

Value Creation at Alkermes: Focused on Innovation, Growth and Profitability

August 2021



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Forward-Looking Statements

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Alkermes' Distinctive Mission



**Advance cutting-edge science, develop innovative medicines, and
engage in patient-focused advocacy to help address critical public health challenges**

Focus on Value Creation in 2021: Three Key Components

1

Grow and Diversify Commercial Revenues

- Drive VIVITROL® and ARISTADA® net sales
- Support VUMERITY® growth
- Launch LYBALV®

2

Demonstrate Value of R&D Investments

- Nemvaleukin alfa
 - Demonstrate anti-tumor activity
 - Determine registration pathway
 - Explore strategic collaborations
- ALKS 1140 (CoREST-selective HDAC inhibitor)
 - Initiate phase 1/FIH study
- Advance portfolio of preclinical neuroscience and oncology candidates

3


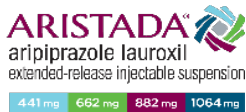


Manage for Growth & Long-Term Profitability

- Operationalize commitment to profitability targets
- Optimize cost structure and drive operating leverage
- Explore strategic opportunities to maximize value and enhance profitability

CoREST: co-repressor of repressor element-1 silencing transcription factor
FIH: first-in-human; HDAC: histone deacetylase

Grow and Diversify
Commercial Revenues

Expected Growth Drivers

		Indications	2020 Net sales CAGR	Patent Life
Proprietary Products		Alcohol dependence (AD) Prevention of relapse to opioid dependence (OD) following opioid detoxification	\$311M 23% 2015-2019*	2029**†
		Schizophrenia	\$241M 50% 2016-2020	2035
		Schizophrenia Bipolar I disorder	Launch expected in Q4'21	2032
Licensed Product (royalty & manufacturing revenue)		Relapsing forms of multiple sclerosis (MS)	\$23M Launched in Q4'19	2033†

* CAGR reported for VIVITROL reflects time period prior to impact of COVID-19.

**Under the terms of a settlement and license agreement entered into in July 2019 with Amneal Pharmaceuticals LLC ("Amneal"), Alkermes granted Amneal a non-exclusive license under certain patents covering VIVITROL, including the remaining patent covering VIVITROL in the U.S., to market and sell a generic formulation of VIVITROL in the U.S. beginning sometime in 2028 or earlier under certain circumstances.

† Subject to Paragraph IV litigation related to an abbreviated new drug application seeking FDA approval of a generic version.

Full prescribing information for VIVITROL, ARISTADA and LYBALVI, including boxed warnings for ARISTADA and LYBALVI, may be found at www.vivitrol.com/content/pdfs/prescribing-information.pdf, www.aristada.com/downloadables/ARISTADA-PI.pdf and www.lybalvi.com/lybalvi-prescribing-information.pdf, respectively.

VIVITROL®: Distinctive Product for a Major Public Health Need

- Extended-release opioid antagonist provides therapeutic levels of naltrexone for a one-month period
- Indicated for the treatment of alcohol dependence
- Indicated for the prevention of relapse to opioid dependence, following opioid detoxification

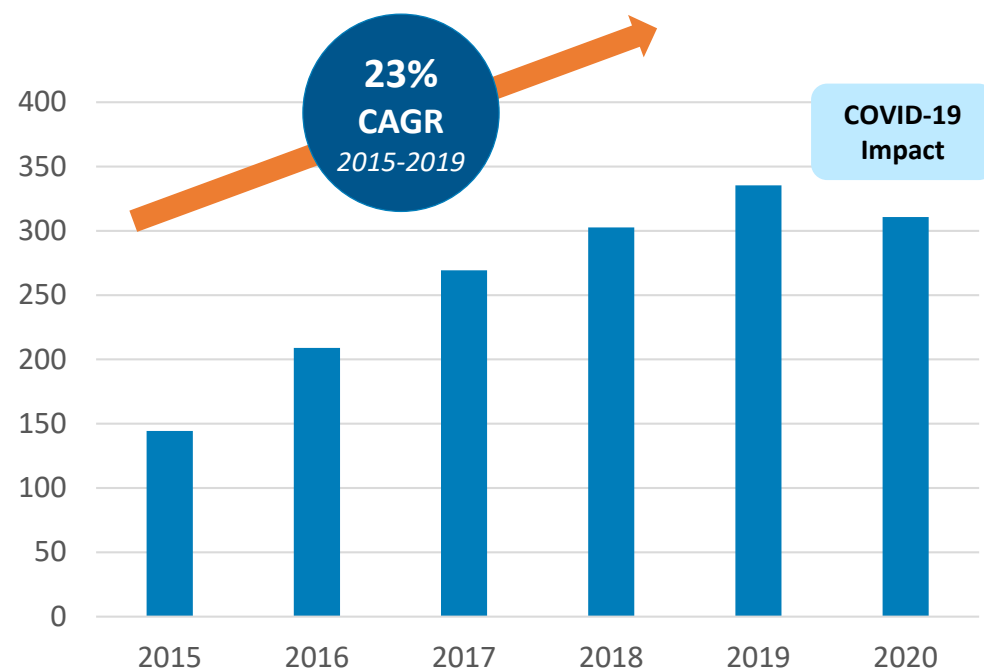
Vivitrol[®]
(naltrexone for extended-release
injectable suspension)



Full prescribing information for VIVITROL may be found at www.vivitrol.com/content/pdfs/prescribing-information.pdf

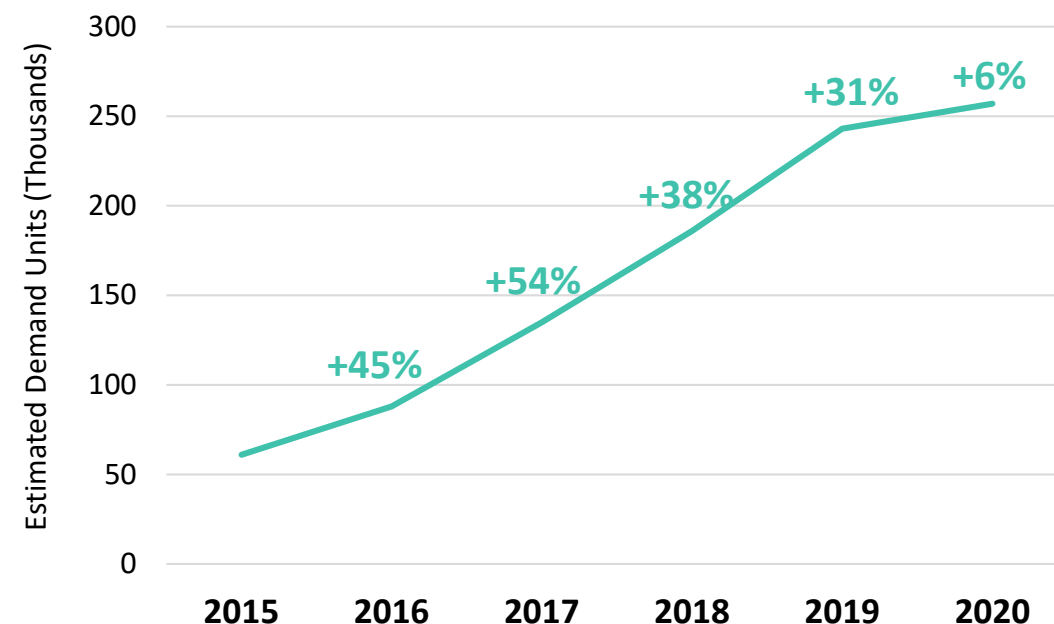
VIVITROL®: Growth in Opioid Dependence and Alcohol Dependence

VIVITROL Net Sales (\$M)



COVID-19 interrupted 5 consecutive years of strong brand growth

VIVITROL Growth in Alcohol Dependence



Alcohol dependence indication – strong source of recent growth

ARISTADA®: LAI for Schizophrenia With Dosing Flexibility

- Long-acting injectable (LAI) atypical antipsychotic indicated for the treatment of schizophrenia
- Novel molecular entity designed to address the real-world needs of patients and providers in the community
- Ability to fully dose on day one for up to two months with ARISTADA INITIO® regimen*

**ARISTADA
INITIO®**
aripiprazole lauroxil
extended-release injectable suspension

675 mg

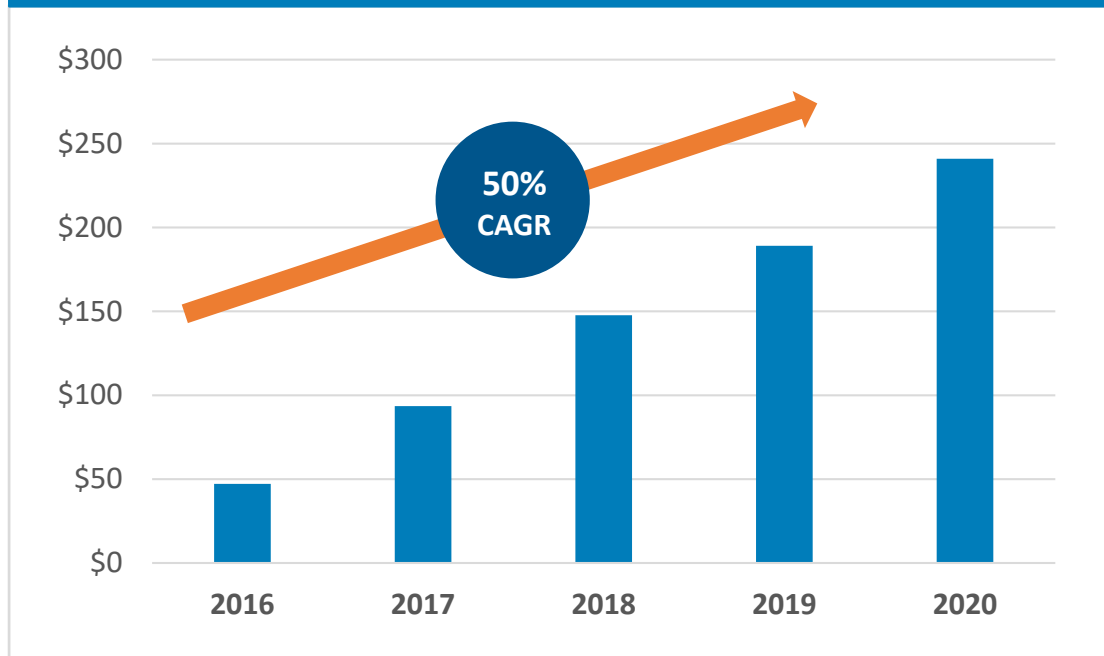
ARISTADA®
aripiprazole lauroxil
extended-release injectable suspension
441mg • 662mg • 882mg • 1064mg



*ARISTADA INITIO + single 30 mg oral dose of aripiprazole replaces need for concomitant three weeks of oral aripiprazole for initiation of ARISTADA. The first ARISTADA dose may be administered on the same day as ARISTADA INITIO or up to 10 days thereafter. Full prescribing information for ARISTADA, including boxed warning, may be found at www.aristada.com/downloadables/ARISTADA-PI.pdf

