in early 2021, HTL'878 was rapidly positioned for success in SZ

*As 1 patient can have several symptoms, number of patients in 3 symptoms is overlapping
**Drug-induced movement disorders including involuntary or uncontrollable movements. tremors. muscle contractions. It is said to be related with D2 receptor occupancy balance.
***Expected efficacy and expected safety derived from ongoing clinical trials of KarXT and CVL-231.
Source : P T. 2014 Sep; 39(9): 638–645, J Clin Psychiatry. 2010;71(3):280–286, Schizophr Bull. 2010 Jan; 36(1): 36–42 and EvaluatePharma

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Modulation of the muscarinic M_4R now an increasingly de-risked and validated target for treating multiple types of SZ

HTL'878

	KARUNA THERAPEUTICS	cerevel	SOSEI HEPTARES
Lead Program	KarXT	CVL-231	**HTL'878**
MoA	M_1R/M_4R Agonist, M_2R/M_3R Antagonist	M_4R PAM[1]	**M_4R Direct Agonist**
Current Phase (most advanced)	Phase 3	Phase 1b	**Phase 2 ready (near term)**
Target	✓ SZ (Psychosis) - Ph3 ✓ SZ (Negative and cognitive symptom) - Ph1 ✓ Dementia-related Psychosis - Ph1	✓ SZ (negative, positive and general psychopathology) – Ph1b	-
Impact of recent Clinical data*	**Ph. 2 met primary endpoint (Nov 18, 2019)**	**Ph. 1b Positive Topline (June 29, 2021)**	-
	$17.68 → $85.10 **($1.7Bn+ Market cap increase)**	$12.57 → $23.20 **($1.6Bn+ Market cap increase)**	

Recent positive trial results with KarXT and CVL-231 are fueling broad investor and pharma industry interest in the muscarinic class - including our highly selective M_4R direct agonist approach for SZ

*Share price change is 5 business days after announcement. [1] PAM = Positive Allosteric Modulator
Source: Company Announcements, FactSet

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HTL’878 is differentiated and is the only highly selective orthosteric agonist of the muscarinic M4 receptor in development

Direct agonism of M_4R is a clinically validated target for psychoses

- Direct agonism of the muscarinic M_4 mechanism is a clinically validated target for the treatment of psychoses (Xanomeline, KarXT), underpinned by strong non-clinical science from around the world
- **HTL’878 has been shown to act via selective direct agonism of the M_4R in non-clinical species and also in humans**

HTL’878 is an orthosteric partial direct M_4R agonist with a potentially improved side-effect profile

- **HTL’878 is an orthosteric partial direct M_4R agonist with a potentially improved side effect profile in comparison with the front-runner (KarXT) and likely CVL-231**
  - HTL’878 has much better selectivity and a potentially improved side-effect profile than KarXT
  - CVL-231 is a Positive Allosteric Modulator (PAM)which therefore requires ACh tone in the CNS making it difficult to achieve a margin over CV side effects
- **Efficacy of an orthosteric agonist does not depend on cholinergic tone, unlike a PAM – we expect also stronger efficacy in Dementia Related Psychosis than a PAM which is unlikely to be effective**

Of the fourth-generation treatments in development, HTL’878 stands out as a potentially superior approach

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4

Q&A

Shinichi Tamura, Chairman and CEO

Thank you for your attention

Summary Financial and Operational Highlights for the 6 months ended 30 June 2021

- Revenue of ¥3,123m
- Robust cash balance of ¥40.6bn
- ~¥10bn new growth capital raised
- New strategic technology collaborations
- Excellent progress across partnered programs with multiple Phase 1 starts
- Potential clinical candidate for SARS-CoV-2 MPro program identified

World-leading platform for identifying and exploiting new druggable targets, and a corporate strategy designed to deliver value creation for all stakeholders

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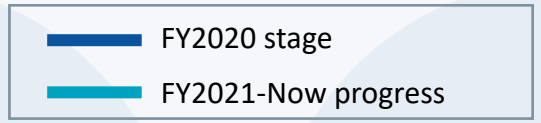
5

