Forward-Looking Statements and Non-GAAP Financial Information

Certain statements set forth in this presentation constitute “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, but not limited to, statements concerning: the company’s expectations with respect to its current and future financial and operating performance, business plans or prospects, including revenue growth from its current commercial product portfolio and the addition of potential new revenue streams, and the company’s plans and ability to manage for growth and profitability, including achievement of its stated profitability targets, through revenue growth, expense management, and optimization of its cost structure and exploration of strategic opportunities; the potential therapeutic and commercial value of the company’s marketed products and development candidates; expectations regarding patient life for the company’s products; expectations regarding the effectiveness and cost-efficiency of the company’s research and development (“R&D”) strategy and the potential of its stated R&D capabilities, including its molecule design and engineering capabilities; timelines, plans and expectations for development activities relating to the company’s products and development candidates, including (i) for nemvaleukin alfa (“nemvaleukin”), plans to initiate studies in mucosal melanoma and platinum-resistant ovarian cancer to support potential registration, further explore the potential synergistic benefits of nemvaleukin to existing cancer treatments, and pursue strategic collaborations, (ii) for ALKS 1140, plans to initiate phase 1 first-in-human trials, (iii) and for the company’s other early-stage programs, including its orexin program, its engineered cytokine platform, including IL-12 and IL-18, and its HDAC inhibitor platform, plans to conduct proof of concept studies and/or other enabling activities, advance towards characterization and nomination of lead candidates, and identify and prioritize initial potential indications; the company’s expectations relating to regulatory activities and interactions, including the U.S. Food and Drug Administration’s (“FDA”) PDUFA target action date for the company’s new drug application (“NDA”) for LYBALVI and plans to advance discussions on registration plans for nemvaleukin; expectations concerning commercial activities relating to the company’s products and product candidates, including preparations for the potential commercial launch of LYBALVI. The company cautions that forward-looking statements are inherently uncertain. These risks, assumptions and uncertainties include, among others: the impacts of the ongoing COVID-19 pandemic and continued efforts to mitigate its spread on the company’s business, results of operations or financial condition; the unfavorable outcome of litigation, including so-called “Paragraph IV” litigation and other patent litigation, related to any of the company’s products, which may lead to competition from generic drug manufacturers; the FDA may not agree with the company’s regulatory approval strategies or components of the company’s NDAs, including clinical trial designs, conduct and methodologies, manufacturing processes and facilities, or the adequacy of the data or other information included in the company’s regulatory submissions to support the FDA’s requirements for approval, and may make adverse decisions regarding the company’s products, including with respect to the NDA for LYBALVI; the company’s development activities may not be completed on time or at all; the results of the company’s development activities may not be positive or predictive of real-world results, and preliminary data from ongoing studies may not be predictive of future or final data from such studies, results of future studies or real-world results; the company and its licensees may not be able to successfully commercialize their products or support growth of revenue from such products; there may be a reduction in payment rate or reimbursement for the company’s products or an increase in the company’s financial obligations to governmental payers; the company’s products may prove difficult to manufacture, be precluded from commercialization by the proprietary rights of third parties, or have unintended side effects, adverse reactions or incidents of misuse; and those risks, assumptions and uncertainties described under the heading “Risk Factors” in the company’s Annual Report on Form 10-K for the year ended Dec. 31, 2020 and in subsequent filings made by the company with the U.S. Securities and Exchange Commission (“SEC”), which are available on the SEC’s website at www.sec.gov and on the company’s website at www.alkermes.com in the “Investors—SEC filings” section. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. Except as required by law, the company disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this presentation.

Non-GAAP Financial Measures: This presentation includes information about certain financial measures that are not prepared in accordance with generally accepted accounting principles in the U.S. (GAAP), including non-GAAP net income and EBITDA. These non-GAAP measures are not based on any standardized methodology prescribed by GAAP and are not necessarily comparable to similar measures presented by other companies. Reconciliations of non-GAAP financial measures to the most directly comparable GAAP financial measures, to the extent reasonably determinable, can be found on the Investors page of the Company’s website.

Note Regarding Trademarks: The company and its affiliates are the owners of various U.S. federal trademark registrations (®) and other trademarks (™), including ARISTADA®, ARISTADA INITIO®, VIVITROL® and LYBALVI™. VUMERITY™ is a registered trademark of Biogen MA Inc., used by Alkermes under license. Any other trademarks referred to in this presentation are the property of their respective owners. Appearances of such other trademarks herein should not be construed as any indicator that their respective owners will not assert their rights thereto.
Scientific and Business Excellence: Focused on New Approaches to Creating Value

Richard Pops
Chief Executive Officer
Diversified Biopharmaceutical Company With Proven Drug Development and Commercialization Capabilities

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

<table>
<thead>
<tr>
<th>Proprietary commercial products that target large markets in addiction and psychiatry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional potential revenue streams as new products launch* and grow</td>
</tr>
</tbody>
</table>

Pipeline of novel development candidates designed to target significant unmet needs

<table>
<thead>
<tr>
<th>Oncology</th>
<th>Neuroscience</th>
</tr>
</thead>
</table>
| Nemvaleukin alfa  
• Phase 2  
• Advanced solid tumors | ALKS 1140  
• IND-enabling  
• Neurodegenerative and neurodevelopmental disorders |
| IL-12  
• Preclinical  
• Advanced solid tumors | 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 NDA under FDA review; PDUFA June 1, 2021
Evolution of Alkermes R&D Strategy