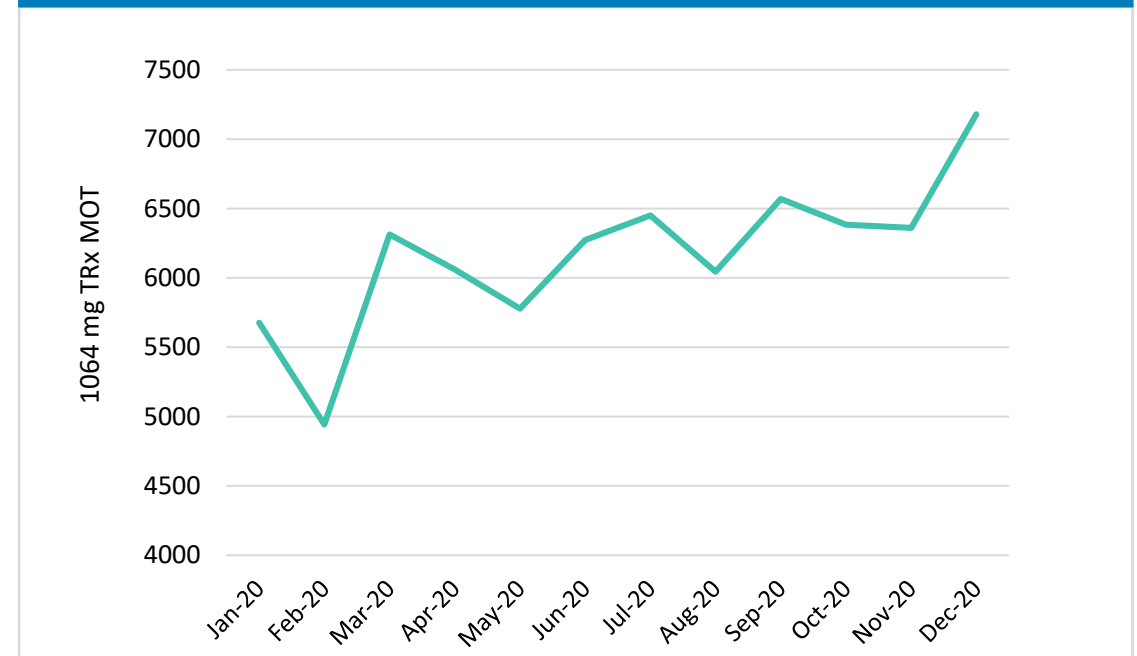
ARISTADA®: Strong Growth Driven by Two-Month Dose

ARISTADA Net Sales* (\$M)



Strong performance reflects favorable product characteristics


ARISTADA 1064 mg TRx MOT increased ~50% in 2020**

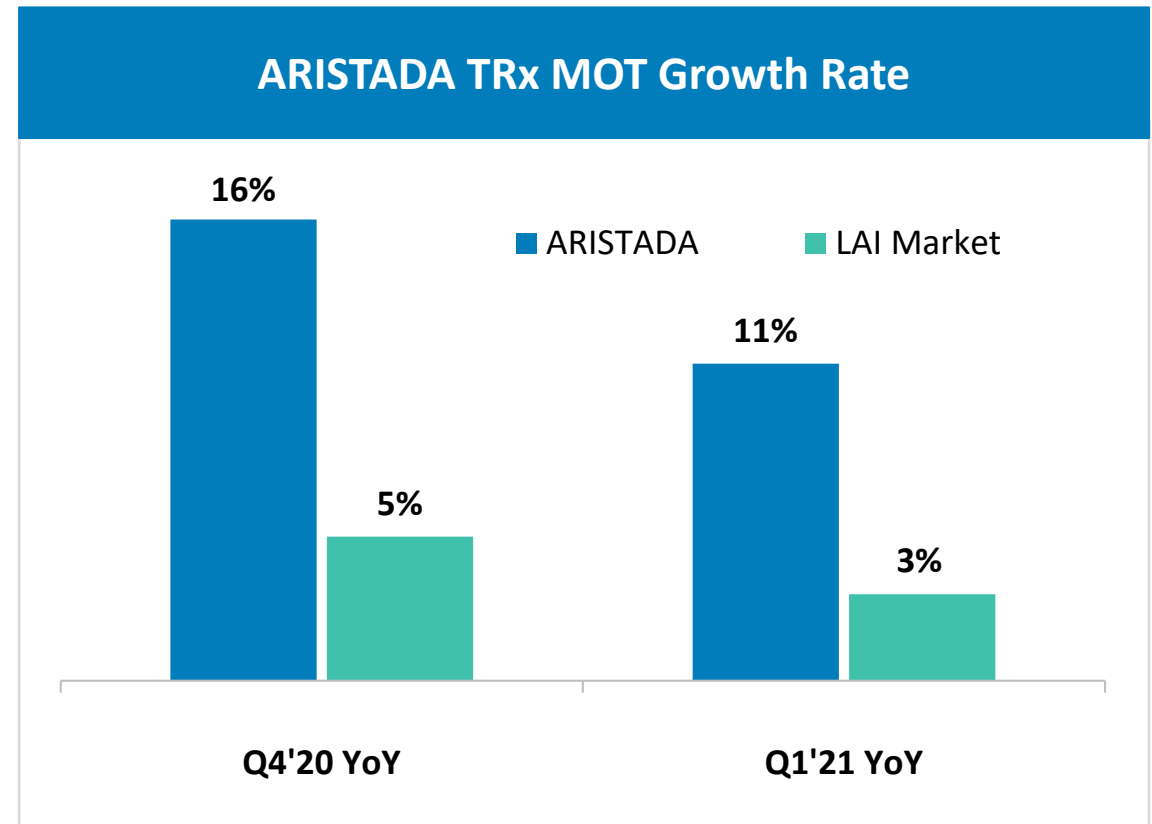


Growth of 2-month 1064 mg dose reflects differentiated value proposition

*Inclusive of ARISTADA INITIO®; **TRx Data: IQVIA NPA data Dec R3; MOT: Months of therapy

ARISTADA®: Growth Outpaced Atypical Long-Acting Injectable (aLAI) Antipsychotic Market

	 aLAIs
Branded Market Size*	~\$3.5B
Annual TRx**	~2M
Market Share**	9% ARISTADA MOT Share



*Includes ARISTADA, ABILIFY MAINTENA®, INVEGA SUSTENNA/TRINZA®, RISPERDAL CONSTA® and PERSERIS®.

** IQVIA NPA Audit.

MOT: Months of therapy

LYBALVI®: Once-Daily, Oral Atypical Antipsychotic

**NOW
APPROVED**

**For the treatment of adults with
schizophrenia or bipolar I disorder**

NEW **LYBALVI**™
olanzapine and samidorphan
5mg/10mg-10mg/10mg-15mg/10mg-20mg/10mg tablets

Full prescribing information, including boxed warning, for LYBALVI may be found at www.lybalvi.com/lybalvi-prescribing-information.pdf

LYBALVI®: Anticipated New Revenue Stream in Oral Atypical Antipsychotic Market

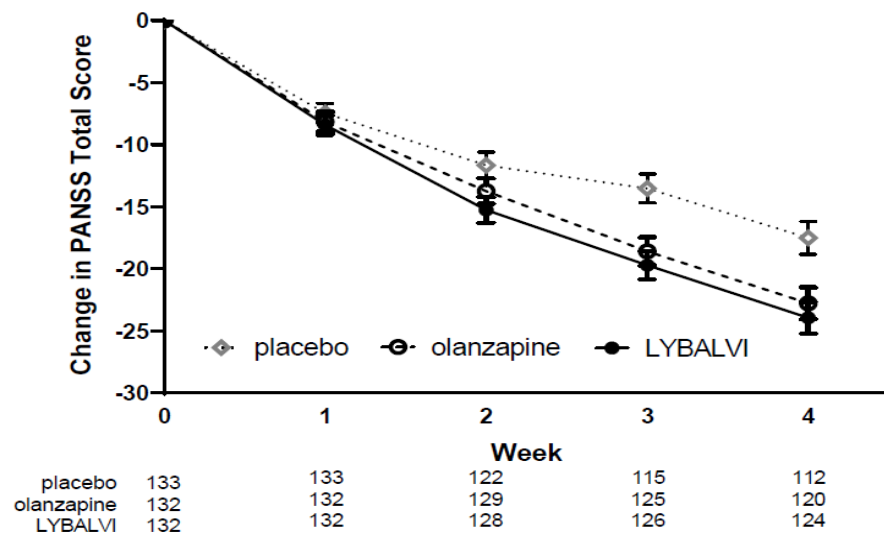
- Once-daily, oral atypical antipsychotic composed of olanzapine, an established antipsychotic agent, and samidorphan, a new chemical entity
- Approved for the treatment of adults with schizophrenia and for the treatment of adults with bipolar I disorder, as a maintenance monotherapy or for the acute treatment of manic or mixed episodes, as monotherapy or an adjunct to lithium or valproate
- Planned launch Q4 2021



Full prescribing information, including boxed warning, for LYBALVI may be found at www.lybalvi.com/lybalvi-prescribing-information.pdf

LYBALVI®: Antipsychotic Efficacy in Patients With Schizophrenia

Figure 4: Change from Baseline in PANSS Total Score by Time (Week) in Patients with Schizophrenia (Study 1)



ENLIGHTEN-1 phase 3 study:

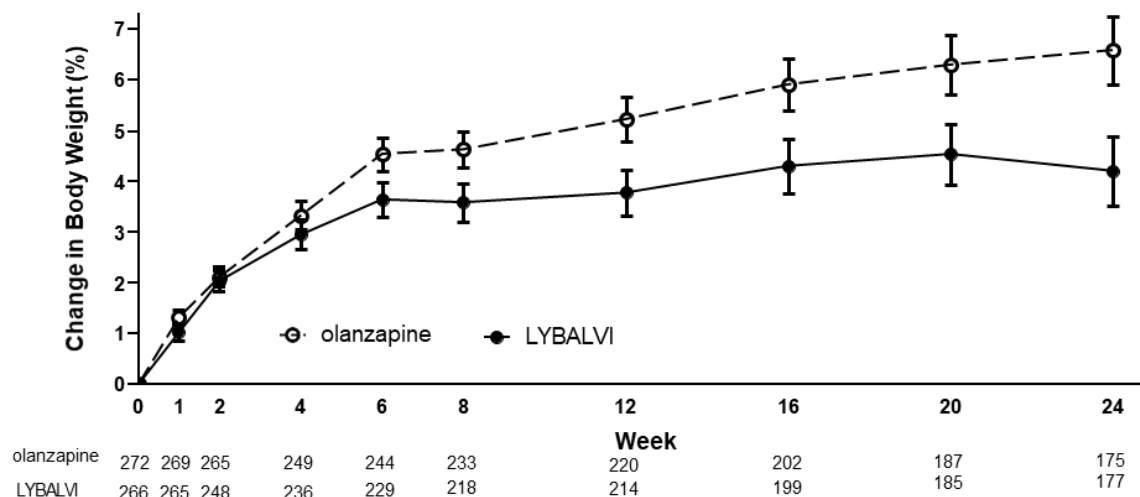
- Evaluated antipsychotic efficacy and safety of LYBALVI versus placebo over four weeks in patients experiencing an acute exacerbation of schizophrenia
- Met primary endpoint: LYBALVI demonstrated statistically and clinically significant improvement in PANSS total score from baseline at week 4 vs placebo
- Improvement in PANSS score was similar to that observed with olanzapine

PANSS: Positive and Negative Syndrome Scale

Full prescribing information, including boxed warning, for LYBALVI may be found at www.lybalvi.com/lybalvi-prescribing-information.pdf

LYBALVI®: Less Weight Gain Compared to Olanzapine in Patients With Schizophrenia

Figure 5: Percent Change from Baseline in Body Weight by Time (Week) in Patients with Schizophrenia (Study 2)



ENLIGHTEN-2 phase 3 study:

- Evaluated weight gain profile of LYBALVI compared to olanzapine over six months in patients with stable schizophrenia
- At week 24, treatment with LYBALVI was associated with:
 - Statistically significantly less weight gain compared to baseline than treatment with olanzapine
 - Statistically significantly lower proportion of patients who gained $\geq 10\%$ body weight compared to patients treated with olanzapine
- Patients treated with LYBALVI had half the risk of gaining $\geq 10\%$ and $\geq 7\%$ of their baseline body weight compared to patients treated with olanzapine

Full prescribing information, including boxed warning, for LYBALVI may be found at www.lybalvi.com/lybalvi-prescribing-information.pdf