Appendix

Progression of Partnered Pipeline



Compound	Target / Mechanism of Action	Modality	Indication	Partner
Traditional Out-licensing Collaborations				
Seebri® Breezhaler®	LAMA	SME	COPD	Novartis
Ultibro® Breezhaler®	LAMA+LABA	SME	COPD	Novartis
Enerzair® Breezhaler®	LAMA+LABA+ICS	SME	Asthma	Novartis
ORAVI®	Antifungal agent miconazole	SME	Oropharyngeal candidiasis	Fujifilm
Imaradenant	Adenosine A2a ant. combo	SME	mCRPC	AstraZeneca
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
BHV3100	CGRP antagonist	SME	Neurology diseases	Biohaven
Not disclosed	GPR35 agonist	SME	Inflammatory bowel disease	GSK
Not disclosed	Multi target	SME	Multiple indications	Pfizer
Not disclosed	Multi target	SME/LME	Multiple indications	Genentech
Not disclosed	Multi target	SME/LME	Gastrointestinal and other	Takeda
Not disclosed	Single target	SME	Inflammatory diseases	AbbVie
Co-development / Profit-share Collaborations				
KY1051	CXCR4 mAb	mAb	Immuno-oncology	Sanofi / Kymab
Not disclosed	PAR-2	Peptide	Inflammatory diseases	PeptiDream
Not disclosed	Targeted Protein Degradation	SME	Gastrointestinal disorders	Captor Therapeutics
Not disclosed	AI-Augmented Drug Discovery	SME	Neurology diseases	Pharmenable
Not disclosed	Ion Channel Drug Discovery	SME	Neurology diseases	Metrion Biosciences
Not disclosed	Multi target AI-powered	SME	Immune diseases	Inveni AI
Co-owned investments				
TMP301	mGlu5 NAM	SME	Substance use disorders	Tempero Bio
Not disclosed	OX1/OX2 agonist(oral and intranasal)	SME	Narcolepsy	Centessa / Orexia Therapeutics

Note: SME = small molecule. LME = large molecule. Seebri®, Ultibro®, Enerzair® and Breezhaler® are registered trademarks of Novartis AG.

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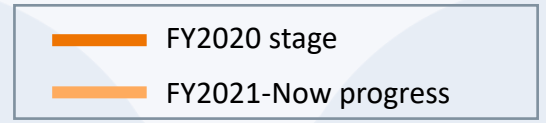
Progression of In-house Pipeline



Compound	Target / Mechanism of Action	Modality	Indication	Originator	Dis	PCC	Ph1	Ph2	Ph3	App	Mkt.
In-house Programs (Not yet partnered)											
HTL'878	Muscarinic M4 agonist	SME	Neurology diseases	sosei HEPTARES							
HTL'318 [1]	Muscarinic M1 agonist	SME	Neurology diseases	sosei HEPTARES							
HTL'936	Muscarinic M1 agonist	SME	Neurology diseases	sosei HEPTARES							
Not disclosed	Muscarinic M1 agonist (B/U)	SME	Neurology diseases	sosei HEPTARES							
Not disclosed	Muscarinic M4 agonist (B/U)	SME	Neurology diseases	sosei HEPTARES							
Not disclosed	Muscarinic M1/M4 agonist	SME	Neurology diseases	sosei HEPTARES							
Not disclosed	H4 antagonist	SME	Atopic Dermatitis	sosei HEPTARES							
Not disclosed	EP4 antagonist	SME	Immuno-oncology	sosei HEPTARES							
Not disclosed	GPR52 agonist	SME	Neurology diseases	sosei HEPTARES							
Not disclosed	PAR-2 mAb	mAb	Atopic Dermatitis	sosei HEPTARES							
SH-879	SARS CoV-2 Mpro	SME	Coronaviruses	sosei HEPTARES							
Not disclosed	EP4 agonist	SME	Inflammatory bowel disease	sosei HEPTARES							
Multiple programs	Not disclosed	SME/LME	Neurology diseases	sosei HEPTARES							
Multiple programs	Not disclosed	SME/LME	GI and Inflammatory diseases	sosei HEPTARES							
Multiple programs	Not disclosed	SME/LME	Immunology diseases	sosei HEPTARES							
In-house Programs (No longer internally funded. Targeting academic / industrial partnership)											
HTL'310	SSTR5 agonist	Peptide	Hypoglycaemic disorders	sosei HEPTARES							
HTL'097	GLP-1 antagonist	Peptide	Hypoglycaemic disorders	sosei HEPTARES							
HTL'023	Dual GLP-2/GLP-1 agonist	Peptide	Intestinal failure / NASH	sosei HEPTARES							
Not disclosed	Apelin agonist	Peptide	Pulmonary Arterial Hypertension	sosei HEPTARES							
HTL'641	Dual orexin antagonist	SME	Insomnia and sleep disorders	sosei HEPTARES							