Legacy R&D Strategy

Target evaluation driven by potential to add new medical value to established medications

Enabled rapid advancement to late-stage development

Yielded VIVITROL®, ARISTADA®, VUMERITY®, LYBALVI™*

*LYBALVI NDA under FDA review; PDUFA June 1, 2021

Advanced formulation science, prodrug chemistry and drug delivery technologies applied to improve established pharmacology
New R&D Strategy

**Focus:**
Two areas of scientific expertise: Neuroscience and Oncology
Programs with validated biology rationale
Leverage established small molecule and protein design capabilities

**Management:**
Utilize an integrated approach to target evaluation
Design development programs to provide key data early
Prioritize and allocate resources based on data

Molecular design, medicinal chemistry and protein engineering expertise applied to develop *novel molecules* to address unmet needs in neuroscience and oncology
Value Enhancement Plan: Growth, Efficiency and Profitability

Value Enhancement Plan

- Establishes clear profitability targets
- Provides framework for capital allocation decisions and prioritization of investments
- Focuses investment on highest-ROI opportunities emerging from new R&D platform
- Incorporates feedback from shareholders, external advisors and peer-group benchmarking data

Management and governance focused on growth, efficiency, and profitability

Business Excellence
Scientific & Business Excellence Drive Enterprise Value

Scientific Excellence

Innovation-driven value creation and profitability

Business Excellence

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Consistent With Alkermes’ Purpose and Values

Our purpose

Great Science
Deep Compassion
Real Impact

Our values

Collaboration at our core
Sharing success
All is possible

Respect each voice
Value every person
Driven by trust

Unwavering commitment
Do the right thing
Beyond passionate
Today’s Agenda

VALUE CREATION

Innovation, Growth and Profitability — Blair Jackson, Executive Vice President and Chief Operating Officer

ALKERMES’ NEW R&D MODEL

Optimizing for Success — Craig Hopkinson, M.D., Executive Vice President and Chief Medical Officer
Focus on Innovative Molecular Design — Markus Haeberlein, Ph.D., Senior Vice President, Research

ONCOLOGY

Nemvaleukin alfa: Clinical Data Updates — Jessicca Rege, Ph.D., Vice President, Clinical Research, Oncology
Nemvaleukin alfa: Preclinical Research — Heather Losey, Ph.D., Senior Director, Research, Oncology
Tumor-Targeted Split IL-12 Fusion Protein — Josh Heiber, Ph.D., Principal Scientist, Research, Oncology

NEUROSCIENCE

Selective HDAC Inhibitors — Markus Haeberlein, Ph.D., Senior Vice President, Research
Orexin 2 Receptor Agonists — Brian Raymer, Ph.D., Senior Director, Research Project Leadership and Strategy

Q&A
Value Creation at Alkermes: Innovation, Growth and Profitability

Blair Jackson
Chief Operating Officer
Strong Operational Foundation to Drive Value Creation

Revenues:
Diverse and positioned for growth

Commitment to Profitability:
Focused on organizational efficiency and cost management

Capital Allocation:
Focused on highest-ROI opportunities

Strong Corporate Governance:
Board refreshment, independence and oversight

*2021 reflects the midpoint of our NGNI expectations. These expectations, and the underlying assumptions and risks, are set forth in Alkermes plc’s (the “Company”) Current Report on Form 8-K (“8-K”) filed with the SEC on February 11, 2021. The Company expressly disclaims any obligation to update or reaffirm these expectations.

**Reconciliations of non-GAAP financial measures to the most directly comparable GAAP financial measures, to the extent reasonably determinable, can be found in the Appendix of this presentation.

NGNI: Non-GAAP net income

Illustrative only.
Revenues:
Growing Commercial Products
Serving Large Markets
Topline Growth and Diversification Reflect Evolving Business

2016

$746M Total Revenue

2020

$1,039M Total Revenue

- VIVITROL®
- ARISTADA®*
- Non-proprietary revenue
- VUMERITY®

* Inclusive of ARISTADA INITIO®.
** VUMERITY® developed by Alkermes and licensed to Biogen.
### Expected Growth Drivers

<table>
<thead>
<tr>
<th>Indications</th>
<th>2020 Net sales CAGR</th>
<th>Patent Life</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current proprietary commercial products</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol dependence (AD)</td>
<td>$311M</td>
<td>2029*†</td>
</tr>
<tr>
<td>Prevention of relapse to opioid dependence (OD) following opioid detoxification</td>
<td>$311M</td>
<td>2029*†</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>$241M</td>
<td>2035</td>
</tr>
<tr>
<td><strong>Proprietary candidate under FDA review; PDUFA June 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Potential launch in 2021</td>
<td>2031</td>
</tr>
<tr>
<td>Bipolar I disorder</td>
<td>Potential launch in 2021</td>
<td>2031</td>
</tr>
<tr>
<td><strong>Licensed Product (royalty &amp; manufacturing revenue)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsing forms of multiple sclerosis (MS)</td>
<td>$23M</td>
<td>2033†</td>
</tr>
</tbody>
</table>

*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 certification related to an ANDA seeking FDA approval of a generic version. A patent infringement lawsuit has been filed against the Paragraph IV filer in response.