LYBALVI® Important Safety Information

Boxed Warning: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LYBALVI is not approved for the treatment of patients with dementia-related psychosis

Contraindications: LYBALVI is contraindicated in patients using opioids, patients undergoing acute opioid withdrawal and, if administered with lithium or valproate, patients for whom contraindications for those products apply

Warnings and Precautions:

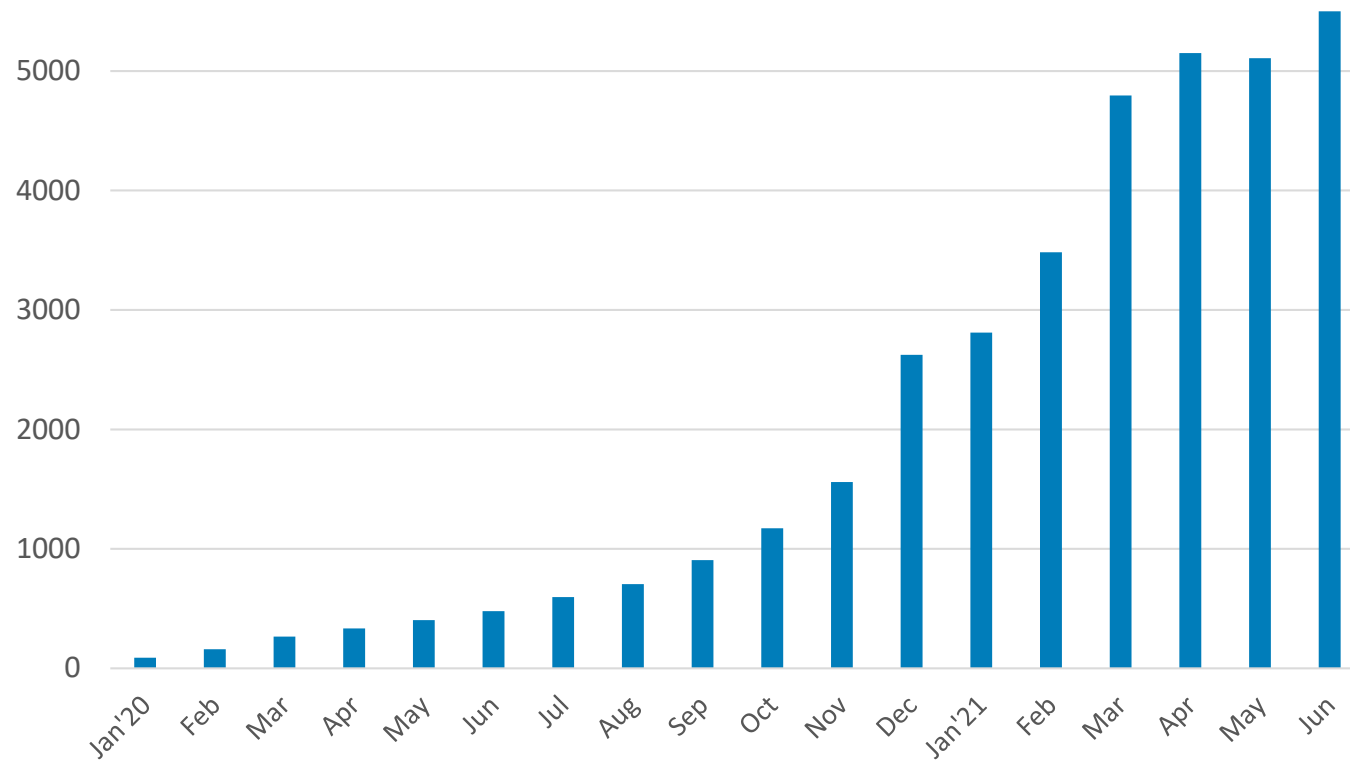
- *Cerebrovascular adverse reactions in elderly patients with dementia-related psychosis* (e.g., stroke, transient ischemic attack, including fatalities)
- *Precipitation of opioid withdrawal in patients who are physiologically dependent on opioids.*⁺ An opioid-free duration is recommended before initiating LYBALVI
- *Vulnerability to life-threatening opioid overdose*⁺:
 - *Risk of opioid overdose from attempts to overcome LYBALVI opioid blockade:* Attempts to overcome LYBALVI opioid blockade with high or repeated doses of opioids may lead to fatal opioid intoxication, particularly if LYBALVI therapy is interrupted or discontinued
 - *Risk of resuming opioids in patients with prior opioid use:* Patients with a history of chronic opioid use prior to LYBALVI treatment may have decreased opioid tolerance if LYBALVI therapy is interrupted or discontinued
- *Neuroleptic malignant syndrome*, with symptoms including hyperpyrexia, muscle rigidity, delirium, autonomic instability, elevated creatinine phosphokinase, myoglobinuria and acute renal failure
- *Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)*, with symptoms including cutaneous reaction, eosinophilia, pneumonitis, myocarditis and/or pericarditis
- *Metabolic changes*, including hyperglycemia, diabetes mellitus, dyslipidemia and weight gain
- *Tardive dyskinesia*, a syndrome of potentially irreversible, involuntary, dyskinetic movements
- *Orthostatic hypotension and syncope*
- *Falls.* LYBALVI may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures and other injuries
- *Leukopenia, neutropenia, and agranulocytosis*
- *Dysphagia*
- *Seizures*
- *Potential for cognitive and motor impairment*
- *Body Temperature Dysregulation*
- *Anticholinergic (antimuscarinic) effects*, including constipation, dry mouth and tachycardia
- *Hyperprolactinemia*

Most Common Adverse Reactions:

- *Schizophrenia (LYBALVI):* weight increased, somnolence, dry mouth, headache
- *Bipolar I Disorder, Manic or Mixed Episodes (olanzapine):* asthenia, dry mouth, constipation, increased appetite, somnolence, dizziness, tremor
- *Bipolar I Disorder, Manic or Mixed Episodes, adjunct to Lithium or Valproate (olanzapine):* dry mouth, dyspepsia, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, paresthesia

VUMERITY® Growth Presents Additional Long-Term Revenue Opportunity

VUMERITY Monthly TRx*



- Novel oral fumarate for the treatment of relapsing forms of multiple sclerosis (MS)
- Biogen holds exclusive, worldwide license to commercialize
- **15%** royalty to Alkermes on worldwide net sales
- ~\$8B oral MS market*

*IQVIA NPA TRx data.

Demonstrate Value of R&D Investments

R&D Objective: Novel Drug Development With Differentiated and Contemporary Approach



Employ integrated approach to target selection, development and lifecycle management with continuous evaluation of medical and economic value



Leverage advanced medicinal chemistry and protein engineering capabilities to develop novel molecular entities with strong intellectual property protection



De-risk programs with front-end loaded development plans utilizing forward- and reverse-translational medicine strategies

Scientific Platforms Serve as Foundation to R&D Strategy and Focus in Neuroscience and Oncology

Neuroscience

Synaptic Dysfunction

HDAC
Inhibitors

Orexin
Agonist

Oncology

Immune Modulation

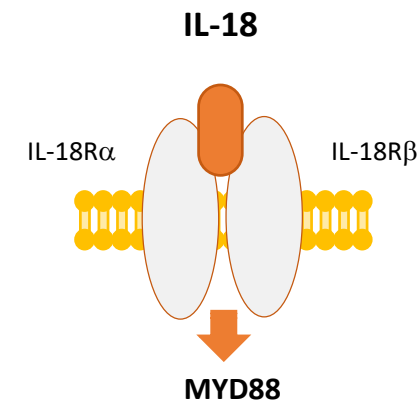
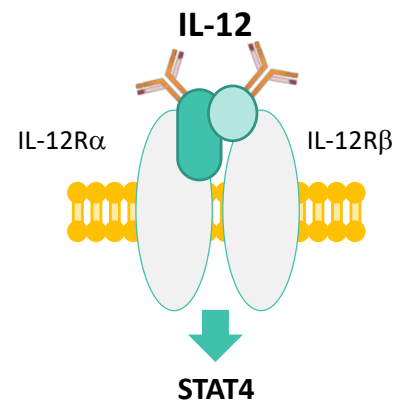
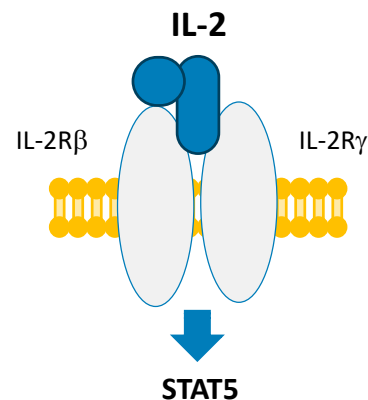
Engineered
Cytokines

HDAC: histone deacetylase

Oncology: Immune Modulation



Immune Modulation Portfolio of Engineered Cytokines



	Nemvaleukin alfa	Tumor-Targeted Split IL-12	Enhanced Efficacy IL-18
Technical challenge	<ul style="list-style-type: none"> Efficacy of rhIL-2 limited by expansion of immunosuppressive T_{reg} cells and other undesirable effects 	<ul style="list-style-type: none"> rhIL-12 has low tolerability when given systemically 	<ul style="list-style-type: none"> Efficacy of rhIL-18 limited by a checkpoint protein that binds to IL-18 (IL-18BP)
Alkermes' protein engineering solution	<ul style="list-style-type: none"> Fusion of circularly permuted IL-2 with the IL-2Rα subunit resulting in only activating intermediate-affinity IL-2R 	<ul style="list-style-type: none"> Separate inactive tumor-targeted IL-12 subunits assemble and activate in the tumor 	<ul style="list-style-type: none"> Engineered IL-18, for which activity is not blocked by suppressive mechanisms
Key anti-tumor mechanisms	<ul style="list-style-type: none"> Expansion of CD8⁺ T cells and NK cells Minimal expansion of T_{reg} cells 	<ul style="list-style-type: none"> Drive proinflammatory responses at the tumor site through potent activation of CD8⁺ T and NK cells 	<ul style="list-style-type: none"> Enhance IL-18 mediated anti-cancer immune responses Reduce T cell exhaustion
Potential cancer types	<ul style="list-style-type: none"> Solid tumors, including melanoma, platinum-resistant ovarian cancer 	<ul style="list-style-type: none"> Solid tumors, including pancreatic, breast, colon and ovarian cancer 	<ul style="list-style-type: none"> Immunosuppressive tumor microenvironment Checkpoint inhibitor-resistant tumors

Nemvaleukin Alfa (“Nemvaleukin”): Unique Cytokine Designed to Harness Validated IL-2 Pathway Biology

Design derives from natural biology, utilizing native IL-2 and IL-2R α sequences to confer differentiated properties