Note: SME = small molecule. LME = large molecule. [1] Voluntarily suspended

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M_4R PAM less likely to be successful in DRP than an M_4R Agonist

- CVL-231 probability of success in dementia remain uncertain as cholinergic system significantly altered
- Xanomeline did show efficacy in psychotic symptoms in Alzheimer's Disease, providing validation for an agonist

- **Is there sufficient ACh tone in AD or will the patient population be too heterogeneous for a PAM to work?**
- **DRP is most prominent in moderate to severe AD where ACh deficiency greatest – a PAM is unlikely to work in this setting?**
- **Merck M_1R PAM had positive data in Phase 1 in volunteers but failed in AD**

	KARUNA THERAPEUTICS	cerevel	sosei HEPTARES
Lead Program	KarXT Fixed dose combination of xanomeline + trospium	CVL-231	HTL'878
Pharmacological approach to tolerability	Mixed muscarinic agonist and peripheral antagonist (combination product)	Pure M_4R Positive Allosteric Modulator	Pure M_4R orthosteric partial agonist
Rationale	Peripheral antagonist **masks** some of the poorly tolerated muscarinic side effects of mixed agonists. **Brings** kinetics and tolerability probs.	**Avoids** non-M_4R muscarinic side effects. *Cannot* reduce peripheral M_4R cardiovascular effects.	**Avoids** non-M_4R muscarinic side effects. *Might* reduce peripheral M_4R cardiovascular effects.
Status	Lilly data on Xanomeline showed positive POC in a small AD trial Strong, positive efficacy data ✓ Significant, GI Adverse Events ✗	PAM cannot produce M_4R system stimulation in this patient group due to the lack of cholinergic tone? ✗ Will CV effects be tolerable in a frail elderly population? ✗	Ready for phase 2; ✓ Well-tolerated dose and regimen for Phase 2 established by thorough Phase 1 ✓

Source: Bymaster et al, DRUG DEVELOPMENT RESEARCH 40:158–170 (1997)

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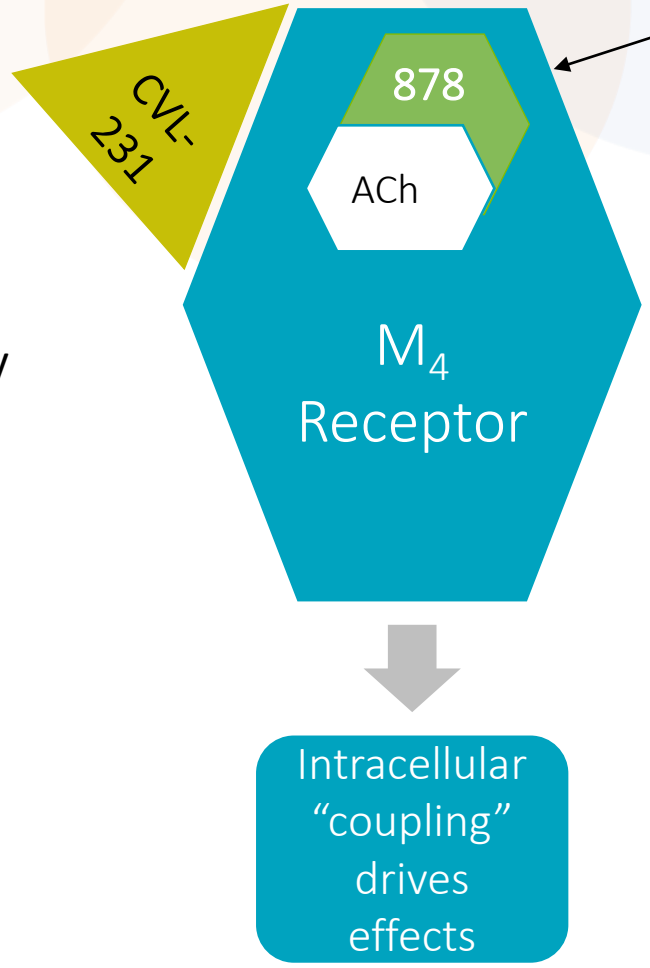
Sosei Heptares M_4R Receptor Orthosteric Partial Agonist HTL'878

- Potentially superior clinical profile compared to a PAM such as CVL-231
- Superior selectivity profile to KarXT

PAM binding to allosteric site, traps ACh slowing its off-rate, potentiating the full agonist response