Full indication and prescribing information for VIVITROL may be found at [www.vivitrol.com](http://www.vivitrol.com) Full prescribing information for ARISTADA may be found at [www.aristada.com](http://www.aristada.com)
VIVITROL®: Growth in Opioid Dependence and Alcohol Dependence

COVID-19 interrupted 5 consecutive years of strong brand growth

Alcohol dependence indication – strong source of recent growth
VIVITROL®: Anticipated Recovery Following COVID-19 Disruption

- **Alcohol dependence***: Resumed growth as new patient starts rebounded from pandemic lows in Q2’20

- **Opioid dependence***: Volumes have stabilized but continue to be impacted by COVID-19-related disruptions to the treatment landscape
  - Reduced patient capacity and treatment services at settings of care where people commonly undergo opioid detoxification (e.g. residential treatment centers, correctional facilities)
  - VIVITROL volume expected to regain growth as access to care improves

*Full indication and prescribing information for VIVITROL may be found at [www.vivitrol.com](http://www.vivitrol.com)
ARISTADA®: Strong Growth Driven by Two-Month Dose

**ARISTADA Net Sales* ($M)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Sales ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td>$50</td>
</tr>
<tr>
<td>2017</td>
<td>$100</td>
</tr>
<tr>
<td>2018</td>
<td>$200</td>
</tr>
<tr>
<td>2019</td>
<td>$300</td>
</tr>
<tr>
<td>2020</td>
<td>$400</td>
</tr>
</tbody>
</table>

50% CAGR

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

**Strong performance reflects favorable product characteristics**

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

**Growth of 2-month 1064 mg dose reflects differentiated value proposition**
ARISTADA®: Growth Outpaced Atypical Long-Acting Injectable (aLAI) Antipsychotic Market

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

*Includes ARISTADA®, Abilify Maintena® (estimated sales), Invega Sustenna/Trinza®, Risperdal Consta® and Perseris®.

** IQVIA NPA Audit.

MOT: Months of therapy

---

**ARISTADA TRx MOT Growth Rate**

<table>
<thead>
<tr>
<th>Year</th>
<th>ARISTADA</th>
<th>LAI Market</th>
</tr>
</thead>
<tbody>
<tr>
<td>2020 YoY</td>
<td>16%</td>
<td>5%</td>
</tr>
<tr>
<td>Q4'20 QoQ</td>
<td>4%</td>
<td>2%</td>
</tr>
</tbody>
</table>
**LYBALVI™**: Potential New Revenue Driver in Oral Atypical Antipsychotic Market

**Alkermes Value Proposition**

- Drive operating leverage from established psychiatry commercial infrastructure
- Expected to be accretive in year 2 of launch

---

**ENLIGHTEN-2 Phase 3 Results**

- **57%**
  - Higher mean percent weight change at six months for patients who received olanzapine vs. LYBALVI

- **2.0x**
  - The risk of clinically meaningful weight gain (≥10%) from baseline (29.8% for olanzapine vs. 17.8% for LYBALVI)

**ENLIGHTEN-2**:
Multicenter, double-blind, randomized, phase 3 study that evaluated the weight gain profile of LYBALVI (ALKS 3831) compared to olanzapine over six months in 561 patients with stable schizophrenia.

Most common adverse events for LYBALVI: weight gain, somnolence & dry mouth.
Most common adverse events for olanzapine: weight gain, somnolence & increased appetite.

**Launch Planning**

- Target well-defined healthcare provider call universe at launch
- Implement patient access programs designed to mitigate payer restrictions early in launch

---

*The brand name LYBALVI™ has been conditionally accepted by the FDA and will be confirmed upon approval.
** NDA resubmission under review following FDA Complete Response Letter and records requests relating to manufacturing of LYBALVI.
## Oral Atypical Antipsychotic (AAP) Markets Represent Large Opportunities

<table>
<thead>
<tr>
<th></th>
<th>ORAL AAPs SCHIZOPHRENIA*</th>
<th>ORAL AAPs BIPOLAR I DISORDER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Branded Market Size</strong></td>
<td>$1.5B</td>
<td>$1.7B</td>
</tr>
<tr>
<td><strong>Annual TRx</strong></td>
<td>~15M</td>
<td>~15M†</td>
</tr>
<tr>
<td><strong>Commercial Payer %</strong></td>
<td>20%</td>
<td>39%</td>
</tr>
<tr>
<td><strong>Market Share</strong></td>
<td>21% olanzapine</td>
<td>12% olanzapine</td>
</tr>
</tbody>
</table>

1 IQVIA reported sales (NSP Audit Dec 2020) factored by indication using IQVIA reported indication mix (SOB Dec 2020); IQVIA reported sales are higher than manufacturer reported net sales because IQVIA does not incorporate all gross-to-net expenses.  
2 IQVIA reported TRxs (NPA Audit Dec 2020) factored by indication using IQVIA reported indication mix (SOB Dec 2020).  
3 IQVIA SOB Data, Q4 2020.  
4 IQVIA reported TRxs (NPA Audit Dec 2020) converted into MOT and factored by indication using IQVIA reported indication mix (SOB Dec 2020).  
5 IQVIA SOB data for the oral atypical antipsychotic market, specific to SZ/BD indications. SZ data includes schizophrenia and schizoaffective disorder, BD data includes BD1, BD2 and other BD indications, switches includes add-on.  
6 IQVIA SOB data Dec 2020, Dec’20 vs. Dec’19, all indications.  