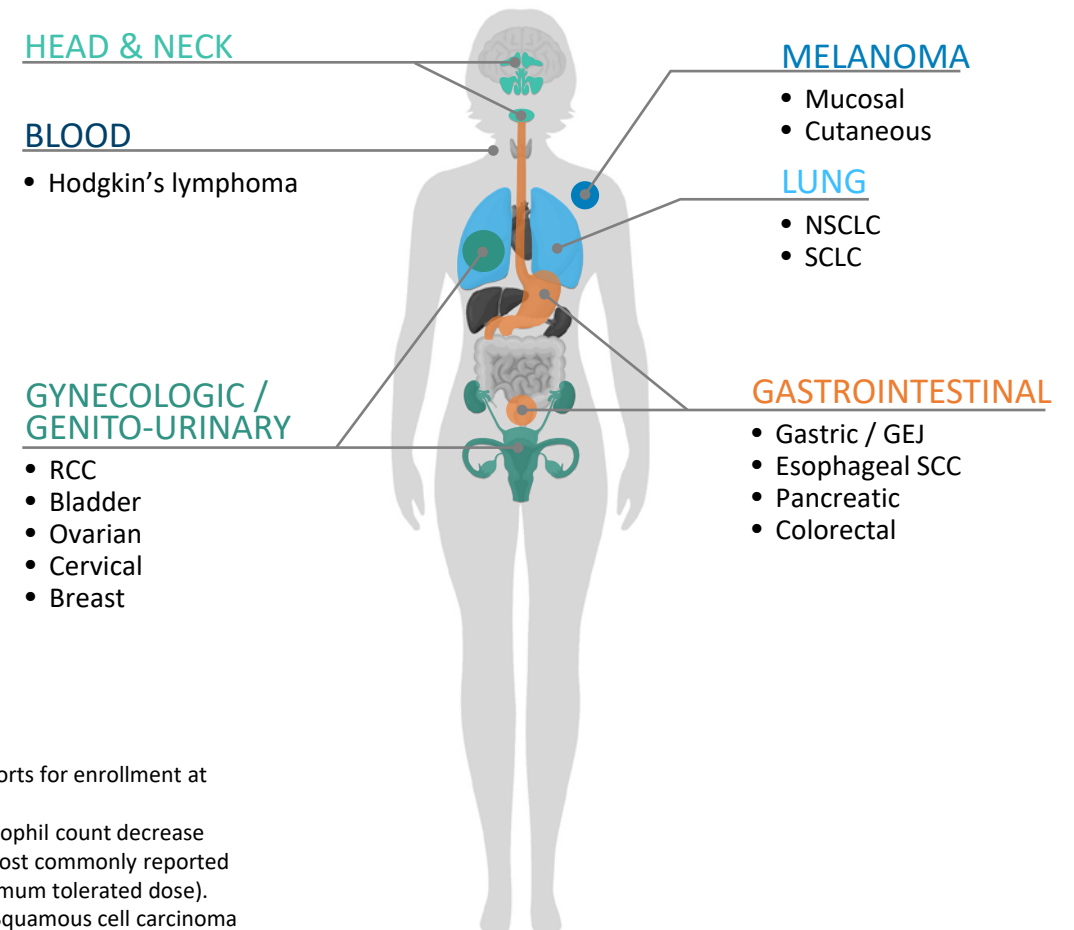
- **Inherently active, stable fusion protein:** Does not require metabolic or proteolytic conversion; does not degrade to native IL-2

Demonstrated **durable and deepening responses** in high unmet need populations with **monotherapy** and in **combination with pembrolizumab** in a range of tumors

- Treatment-related adverse events (AEs) across the program have been consistent with expectations based on nemvaleukin’s mechanism of action and were mostly transient and manageable**

Differentiated and rapidly advancing clinical development program in high unmet need, difficult-to-treat populations, including patients with checkpoint inhibitor (CPI)-unapproved tumor types and in post-CPI settings

Monotherapy and Combination Responses*



*Includes one response from ARTISTRY-2 study evaluating subcutaneous nemvaleukin, which has recently opened expansion cohorts for enrollment at the recommended phase 2 dose.

**ARTISTRY-1: Pyrexia, chills and nausea were the most commonly reported AEs. Transient and asymptomatic neutropenia/neutrophil count decrease were the most commonly reported events of grade ≥ 3 ; ARTISTRY-2: Pyrexia, fatigue, chills and injection site reactions were the most commonly reported AEs. Three dose-limiting toxicities were reported, all in the highest doses evaluated in each dosing regimen (declared as the maximum tolerated dose). NSCLC: Non-Small Cell Lung Cancer; SCLC: Small Cell Lung Cancer; RCC: Renal cell carcinoma; GEJ: Esophagogastric junction; SCC: Squamous cell carcinoma

Overview of Nemvaleukin Clinical Development Program

ARTISTRY-1 Phase 1/2	<ul style="list-style-type: none"> Intravenous (IV) nemvaleukin as monotherapy and in combination with pembrolizumab Monotherapy cohorts: anti-PD-1/L1-experienced melanoma and renal cell carcinoma Combination cohorts: multiple solid tumor types (including PD-1/L1 approved and unapproved)
ARTISTRY-2 Phase 1/2	<ul style="list-style-type: none"> Subcutaneous (SC) nemvaleukin dose escalation and dose expansion Phase 2 dose expansion cohorts in combination with pembrolizumab: NSCLC, HNSCC, gastric/gastroesophageal junction adenocarcinoma, platinum-resistant ovarian cancer
ARTISTRY-3 Phase 2	<ul style="list-style-type: none"> IV nemvaleukin as monotherapy and in combination with pembrolizumab Assessment of treatment-emergent changes in TME in paired biopsies and clinical anti-tumor activity
ARTISTRY-6 Phase 2	<ul style="list-style-type: none"> Monotherapy nemvaleukin in anti-PD-1/L1 experienced melanoma patients IV administration in advanced mucosal melanoma SC administration in advanced cutaneous melanoma
ION-01 Phase 2	<ul style="list-style-type: none"> IV nemvaleukin in combination with pembrolizumab in anti-PD-1/L1 pretreated HNSCC patients Assessment of TME in paired biopsies; predictive biomarker assessments; anti-tumor activity Collaboration with the Fred Hutchinson Cancer Research Center
ARTISTRY-7 Phase 3	<ul style="list-style-type: none"> IV nemvaleukin in combination with pembrolizumab in patients with platinum-resistant ovarian cancer, compared to investigator choice chemotherapy Planned to begin H2 2021 Clinical trial and supply agreement with MSD (a tradename of Merck & Co., Inc. Kenilworth, NJ, USA)

NSCLC: Non-small cell lung cancer; HNSCC: Head and neck squamous cell carcinoma; TME: Tumor Microenvironment; PD-1: programmed cell death protein 1

ARTISTRY-1 Safety Summary

- Safety profile of IV nemvaleukin in combination with pembrolizumab generally consistent with monotherapy profile
- In combination, no evidence of additive toxicities has emerged beyond those already established for pembrolizumab alone

Monotherapy (Part B only; n=62)

- Chills, pyrexia, nausea and hypotension were most frequently (>30%) reported treatment-emergent adverse events (TEAEs); consistent with anticipated effects of cytokine administration
 - Transient, majority Grade ≤ 2 in severity
- Most frequent (>10%) Grade 3-4 treatment-related adverse event (TRAE) was neutropenia
- No deaths due to TRAEs
- Two patients discontinued due to TRAEs (Grade 3 bronchospasm and Grade 3 failure to thrive)

Combination with Pembrolizumab (Part C only; n=128)

- Chills, pyrexia, nausea and fatigue were most frequently (>30%) reported TEAEs; consistent with anticipated effects of cytokine and/or pembrolizumab administration
 - Transient, majority Grade ≤ 2 in severity
- Most frequent (>10%) Grade 3-4 TRAEs were anemia and neutrophil count decrease
- Discontinuations due to TRAEs included: Grade 3 fatigue, Grade 3 pneumonitis, Grade 2 infusion-related reaction (IRR), Grade 5 inanition
- One death due to TRAE (reported at ESMO 2020): Death due to inanition in a pancreatic cancer patient

Data as of March 19, 2021

ARTISTRY-1: IV Nemvaleukin Monotherapy Anti-Tumor Activity in Melanoma

Tumor Type	Number of Prior Therapies*	Best Overall Response	Max Decrease in Target Lesions	Time on Therapy (Weeks)	Continued on Therapy?
Mucosal melanoma	1	PR	44%	79	Yes
Mucosal melanoma	1	uPR	39%	16	No [†]
Cutaneous melanoma	4	uPR	44%	19	Yes Rolled over to Part C combination treatment
Cutaneous melanoma	2	PR, awaiting confirmation	35%	13	Yes

* For full list of prior therapies, please see poster entitled 'ARTISTRY-1: Nemvaleukin Alfa Monotherapy and in Combination With Pembrolizumab in Patients With Advanced Solid Tumors' from the 2021 ASCO Annual Meeting;

[†] Patient discontinued therapy following progressive disease

PR: Partial response; uPR: Unconfirmed partial response

Data cut off May 3, 2021

ARTISTRY-1: IV Nemvaleukin in Combination With Pembrolizumab

PD-1/L1 Unapproved Tumor Types

Tumor Type		Number of Prior Therapies*	Best Overall Response	Max Decrease in Target Lesions	Time on Therapy (Weeks)	Continued on Therapy?
Nemvaleukin (3 µg/kg) + pembrolizumab (200 mg)						
PD-1/L1 Unapproved Tumor Types	Platinum-resistant ovarian	5	CR	70%	121	Yes
	Platinum-resistant ovarian	2	PR	95%	65	Yes
	Platinum-resistant ovarian	7	uPR	45%	34	No
	Platinum-resistant ovarian	6	PR	41%	55	Yes
	Triple negative breast	8	iPR	66%	95	No
	Pancreatic	3	PR	63%	17	No
	Esophageal SCC	1	PR	48%	58	Yes

Preliminary data (ongoing study):

- Out of the 14 evaluable patients with ovarian cancer
 - 1 complete response (CR) in a PROC patient
 - 3 PRs (1 unconfirmed) in PROC patients
 - 3 of the 4 PROC patients with objective responses had been on treatment for more than a year and continued on therapy
 - 6 had SD
- Partial responses were also observed in patients with esophageal, triple negative breast and pancreatic cancers

* For full list of prior therapies, please see poster entitled 'ARTISTRY-1: Nemvaleukin Alfa Monotherapy and in Combination With Pembrolizumab in Patients With Advanced Solid Tumors' from the 2021 ASCO Annual Meeting; iPR: Immune partial response; PR: Partial response; PROC: Platinum-resistant ovarian cancer; uPR: Unconfirmed partial response; SCC: Squamous cell carcinoma; SD: Stable disease

Data cut off May 3, 2021

ARTISTRY-1: IV Nemvaleukin in Combination With Pembrolizumab

PD-1/L1 Approved Tumor Cohort and Tumor-Specific Cohorts

Tumor Type		Number of Prior Therapies*	Best Overall Response	Max Decrease in Target Lesions	Weeks on Therapy	Continued on Therapy?
Nemvaleukin (3 µg/kg) + pembrolizumab (200 mg)						
PD-1/L1 Approved Tumor Types	Gastric/GEJ	4 (PD-1/L1 treatment naïve)	PR	52%	68	Yes
	Cervical	2 (PD-1/L1 treatment naïve)	PR	39%	41	Yes
	Cervical	1 (PD-1/L1 treatment naïve)	PR ^a	39%	28	Yes
	Bladder	1 (PD-1/L1 treatment naïve)	PR	59%	30	Yes
	Hodgkin's lymphoma	1 (PD-1/L1 treatment naïve)	PR	47%	31	Yes
	ER+/HER2- breast	3 (PD-1/L1 pretreated)	uPR	32%	16	No
	SCLC	2 (PD-1/L1 treatment naïve)	PR ^a	33%	20	Yes
	Colorectal	2 (PD-1/L1 treatment naïve)	PR ^a	35%	25	Yes
	Renal cell carcinoma (rollover)	2	PR	71%	5 (mono) + 36 (combo)	Yes
Nemvaleukin (6 µg/kg) + pembrolizumab (200 mg)						
	Mucosal melanoma	Treatment naïve	PR	100%	38	Yes
	Non-small-cell lung	3	PR	63%	25	Yes
	Head & neck SCC	1	PR ^a	45%	27	Yes

- Cervical cancer: Of 4 evaluable patients, 2 achieved PR (1 awaiting confirmation); 3 of the 4 patients continued on therapy
- Responses also observed in bladder, Hodgkin's lymphoma, breast, RCC, mucosal melanoma, head & neck, lung cancer

* For full list of prior therapies, please see poster entitled 'ARTISTRY-1: Nemvaleukin Alfa Monotherapy and in Combination With Pembrolizumab in Patients With Advanced Solid Tumors' from the 2021 ASCO Annual Meeting; ^a Awaiting confirmation ER+/HER2-: Estrogen Receptor+ Human Epidermal Growth Factor Receptor 2-; SCLC: Small cell lung cancer; GEJ: Esophagogastric junction; RCC: Renal cell carcinoma; SCC: Squamous cell carcinoma; PR: Partial response; uPR: Unconfirmed partial response