HTL'878 binds to a partial agonist receptor conformation acting as a replacement for Ach
' 878 distributes well to brain (Ph I data)



- A PAM such as CVL-231 requires ACh to be present to have efficacy
- ACh release in DRP is reduced and a PAM will have less effect
- **PAM unlikely effective in DRP**
- Central and peripheral receptors affected identically, will also drive effects in the periphery
- **Peripheral AEs are unavoidable**

HTL'878 is a highly selective partial agonist :

- Specific activation of the M_4R without the need for Ach – **More effective in DRP**
- Better control of ACh release to modulate DA
- No unwanted effects from M_1, M_2, M_3 or M_5 receptors due to high selectivity
- Partial agonist drives well coupled central effects with reduced effects on peripheral less-well coupled systems
- **Separation of central and peripheral effects focussing M_4R effects in the brain**

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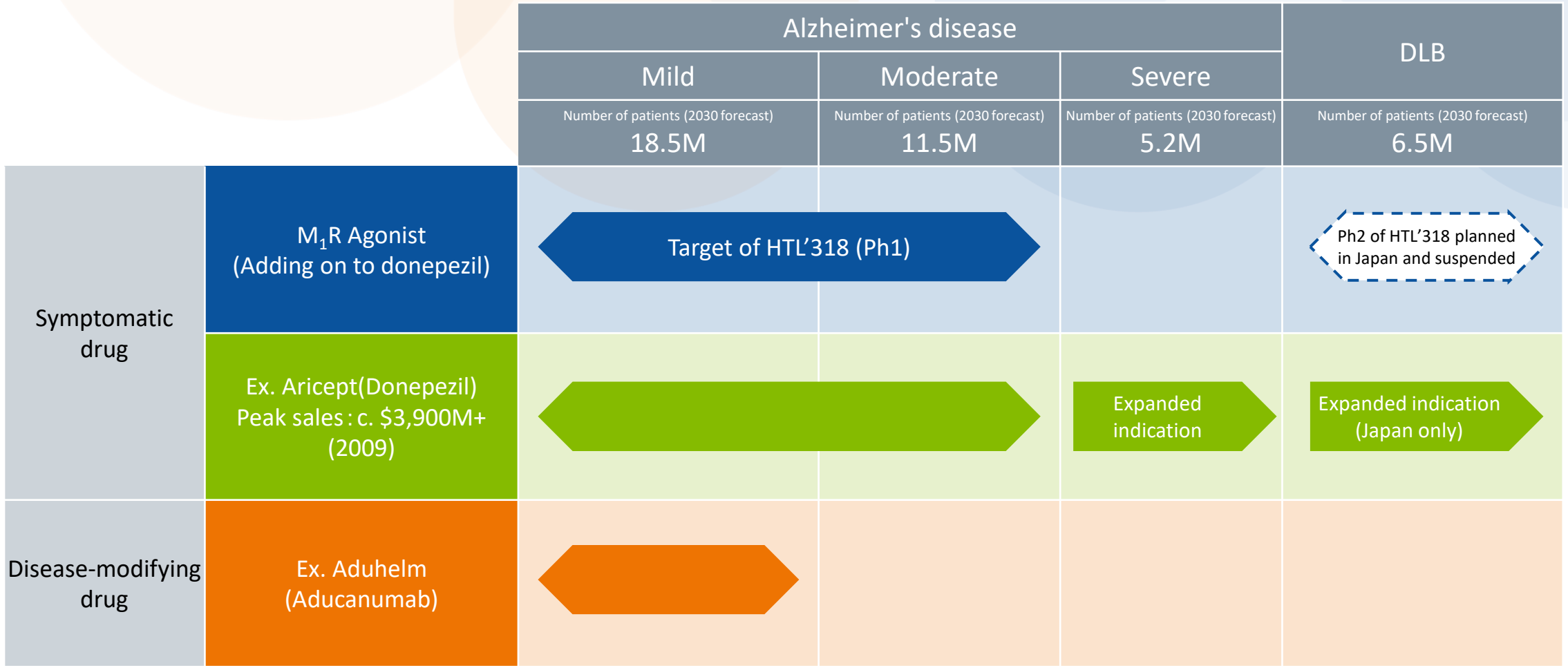
Potential Market of M_1 Ag

Adding on to Donepezil (standard therapy, peak sales was $3,9BN+), potential to be best in class



Source : EvaluatePharma

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