*Due to data limitations, schizophrenia data includes schizoaffective disorder (for which LYBALVI will not be indicated)  
† Due to data limitations, BD1 data includes other BD indications (for which LYBALVI will not be indicated)
VUMERITY® Growth Presents Additional Long-Term Revenue Opportunity

- 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.
# Near-Term Expected Revenue Drivers

<table>
<thead>
<tr>
<th>Current Proprietary Commercial Products</th>
<th>Expected 2021 Net Sales:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vivitrol</strong> (naclrete for extended-release injectable suspension)</td>
<td>Alcohol dependence (AD) Prevention of relapse to opioid dependence (OD) following opioid detoxification $315-345M*</td>
</tr>
<tr>
<td><strong>ARISTADA</strong></td>
<td>Schizophrenia $260-290M*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Under FDA Review – PDUFA June 1</th>
<th>Schizophrenia</th>
<th>&lt;$10M*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LYBALVI</strong></td>
<td>Bipolar I disorder</td>
<td>*Potential launch H2’21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Royalty Stream</th>
<th>Relapsing forms of multiple sclerosis (MS) Launched in Q4’19</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VUMERITY</strong> (gabapentin enacemate)</td>
<td>(Commercialized by Biogen)</td>
</tr>
</tbody>
</table>

*These expectations, and the underlying assumptions and risks, are set forth in the Company’s 8-K filed with the SEC on February 11, 2021. The Company expressly disclaims any obligation to update or reaffirm these expectations.

Full indication and prescribing information for VIVITROL may be found at [www.vivitrol.com](http://www.vivitrol.com). Full prescribing information for ARISTADA may be found at [www.aristada.com](http://www.aristada.com).
Capital Allocation:
Focused on Organizational Efficiency and Cost Management
Conducted Comprehensive Analysis of Operations and Cost Structure and Implemented Significant Changes

<table>
<thead>
<tr>
<th>Comprehensive Cost Structure Review</th>
<th>Optimization Initiatives Undertaken</th>
</tr>
</thead>
</table>
| • Conducted extensive review of operations and cost structure both internally and with external advisors to identify potential areas for efficiencies and savings  
  o Completed peer benchmarking to identify areas of focus for potential saving initiatives  
  o Assessed resource requirements across multiple functions to determine optimal in-house/outsourcing strategy  
  o Evaluated enterprise system/processes that could drive long-term efficiencies | **Commercial infrastructure reorganization**  
  ✓ Addiction salesforce refocused to increase emphasis on alcohol dependence  
  ✓ Psychiatry infrastructure realigned to drive efficiencies and reallocate resources to support potential launch of LYBALVI™  
**R&D prioritization**  
  ✓ Prioritized highest-ROI development programs  
  ✓ Determined optimal balance of internal/external resources  
**G&A leverage**  
  ✓ Identified efficiency opportunities; implementation ongoing |
Disciplined Capital Allocation Supports Highest ROI Priorities

- Support profitable commercial portfolio
- Prepare for anticipated launch of LYBALVI™
- Advance nemvaleukin alfa
- Develop next generation of pipeline candidates

- Drive operating margins of commercial business and focus on profitability
- Create value through innovation and position ALKS for future growth
Disciplined Capital Allocation Supports Highest-ROI Priorities

Support profitable commercial portfolio

**VIVITROL®**
- Awareness and marketing campaign for alcohol dependence indication
- Addiction sales infrastructure

**ARISTADA®**
- Drive growth through continued focus on two-month dose plus ARISTADA INITIO®
- Psychiatry sales infrastructure

- **Shared commercial services support**
  - Market Access and key account management infrastructure
  - Patient access services
  - Digital marketing capabilities

- **Policy initiatives in addiction and serious mental illness**
Disciplined Capital Allocation Supports Highest-ROI Priorities

Prepare for anticipated launch of LYBALVI™*

**Commercial Launch**

- Complete sales force hiring
- Support patient access programs
- Commence planned marketing campaign
- Initiate physician outreach & payer interactions

**Life Cycle Management**

- Complete early-in-illness phase 3 study
- Initiate planned pediatric program

*LYBALVI NDA under FDA review; PDUFA June 1, 2021
Disciplined Capital Allocation Supports Highest-ROI Priorities

Advance nemvaleukin alfa

- Initiate studies to support potential registration pathways in mucosal melanoma and platinum-resistant ovarian cancer (PROC)
- Continued enrollment in ARTISTRY-2 dose expansion evaluating nemvaleukin subcutaneous anti-tumor activity
- Continue to build objective response data in multiple tumor types in ARTISTRY-1 and ARTISTRY-2
Disciplined Capital Allocation Supports Highest-ROI Priorities

Develop next generation of pipeline candidates

**Neuroscience**

ALKS 1140
- Complete phase 1 enabling activities
- Initiate phase 1 first-in-human study
- Initiate phase 0 biomarker study

Orexin
- Nominate orexin candidate to the clinic

**Oncology**

IL-12
- Lead candidate generation

IL-18
- Advance lead candidate identification
Pairing Revenue Strength With Active Expense Management to Achieve Profitability Targets

Plan to achieve profitability targets through active management of cost structure, adapted to revenue growth profile

Profitability Targets

<table>
<thead>
<tr>
<th></th>
<th>FY ‘23</th>
<th>FY ‘24</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGNI/Revenue*</td>
<td>25%</td>
<td>30%</td>
</tr>
<tr>
<td>EBITDA/Revenue*</td>
<td>20%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Profitability Target Bridge

- For illustrative purposes. Estimated ranges.