Data cut off May 3, 2021

ARTISTRY-1 Data Summary

IV nemvaleukin monotherapy activity was seen in CPI-experienced melanoma and RCC patients, consistent with its molecular design

- 2 PRs (1 unconfirmed) reported in mucosal melanoma; 2 PRs (1 unconfirmed, 1 awaiting confirmation) reported in cutaneous melanoma; 2 PRs (1 awaiting confirmation) reported in RCC

Combination activity of IV nemvaleukin with pembrolizumab has been observed across a broad range of tumor types, including in PD-1/L1 approved and unapproved tumors

- Durable and deepening responses observed in PROC: 1 CR, 3 PRs (1 unconfirmed); 3 of these 4 patients had been on treatment for more than a year and continued on therapy
- Objective responses observed in cervical cancer: 2 PRs (1 awaiting confirmation) out of 4 patients
- Objective responses also observed in esophageal, bladder, Hodgkin's lymphoma, breast, RCC, mucosal melanoma, gastric, pancreatic, head & neck, and lung cancer

In Parts B and C evaluating IV nemvaleukin as monotherapy or in combination with pembrolizumab, treatment-related adverse events were mostly transient and manageable

ARTISTRY-2: Safety Profile of Subcutaneous Nemvaleukin Consistent With Mechanism of Action and IV Nemvaleukin

RP2D Regimens Selected

SC **3 mg q7d** declared as RP2D based on totality of data

- 6 mg q21d dose may offer additional flexibility in treating certain tumor types and/or in combination settings in the future
- MTD for SC nemvaleukin determined to be 6 mg q7d and 10 mg q21d

Most Commonly Reported AEs at RP2D Monotherapy

3 mg q7d (n=7):

- Pyrexia, fatigue, nausea, anemia, chills, injection site reaction, and lymphopenia were most frequently (>30%) reported TEAEs;
 - Transient; majority anticipated effects of cytokine administration
- Most frequent (>10%) Grade 3-4 TRAEs were lymphopenia and neutrophil count decrease
- No treatment-related discontinuations or deaths

6 mg q21d (n=8):

- Safety profile was consistent with 3 mg q7d
- Most frequent (>10%) Grade 3-4 TRAEs were AST/ALT increase, arthralgia, neutropenia and fatigue
- No treatment-related discontinuations or deaths

No additional toxicities were reported in combination with pembrolizumab

DLTs at MTD

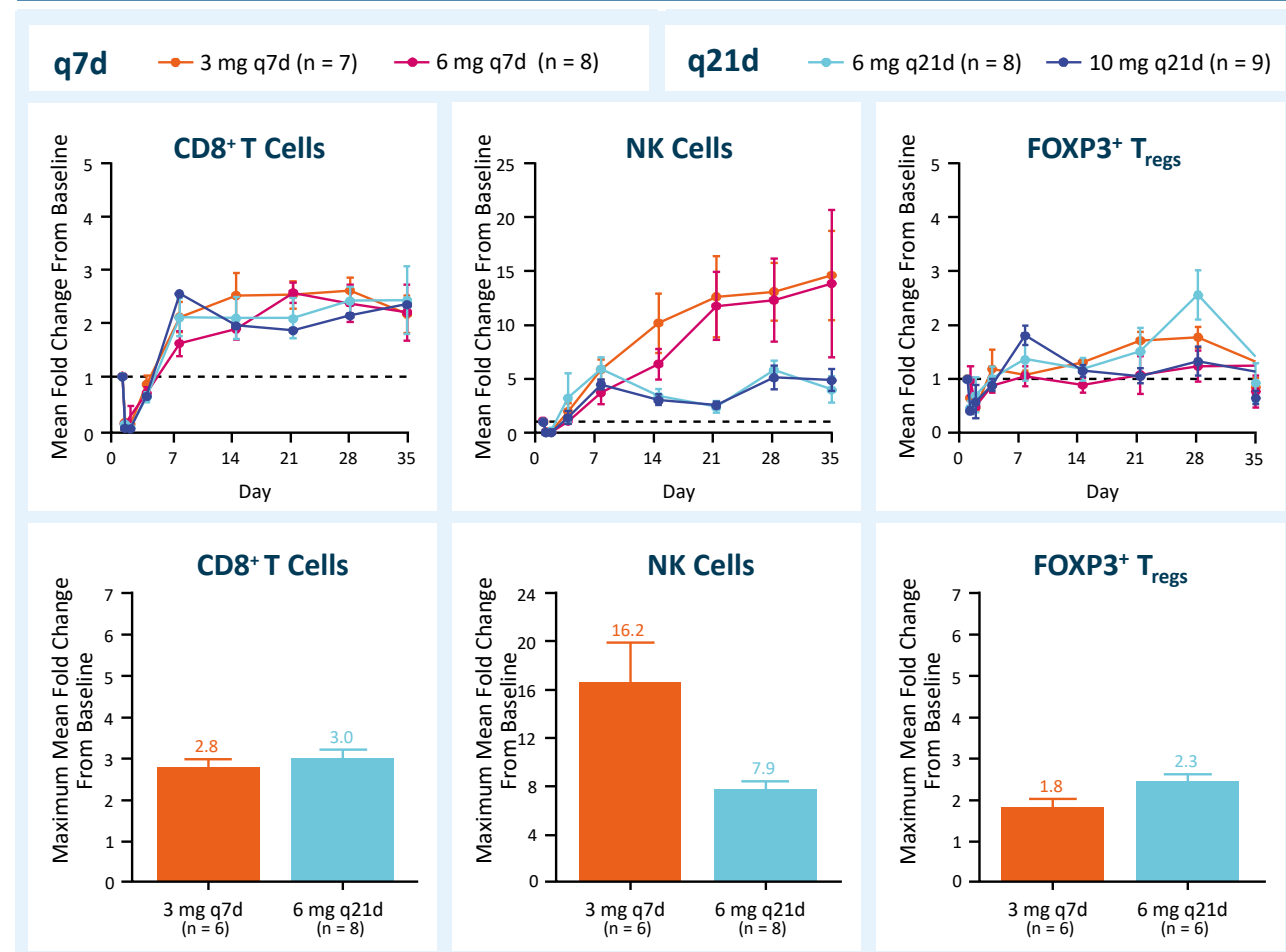
Three DLTs reported at MTD of 6 mg q7d and 10 mg q21d

- DLTs were manageable with either dose interruption, discontinuation and/or standard of care treatment
 - Atypical Capillary Leak Syndrome, without hypotension (Grade 3)
 - Non-serious injection site reaction (Grade 3)
 - Non-serious, transient fatigue, nausea, vomiting (Grade 3)

AEs: Adverse Events; ALT/AST: aspartate aminotransferase / alanine aminotransferase; TRAEs: Treatment-related adverse events; DLTs: Dose-limiting toxicities; MTD: Maximum tolerated dose; RP2D: Recommended phase 2 dose; SC: Subcutaneous, IV: Intravenous

Data as of March 19, 2021

SC Nemvaleukin Selectively Expanded Circulating NK and CD8+ T Cells, and Demonstrated Initial Anti-Tumor Activity



- 3 mg q7d SC nemvaleukin provided greater expansion of CD8+ T cells and NK cells relative to IV nemvaleukin
- Antidrug antibodies (ADAs) were observed in a subset of patients*; the presence of ADAs did not appear to have a clinically meaningful effect on the pharmacokinetics, pharmacodynamics, or safety of nemvaleukin

Initial anti-tumor activity observed in dose escalation cohorts

- Of 57 patients with ≥ 1 on-treatment scans, 31 (54%) had stable disease on first scan
- Of 37 patients with ≥ 2 on-treatment scans, 17 (46%) had stable disease on 2 or more consecutive scans

1. Wu, SY., Fu, T., Jiang, YZ. et al. Natural killer cells in cancer biology and therapy. Mol Cancer 19, 120 (2020). NK cells: Natural Killer cells; T_{regs}: Regulatory T cells

* The prevalence of ADAs did not appear to be related to dose or dosing frequency (q7d or q21).

Data cut off March 19, 2021

Nemvaleukin Program Summary

- Unique cytokine designed to harness validated IL-2 pathway biology, utilizing **native IL-2 and IL-2R α sequences to confer differentiated properties**
- **Intravenous (IV) nemvaleukin demonstrated monotherapy activity** in tumors where rhIL-2 is known to be active: melanoma and RCC
 - Granted FDA Fast Track and Orphan Drug Designation in mucosal melanoma
 - Initiated ARTISTRY-6 study in patients with melanoma
- **IV nemvaleukin demonstrated durable and deepening responses** in combination with pembrolizumab in platinum-resistant ovarian cancer
 - Planned phase 3 study expected to initiate in H2 2021 in collaboration with MSD (a tradename of Merck & Co., Inc. Kenilworth, NJ, USA)
- Anti-tumor activity observed in a range of difficult-to-treat tumors, suggesting broad potential applicability*
- ARTISTRY-2 study evaluating **potential dosing optionality** with subcutaneous administration

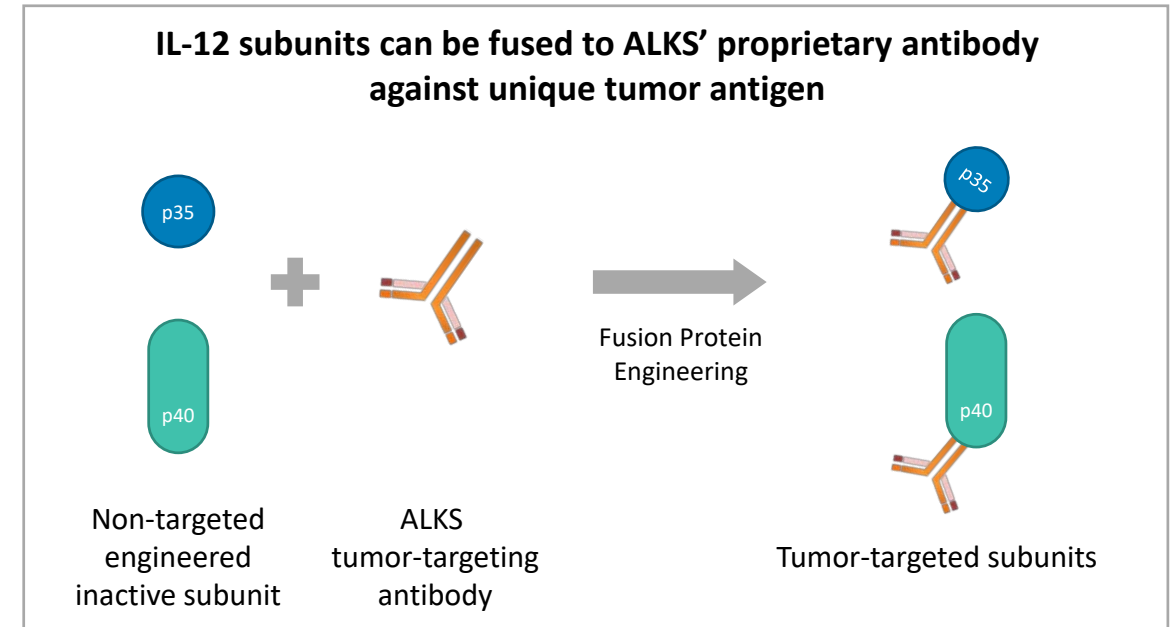
*Includes one response from ARTISTRY-2 study evaluating subcutaneous nemvaleukin, which has recently opened expansion cohorts for enrollment at the recommended phase 2 dose.

IL-12 Program Design: Build Functional IL-12 in the Tumor Through Engineered Tumor-Targeted IL-12 Subunits

IL-12 has demonstrated anti-tumor efficacy in preclinical studies; however, clinical evaluation is limited due to severe toxicities associated with systemic exposure to IL-12, resulting in a narrow therapeutic index^{1,2,3}

Alkermes' key design goals:

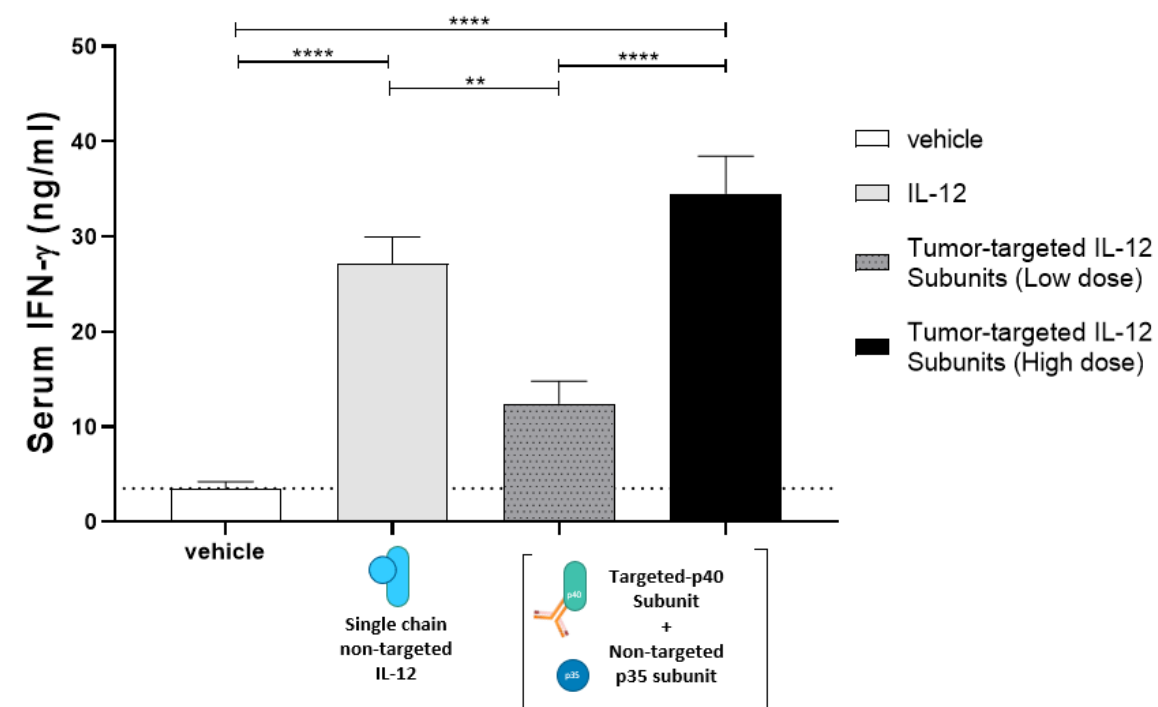
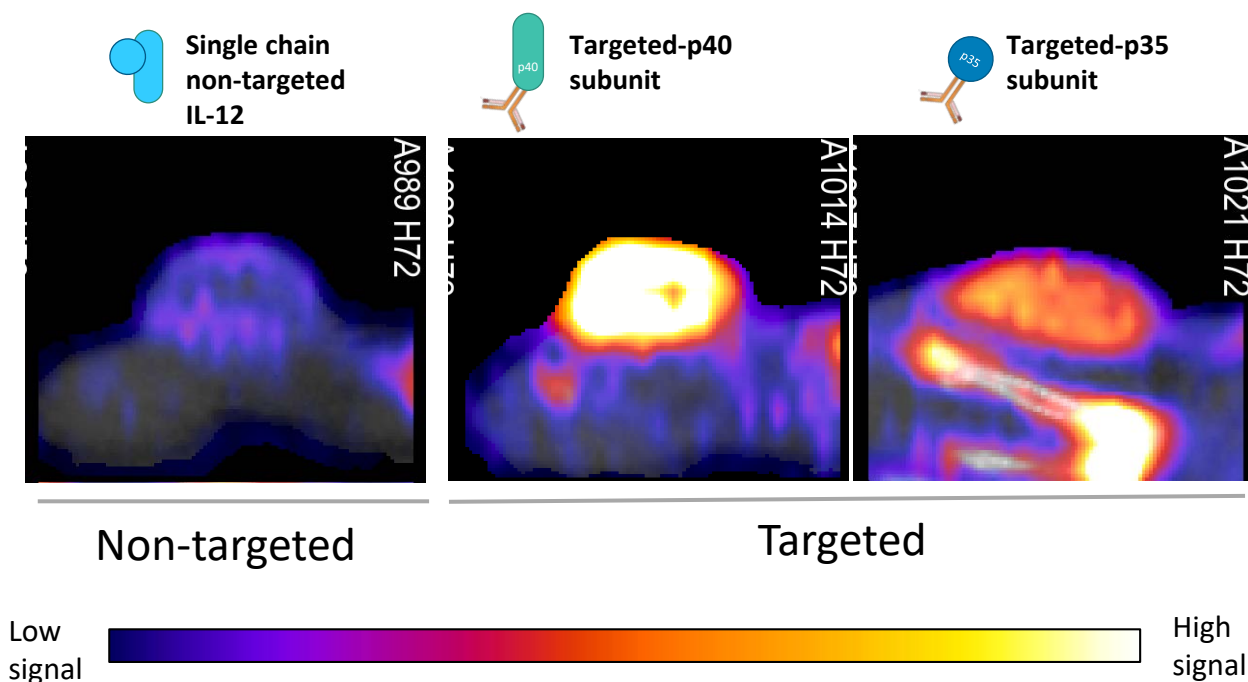
- **Split IL-12** to create functionally inactive subunits to be directed to the tumor microenvironment
- **Engineer** IL-12 subunits to address inherent stability challenges in p35 production and enhance the affinity of non-covalently linked p35 and p40 subunits
- **Identify** unique tumor-targeting antigen and **generate** proprietary antibodies
- **Produce** novel engineered tumor-targeted fusion proteins using proprietary antibodies



1. Nguyen KG et. al. Cancer Immunotherapy. Front. Immunol. October 15 2020 11:575597
2. Vecchio MD et. al. Clin Cancer Res August 15 2007 (13) (16) 4677-4685
3. Strauss J et. al. Clin Cancer Res January 1 2019 (25) (1) 99-109

Alkermes' Tumor-Targeted Split IL-12 Subunits Accumulated in Tumor and Induced Dose-Dependent PD Response in Preclinical Study

PET/CT Imaging of Tumor⁺ (72 hours post treatment)



*Alkermes internal data on file; Murine CT-26 tumors in Balb/c mice; %ID/g = percent of injected dose per gram of tissue
PD: Pharmacodynamic

Alkermes internal data on file; PBMC humanized NCG mice

Neuroscience: Synaptic Dysfunction

Development Candidates Emerging From Neuroscience Platform

Mechanism		Programs and Potential Indications
CoREST-selective HDAC inhibitors	Pro-synaptic	ALKS 1140: Orphan indications in neurodevelopmental and neurodegenerative disorders Follow-on Candidate: Non-orphan indications in neurodegenerative and neuropsychiatric spaces
	Increase of progranulin and pro-synaptic	Frontotemporal Dementia with Granulin Precursor Mutations (FTD-GRN): FTD-GRN and other FTD variants
Orexin	Restoration of abnormal neurotransmission	Orexin 2 Receptor Agonist: Narcolepsy and indications with excessive daytime sleepiness, fatigue or attention/cognition issues

CoREST: co-repressor of repressor element-1 silencing transcription factor; HDAC: histone deacetylase

ALKS 1140: Novel CoREST-Selective HDAC Inhibitor Candidate

For the Treatment of Neurodegenerative and Neurodevelopmental Disorders

- First candidate nominated from platform of selective HDAC inhibitor compounds
- Inhibition of the CoREST HDAC complex is a novel approach designed to increase functional synaptic connections and synaptic integrity

Potential Indications: Focused on Rare and Orphan Diseases



NEURODEGENERATIVE

- Huntington's Disease
- Dementia in Down Syndrome



NEURODEVELOPMENTAL

- Angelman Syndrome
- Phelan-McDermid Syndrome
- Rett Syndrome
- Tuberous Sclerosis Complex

Plan to select lead indications based on preclinical and human biomarker data

ALKS 1140 Achieved Alkermes' HDAC Compound Design Goals:

Selectivity:

Selectively inhibited HDAC-CoREST complex

*80-250-fold selectivity vs. other HDAC Class I complexes**

Safety:

Demonstrated favorable hematological safety

*Minimal effects in vitro and in preclinical in vivo assessments**

Brain penetration:

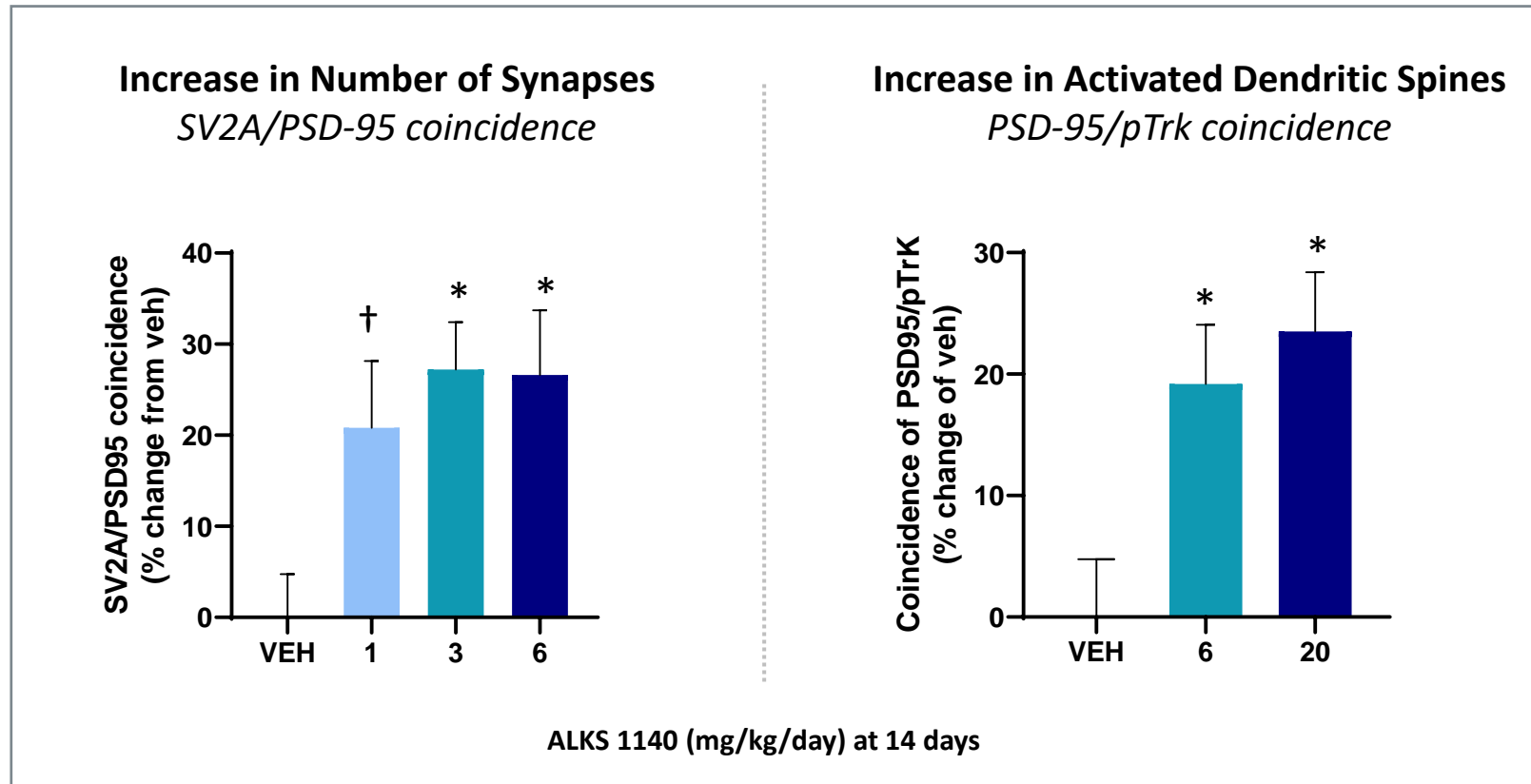
Exhibited desired brain exposure

*CSF/Cplasma, unbound ratio in rat/dog/NHP = 0.6-1.5**

CoREST: Co-repressor of repressor element-1 silencing transcription factor; HDAC: Histone deacetylase