* Reconciliations of non-GAAP financial measures to the most directly comparable GAAP financial measures, to the extent reasonably determinable, can be found in the Appendix of this presentation.

NGNI: Non-GAAP net income; EBITDA: Earnings before interest, tax, depreciation, amortization.
Value Enhancement Plan Includes Evaluation of Strategic Opportunities

**Evaluation of Strategic Opportunities**

- Monetization of non-core assets
- Strategic collaboration for nemvaleukin and other oncology assets

**Operational**

- Elements of legacy drug delivery/drug manufacturing business
  - Platforms
  - Intellectual property
- Preclinical and clinical assets outside of strategic portfolio

**Financial**

- Monetization of royalty revenue streams from third-party products
- Risk-sharing product development structures
Strong Corporate Governance:
Board Refreshment, Independence and Oversight
Maintaining Strong Board of Directors and Corporate Governance

Board Composition and Refreshment

• Board skills and expertise support strategy and long-term value creation

• Appointed 4 new, independent directors since September 2019
  o New directors bring financial, operational and oncology expertise
  o Three longer-serving directors have recently retired or announced their retirement from the Board

• Average director tenure: 3.4 years*

• Continued board refreshment efforts announced for 2021

• Proposal to shareholders to declassify the Board to be included in 2021 proxy statement

Board Oversight of Value Enhancement Plan

• Formed Financial Operating Committee to oversee implementation of Value Enhancement Plan

• Compensation Committee incorporated objective, performance-based elements related to Value Enhancement Plan into company’s 2021 long-term incentive plan for executives

*Does not include two directors retiring at close of the Company’s 2021 Annual General Meeting
Board Refreshment

David W. Anstice AO
Lead Independent Director
• More than 30 years of experience in pharmaceutical drug development and commercialization
• Former EVP of Merck

Robert A. Breyer
• Significant management and operations experience
• Former COO of Alkermes

Shane M. Cooke
• Global experience in the biopharmaceutical industry, including in business development
• Former CFO of Elan Corporation, plc; former President of Alkermes

David A. Daglio, Jr.
• Experience in institutional investment management, value creation and transactional matters
• Former EVP, CIO and Executive Director of Mellon Investments

Wendy L. Dixon, Ph.D.
• Experience in product development, regulatory affairs and commercialization of pharmaceuticals
• Former Chief Marketing Officer at Bristol-Myers Squibb; former executive at Merck

Richard B. Gaynor, M.D.
• Experience in scientific research and academia
• Current President, Chief of Research and Development at BioNTech; formerly at Eli Lilly

Brian P. McKeon
• Experience in finance, strategic planning, corporate development and investor relations
• Current CFO and Treasurer of IDEXX Labs
• Former CFO of Iron Mountain

Paul J. Mitchell
• Significant experience in financial reporting and compliance
• Former CFO and Treasurer of Kenet; former CFO of Kopin

Richard F. Pops
• Leadership experience and deep industry knowledge gained through >25 years in the industry
• Current CEO of Alkermes
• Board member of BIO and PhRMA

Nancy L. Snyderman, M.D.
• Experience as a practicing physician, veteran healthcare journalist, advisor to policy organizations
• Former Chief Medical Editor at NBC News
• Former SVP Corporate Communications at Johnson & Johnson

Andy Wilson
• Experience in finance and accounting, strategic planning, investor relations and business development
• Former CFO of PerkinElmer; former executive at Danaher

Nancy J. Wysenski
• Experience building and leading life sciences companies and in overseeing key operational and commercial functions
• Former EVO and CCO of Vertex; former COO of Endo

Announced retirement as of the close of the Alkermes 2021 annual general meeting of shareholders

New Director in 2019/2020
Diversified Biopharmaceutical Company With Proven Drug Development and Commercialization Capabilities

<table>
<thead>
<tr>
<th>Significant, diverse revenues driving &gt;$1B topline and positioned for growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proprietary commercial products that target large markets in addiction and psychiatry</td>
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<tr>
<td>Additional potential revenue streams as new products launch* and grow</td>
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</tbody>
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<table>
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<tr>
<th>Pipeline of novel development candidates designed to target significant unmet needs</th>
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</thead>
<tbody>
<tr>
<td>Oncology</td>
</tr>
<tr>
<td>Nemvaleukin alfa</td>
</tr>
<tr>
<td>• Phase 2</td>
</tr>
<tr>
<td>• Advanced solid tumors</td>
</tr>
<tr>
<td>IL-12</td>
</tr>
<tr>
<td>• Preclinical</td>
</tr>
<tr>
<td>• Advanced solid tumors</td>
</tr>
<tr>
<td>Neuroscience</td>
</tr>
<tr>
<td>ALKS 1140</td>
</tr>
<tr>
<td>• IND-enabling</td>
</tr>
<tr>
<td>• Neurodegenerative and neurodevelopmental disorders</td>
</tr>
<tr>
<td>Orexin 2R Agonist</td>
</tr>
<tr>
<td>• Preclinical</td>
</tr>
<tr>
<td>• Narcolepsy</td>
</tr>
</tbody>
</table>

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 NDA under FDA review; PDUFA June 1, 2021
Developing New Treatments to Address Unmet Patient Need in Neuroscience and Oncology: Optimizing for Success

Craig Hopkinson
Executive Vice President, R&D and Chief Medical Officer
Alkermes R&D Objective

• Develop innovative medicines with clear value propositions relative to current and anticipated future standards of care in neuroscience and oncology
  ◦ Based on strong **biological rationale**
  ◦ Embodied in **new molecular entities** that leverage Alkermes’ advanced small molecule drug development and protein engineering capabilities
  ◦ Developed **efficiently and cost effectively** with rigorous governance
• Rooted in Alkermes’ patient-centric approach to developing medicines
Evolution to 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
Integrated Approach to Target Evaluation and Portfolio Assessment

- Biology rationale
- Unmet need
- High-Value Development Candidate
- Technical feasibility
- Regulatory pathway
- Clinical pathway
- Commercial opportunity
Efficient Development Designed to Expedite Answers to Critical Go/No-Go Questions

Preclinical Research & Development

• Early demonstration of preclinical proof-of-concept in disease-relevant models
• Thorough molecular design feasibility assessment
• In-depth drug metabolism, pharmacokinetics and human dose prediction
• Embedded reverse translational mindset, tailoring the medication to the patient
• Establishment of scale-up path
• Strong foundational intellectual property

Clinical Development

• Accelerate generation of decision-driving data
  ◦ Innovative clinical trial designs including adaptive and/or basket approaches
  ◦ Comprehensive biomarker strategy
  ◦ Expeditious and cost-efficient execution
• Early engagement with regulators to establish clear and expeditious regulatory pathways
• Proactive and pragmatic approach to indication expansion
Portfolio Management and Investment Prioritization:
Data-Driven Decision Making

• **Pre-established success criteria and stage-gates throughout development process**
  – Enables ‘quicker kills’ and de-risks overall R&D investment

• **Cross functional, integrated governance to enable strategic decision making**
  – Extends beyond R&D (legal, commercial and manufacturing)
  – Incorporates broader perspectives into decision making

### Recently Discontinued Programs

<table>
<thead>
<tr>
<th>Program</th>
<th>Reason for discontinuation</th>
<th>Phase of development</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDN-929 (neuroscience)</td>
<td>Suboptimal pharmaceutical properties</td>
<td>Phase 1</td>
</tr>
<tr>
<td>IL-10 (oncology)</td>
<td>Failure in third-party competitive program</td>
<td>IND-enabling</td>
</tr>
<tr>
<td>Epigenetic target (oncology)</td>
<td>Strategic portfolio fit</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Stress-signaling target</td>
<td>Research proof-of-concept not achieved</td>
<td>Preclinical</td>
</tr>
<tr>
<td>(neuroscience)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
R&D Strategic Planning and Execution Integrates Ongoing Feedback from External Advisory Boards

• Dedicated neuroscience and oncology Scientific Advisory Boards comprised of leading experts in medicinal chemistry, translational medicine and academic science
  ◦ Offer insight into current scientific state-of-the-art approaches
  ◦ Provide independent program assessments
  ◦ Identify opportunities to de-risk and/or accelerate programs
  ◦ Engage routinely with internal teams to address emerging challenges

• Clinical Advisory Boards comprised of global thought leaders in areas of therapeutic focus
  ◦ Validate clinical trial designs
  ◦ Support endpoint selections
  ◦ Advise on regulatory strategy and expedited pathways
  ◦ Provide insights on disease landscape
Alkermes New R&D Approach is Designed to Increase the Probability of Technical, Regulatory and Commercial Success

- Design medicines with compelling value propositions
- Accelerate time to data and decision milestones
- Establish and adhere to clear go/no-go criteria

Efficiently bring important new medicines to patients
Focus on Innovative Molecular Design: Harnessing Alkermes’ Scientific & Technical Capabilities

Markus Haeberlein, Ph.D.
Senior Vice President, Research
Alkermes’ Expertise: Molecular Design

- Strong biology rationale:
  - Capabilities focused within defined scientific platforms
  - Targets externally validated and vetted with scientific advisors
  - Potential opportunity for first-in-class or best-in class therapies
  - Structure/activity insight guides molecular design

- Technical feasibility:
  - Integrated capabilities in Medicinal Chemistry, Protein Engineering and Molecular Modeling utilized to address technical challenges
Customized Medicinal Chemistry or Protein Engineering Approach for Each Target

**Medicinal Chemistry**
- Computationally-guided internal medicinal chemistry design
- Internal synthesis expertise enables work in “difficult-to-make space”
- Access to specialized chemistry capabilities
  - e.g., Protein degrader technology, DNA-encoded libraries