CSF: cerebrospinal fluid
*Alkermes data on file

ALKS 1140 Increased Proteins Related to Number of Synapses and Activated Dendritic Spines



†p<0.1; *p<0.05; Data from wild type mouse model in hippocampus slices
Alkermes data on file

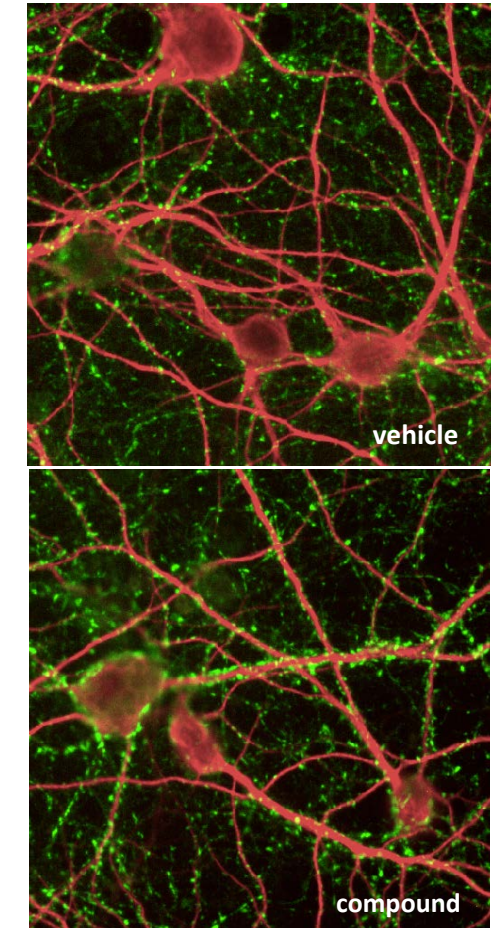
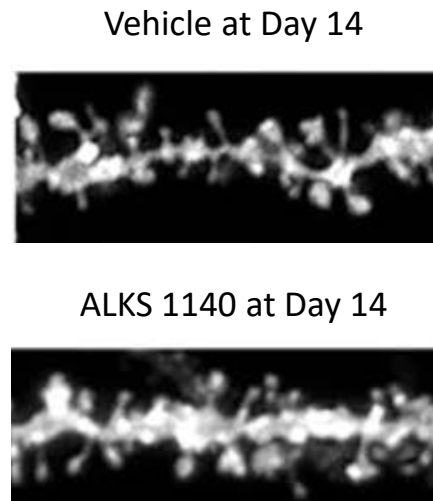
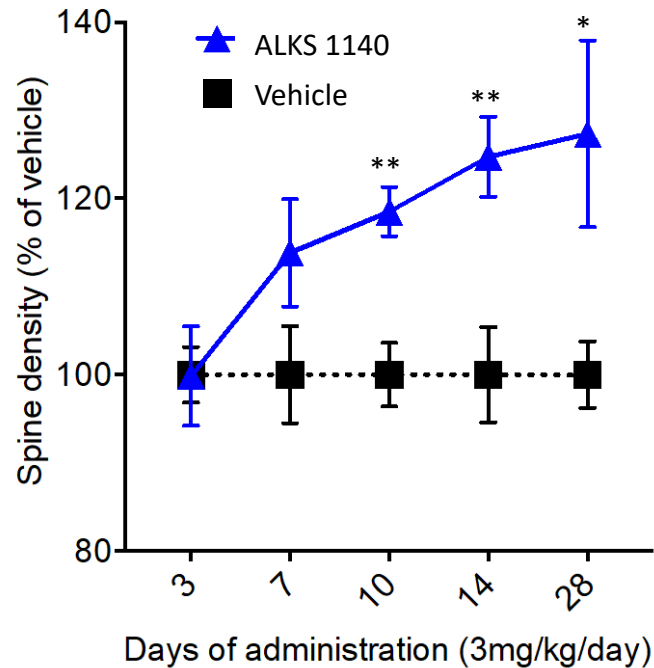


Illustration of SV2A puncta (green) in culture overlaid on MAP2 (dendrites); Alkermes data on file

ALKS 1140 Increased Density and Persistence of Dendritic Spines

Increased Dendritic Spine Density



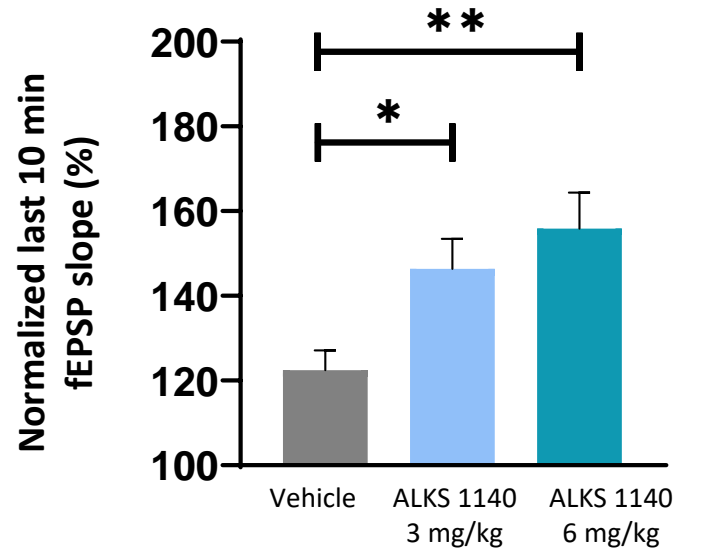
Persistence of Dendritic Spines



†p<0.1; *p<0.05; **p<0.01; Data from wild type mouse model
Alkermes data on file

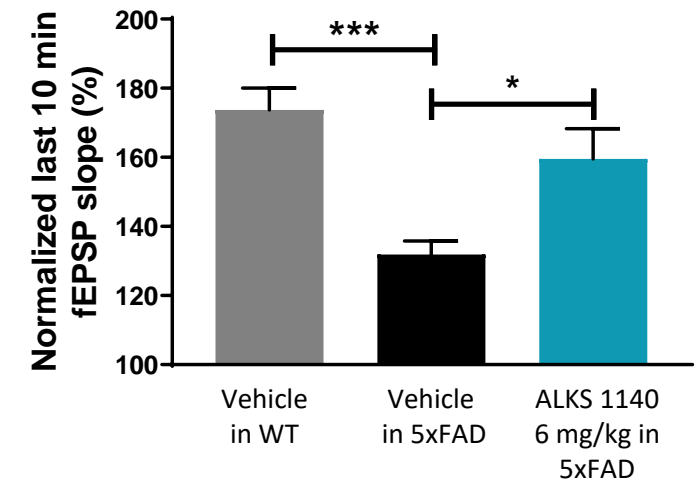
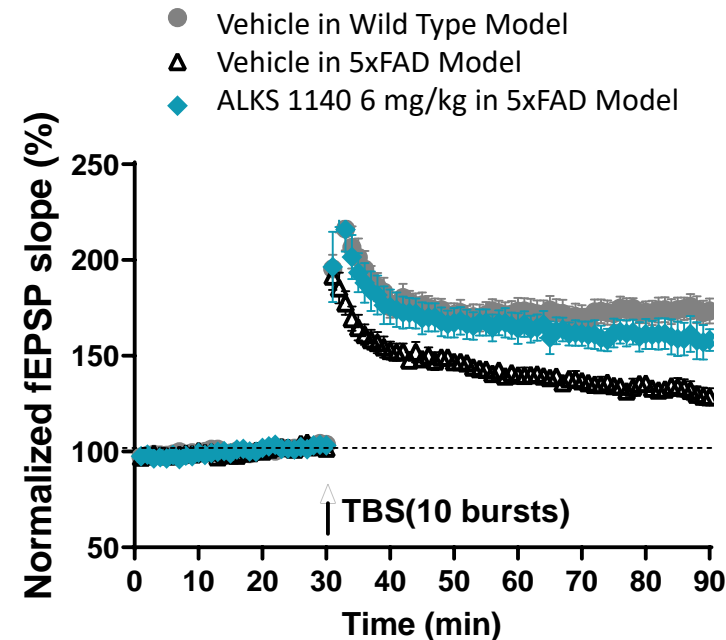
ALKS 1140 Improved Synaptic Efficacy in Wild Type Mice and Restored Synaptic Function in Disease Model

Long-term Potentiation in Wild Type Mice



Ordinary one-way ANOVA, Holm Sidak post hoc

Long-term Potentiation in Transgenic Mice with Hippocampal Synaptic Deficit (5xFAD)



* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$
Alkermes data on file

fEPSP: field excitatory postsynaptic potential; WT: wild type mouse model
5xFAD: Five Alzheimer's Disease-linked mutations in 9-10-month-old mice

ALKS 1140 Development Plan: Seek Early Clinical Evidence of Activity

Synaptic biomarkers and neurocognitive assessments are core components of the early clinical development plan and program decision-making

Early Clinical Development Plan	Objectives
Phase 0 Biomarker Study Planned initiation: 2021	<ul style="list-style-type: none">Identify differences in synaptic biomarkers between healthy volunteers and patients with neurodegenerative/neurodevelopmental diseases and inform indication selection
Phase 1 SAD/MAD Planned initiation: 2021	<ul style="list-style-type: none">Determine PK/PD relationship and MTD in healthy volunteersDetermine ALKS 1140's effects on select biomarkers



Phase 1b: Basket studies in neurodevelopmental and neurodegenerative disorders

- Confirm ALKS 1140's effect on biomarkers of synaptopathy and neurocognitive function
- Prioritize indications and biomarkers for proof-of-concept studies

SAD: single-ascending dose; MAD: multiple-ascending dose; PK: pharmacokinetic; PD: pharmacodynamic; MTD: maximum tolerated dose

Orexin 2 Receptor Agonist

For the Treatment of Narcolepsy and Other Sleep Disorders

- Narcolepsy affects ~200,000 people in U.S. and 3M people globally¹
- 70% of narcolepsy patients have narcolepsy type 1², distinguished by:
 - Cataplexy, a sudden muscle weakness triggered by strong emotions
 - Low or no orexin in the brain
- Current approved medicines treat symptoms but do not address underlying orexin deficiency
 - Stimulant medications often associated with potential abuse and safety concerns, including effects on heart rate and blood pressure

Alkermes Orexin 2 Receptor Agonist Design Goals:

Robust Efficacy

- Increased wakefulness duration
- Improved cataplexy control

Convenient Dosing

- Once-daily, oral medication
- Dose to allow for 8-12 hours wakefulness with no later insomnia