**Protein Engineering**
- Close integration with modeling team to guide protein design
- Advanced protein engineering capabilities
  - Cytokine re-engineering
  - Tumor-targeting platform
  - Bispecific fusion proteins
Sophisticated, Purpose-Built, State-of-the-Art Toolbox for Advanced Molecular Design

**ALKSketch**
Proprietary molecular design platform with on-the-fly in silico predictions

- **Molecular dynamics**
  - Binding energy calculations

- **Protein design**
  - Computational optimization

- **Artificial Intelligence** for generative design
  - Machine-designed molecular structures

- **Machine Learning models**
  - In silico assay panel with pharmacology, DMPK and safety predictions
Scientific Platforms Serve as the Foundation to R&D Strategy and Focus in Neuroscience and Oncology

**Neuroscience**
- Synaptic Dysfunction
  - HDAC Inhibitors
  - Orexin Agonist

**Oncology**
- Immune Modulation
  - Engineered Cytokines
Synaptic Dysfunction: A Versatile Platform Across Neurology and Psychiatry

• Synaptic loss is the best current pathologic correlate of cognitive decline\(^1\)

• Improving synaptic function is critical to slow progression and preserve cognitive and functional abilities in neurological disorders\(^2\)

• Targeting synaptic integrity and function at different levels
  ◦ Synapse structure: Restore integrity and number of synapses
  ◦ Synapse function: Increase efficiency of synapses and restore function in deficient circuitry
  ◦ Synapse environment: Improve efficiency of supporting cells, such as microglia and astrocytes

\(^1\) Morrison, J., Baxter, M. *Nat Rev Neurosci*. 2012
\(^2\) Verstraelen, P et al. *Front. Neurosci*. 2018
## Development Candidates Emerging From Neuroscience Platform

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

- Proinflammatory cytokines have pleiotropic effects and can act on every phase of the cancer immunity cycle\(^1\)

- Alkermes is focusing on cytokine-based therapies designed to:
  - Increase visibility of tumor cells to immune system
  - Increase tumor-killing potential of CD8+ T and NK cells
  - Remove suppressive signals in the tumor microenvironment

- Modern cytokine-based drugs need a high degree of engineering to:
  - Reduce side effects
  - Improve pharmacokinetics
  - Enhance efficacy

NK: natural killer

\(^1\) Berraondo, et al. *British Journal of Cancer*. 2019
Immune Modulation Portfolio of Engineered Cytokines

Nemvaleukin alfa  |  Tumor-Targeted Split IL-12  |  Enhanced Efficacy IL-18

Technical challenge
- Efficacy of rhIL-2 limited by expansion of immunosuppressive Treg cells and other undesirable effects
- rhIL-12 has low tolerability when given systemically
- Efficacy of rhIL-18 limited by a checkpoint protein that binds to IL-18 (IL-18BP)

Alkermes’ protein engineering solution
- Fusion of circularly permuted IL-2 with the IL-2Rα subunit resulting in only activating intermediate-affinity IL-2R
- Separate inactive tumor-targeted IL-12 subunits assemble and activate in the tumor
- Engineered IL-18, for which activity is not blocked by suppressive mechanisms

Key anti-tumor mechanisms
- Expansion of CD8+ T cells and NK cells
- Minimal expansion of Treg cells
- Drive proinflammatory responses at the tumor site through potent activation of CD8+ T and NK cells
- Enhance IL-18 mediated anti-cancer immune responses
- Reduce T cell exhaustion

Potential cancer types
- Solid tumors, including melanoma, platinum-resistant ovarian cancer
- Solid tumors, including pancreatic, breast, colon and ovarian cancer
- Immunosuppressive tumor microenvironment
- Checkpoint inhibitor-resistant tumors
Focus and Discipline Integral to R&D Portfolio Advancement

<table>
<thead>
<tr>
<th>Drug/Indication</th>
<th>Discovery Phase</th>
<th>IND Enabling Phase</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nemvaleukin alfa Intravenous Dosing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nemvaleukin alfa Subcutaneous Dosing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALKS 1140 Neurology (Orphan)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orexin 2R Agonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDAC Inhibitors Neurology/Neuropsychiatry (Non-Orphan)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDAC Inhibitors Frontotemporal Dementia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor-targeted Split IL-12</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDAC Inhibitors Oncology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-18</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Oncology

Neuroscience
Nemvaleukin alfa: A Novel, Engineered Interleukin-2 (IL-2) Variant Immunotherapy

Clinical Data Updates from ARTISTRY-1 and ARTISTRY-2 Trials

Jessica Rege, Ph.D.
Vice President, Clinical Research, Oncology
Today’s Agenda

1. Harnessing the potential of the IL-2 pathway

2. Advancing a differentiated IL-2
   – Nemvaleukin alfa (nemvaleukin) molecular design
   – Nemvaleukin clinical development strategy

3. Clinical data overview
   – ARTISTRY-1 (intravenous dosing): Focus on melanoma and platinum-resistant ovarian cancer
   – ARTISTRY-2 (subcutaneous dosing): Subcutaneous recommended phase 2 dose and preliminary objective response