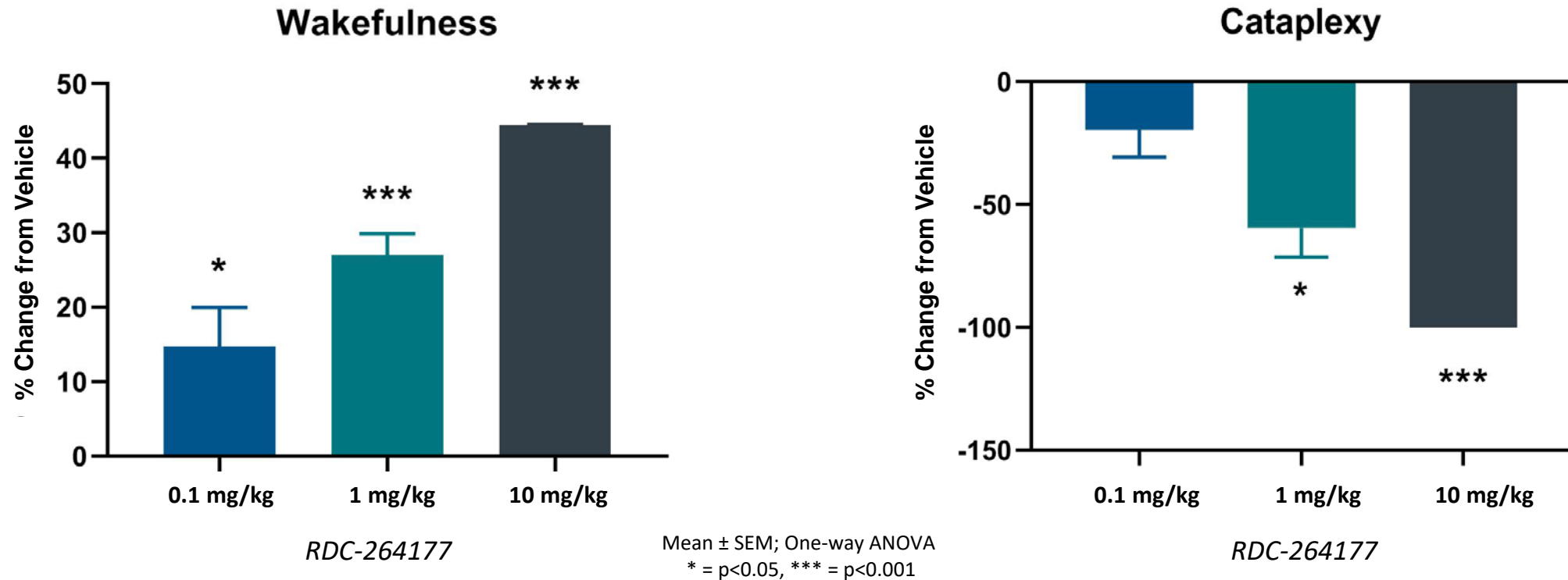
Favorable Tolerability

- Reduced risk of heart rate and blood pressure effects seen with stimulants

¹ Global Narcolepsy Drugs Market, Forecast 2019-2025. Allied Market Research

² Swick TJ. Treatment paradigms for cataplexy in narcolepsy: past, present, and future. *Nat Sci Sleep*. 2015;7:159-169

Alkermes' Orexin Candidate RDC-264177 Demonstrated Dose-Dependent Increased Wakefulness and Reduced Cataplexy

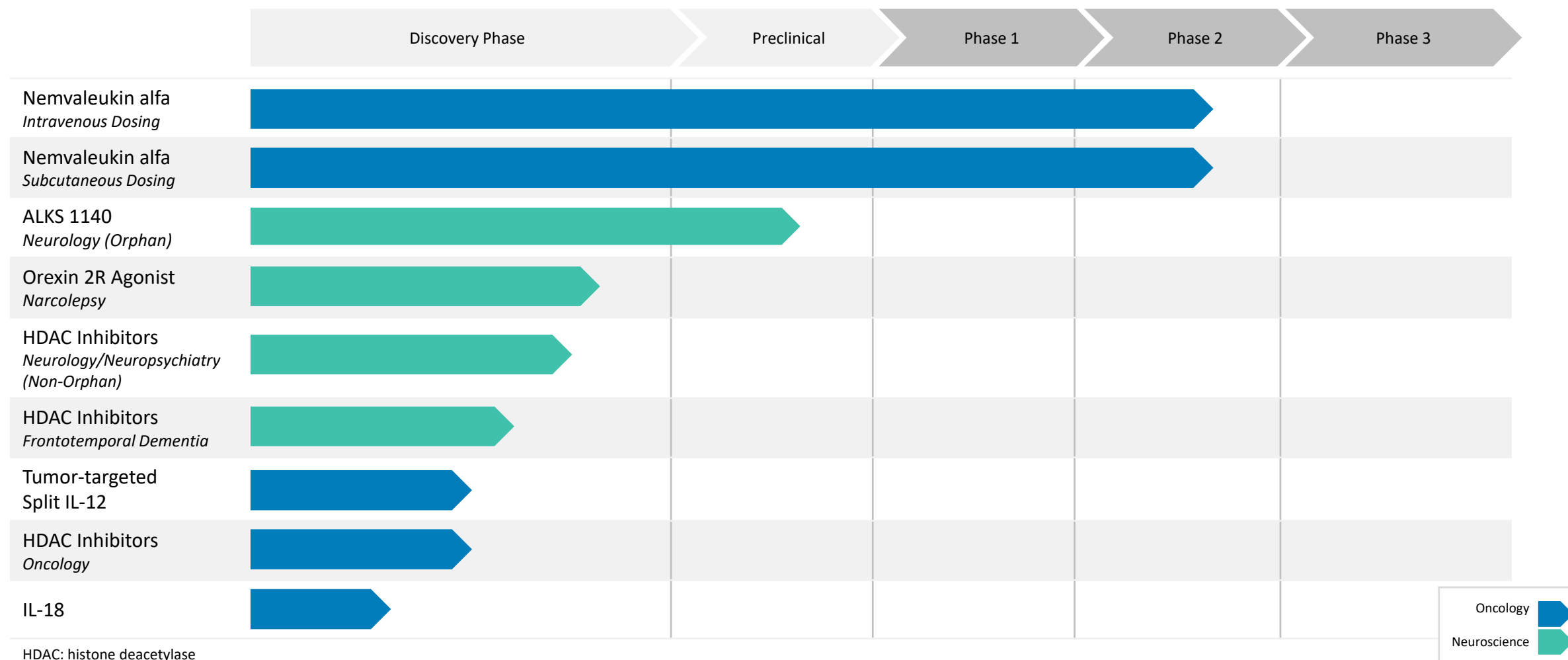


DTA mouse model of narcolepsy^{1,2} serves as a predictive disease model of narcolepsy in humans

¹Tabuchi S, Tsunematsu T, Black SW, et al. Conditional ablation of orexin/hypocretin neurons: a new mouse model for the study of narcolepsy and orexin system function. *J Neurosci*. 2014;34(19):6495-6509

² In collaboration with SRI International

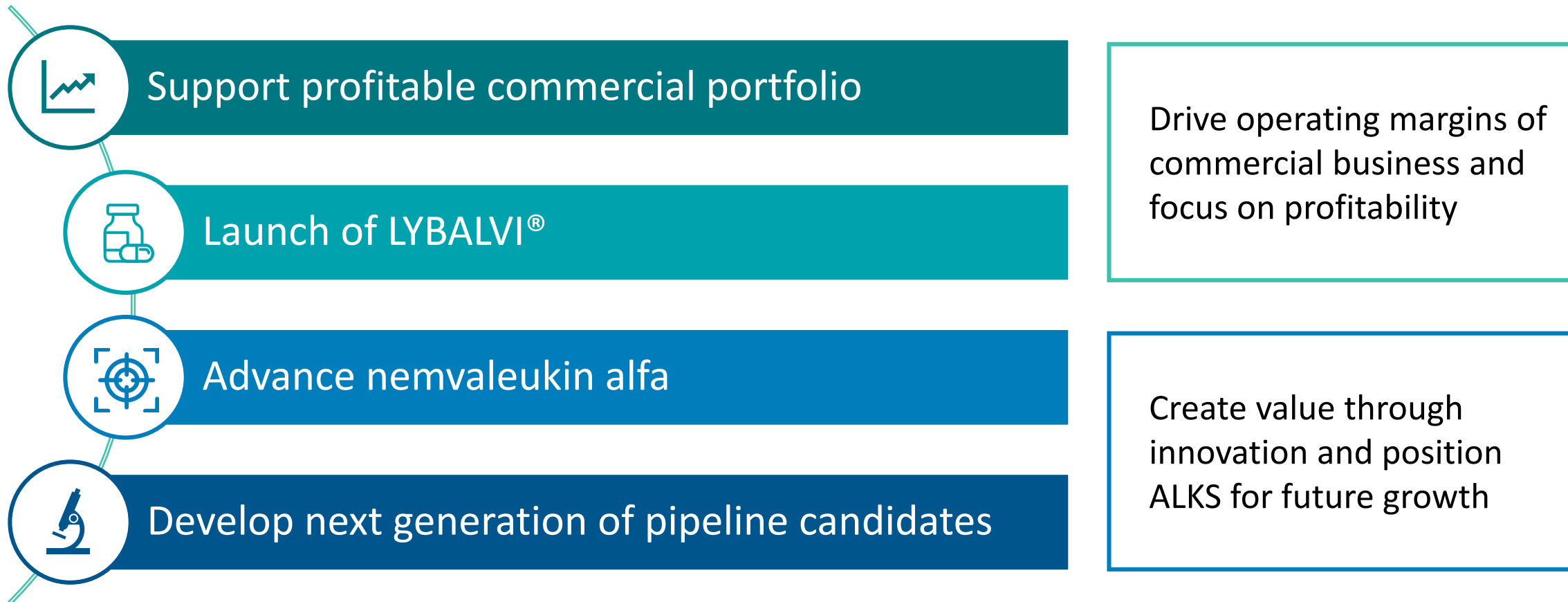
R&D Portfolio Advancement



Manage for Growth and Long-Term Profitability



Disciplined Capital Allocation Supports Highest ROI Priorities



Value Enhancement Plan and Board Refreshment

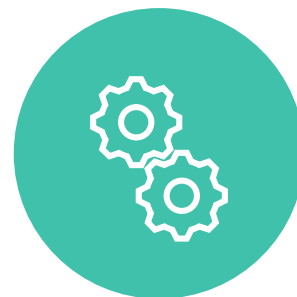


Profitability Targets and Cost Structure Optimization

- Commitment to achieving:

	FY 2023	FY 2024
NGNI/Revenue	25%	30%
EBITDA/Revenue	20%	25%

- Ongoing review to identify potential areas for improved efficiencies



Evaluation of Strategic Opportunities

- Potential monetization or divestiture of non-core assets
- Commitment to exploring strategic collaboration for nemvaleukin alfa



Board Refreshment

- Appointed five new, independent directors in past two years, adding strong financial, strategic, operational and oncology expertise to the Board

NGNI: Non-GAAP net income; EBITDA: Earnings before interest, tax, depreciation, amortization

Reconciliations of these forward-looking non-GAAP financial measures to GAAP are not provided, as such reconciliations are not determinable by the Company without unreasonable efforts due to the inherent difficulty in forecasting and quantifying certain future financials that would be necessary for such reconciliations. The Company has not provided financial expectations for time periods after the year ending December 31, 2021.

Diversified Biopharmaceutical Company With Proven Drug Development and Commercialization Capabilities

Significant, diverse revenues driving >\$1B topline and positioned for growth



Established proprietary commercial products that target large markets in addiction and psychiatry



Additional potential revenue streams as newer products launch* and grow

Pipeline of novel development candidates designed to target significant unmet needs

Oncology

Nemvaleukin alfa

- Phase 2
- Advanced solid tumors

IL-12

- Preclinical
- Advanced solid tumors

Neuroscience

ALKS 1140

- IND-enabling
- Neurodegenerative and neurodevelopmental disorders

Orexin 2R Agonist

- Preclinical
- Narcolepsy

Focus on Profitability

Focus on driving cost efficiencies and operating leverage while investing in the long-term growth of high-potential commercial and development-stage products

*LYBALVI® commercial launch expected in Q4 2021.

www.alkermes.com



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