4. Upcoming data and next steps
IL-2 Therapy Has Proven Anti-Tumor Efficacy

- IL-2 is a natural regulator of the activity of lymphocytes involved in the immune response
- Recombinant human IL-2 as monotherapy can drive **complete and durable responses** in certain tumor types, but its toxicity profile significantly limits its potential broader application
- A molecule with differentiated tolerability that targets the IL-2 pathway could be complementary to a wide range of other therapeutic approaches

---

**Non-specific Agents**

- Cytotoxic Chemotherapy
- First generation cytokines
- Native IL-2 Proleukin®

**Specific Agents**

- Targeted Agents
- Engineered cytokines
- Nemvaleukin

**Scientific Insight Enabled by Biotechnology**

New molecule with engineered specificity
Nemvaleukin is Sterically Occluded From Binding to the High-Affinity IL-2 Receptor

For illustrative purposes only; T_{reg}: regulatory T cell; NK cell: natural killer cell
# Nemvaleukin Key Differentiation Parameters Support Broad Potential Utility

<table>
<thead>
<tr>
<th>Validate Molecular Design</th>
<th>Demonstrate Anti-tumor Activity</th>
<th>Create Dosing Flexibility</th>
<th>Support Broad Potential Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demonstrated selective expansion of CD8+ T and NK cells</td>
<td><strong>Monotherapy:</strong> Single-agent activity observed with IV nemvaleukin</td>
<td><strong>IV:</strong> Plans to progress into registration-enabling studies</td>
<td>Monotherapy activity observed with IV nemvaleukin in CPI-experienced patients</td>
</tr>
<tr>
<td>Demonstrated minimal changes in peripheral regulatory T cells</td>
<td><strong>Combination:</strong> Activity observed in combination with anti-PD-1 (both IV and SC nemvaleukin), in hard-to-treat tumors</td>
<td><strong>SC:</strong> Only SC IL-2 variant in development</td>
<td>Combination activity observed with pembrolizumab</td>
</tr>
<tr>
<td>In both intravenous (IV) and subcutaneous (SC) administrations</td>
<td></td>
<td>Identified RP2D based on PK/PD, safety and anti-tumor activity</td>
<td>Combination activity observed with multiple agents in preclinical studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Achieved first objective SC response</td>
<td>May offer dosing flexibility</td>
</tr>
</tbody>
</table>

**RCC = renal cell carcinoma, RP2D = Recommended Phase 2 Dose, PK/PD = Pharmacokinetic/Pharmacodynamic, CPI = Checkpoint Inhibitors**
Clinical Development Strategy Focused on Difficult to Treat Cancers With Clear Unmet Need

CPI-Approved Tumor Types

CPI-Unapproved Tumor Types

Post-CPI Failure

Combo with anti-PD-(L)1

Combo with anti-PD-1 PROC

Combo with anti-PD-1

Monotherapy Mucosal melanoma*

Addition to standard-of-care

New potential therapies designed to address important unmet needs where checkpoint inhibitors are not successful

*Granted Orphan Drug Designation; PROC = Platinum-Resistant Ovarian Cancer; CPI = Checkpoint Inhibitors
ARTISTRY-1 Intravenous Dosing Study
## IV Nemvaleukin: Demonstrated Monotherapy Anti-Tumor Activity in Melanoma and Renal cell Carcinoma

Dose: Nemvaleukin (IV RP2D 6 µg/kg) Monotherapy

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Prior Therapy (Lines)</th>
<th>Best Overall Response</th>
<th>Max Decrease in Target Lesions</th>
<th>Time on Therapy (weeks)</th>
<th>Continuing therapy?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosal melanoma</td>
<td>Nivolumab (1)</td>
<td>PR</td>
<td>41%</td>
<td>72</td>
<td>Yes</td>
</tr>
<tr>
<td>Mucosal melanoma</td>
<td>Nivolumab (1)</td>
<td>Unconfirmed PR</td>
<td>39%</td>
<td>15</td>
<td>No</td>
</tr>
<tr>
<td>Cutaneous melanoma</td>
<td>Atezoliseptin, nivolumab, melanoma vaccine AGI-101H, carboplatin/paclitaxel (3)</td>
<td>PR, awaiting confirmation*</td>
<td>44%</td>
<td>10</td>
<td>Yes</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>Sunitinib, nivolumab (2)</td>
<td>PR, awaiting confirmation</td>
<td>31%</td>
<td>21</td>
<td>Yes</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>Ipilimumab, nivolumab, cabozantinib/placebo (1)</td>
<td>PR, awaiting confirmation</td>
<td>43%</td>
<td>16</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Data cutoff March 1, 2021. *Reported after data extraction
PR=partial response, RP2D = Recommended Phase 2 Dose.
### ARTISTRY-1 Safety Summary

- Safety profile of nemvaleukin in combination with pembrolizumab generally consistent with monotherapy profile
- In combination, no emerging evidence of additive toxicities to those already established for pembrolizumab alone

### Monotherapy (Part B only; n=42)

- Chills, pyrexia, nausea & hypotension are most frequently (>30%) reported treatment-related adverse events (TRAEs); anticipated effects of cytokine administration
  - Transient, majority Grade ≤2 in severity
- Most frequent (>10%) Grade 3-4 TRAE was neutropenia
- No discontinuations due to treatment-related AEs
- No deaths due to treatment-related AEs

### Combination with Pembrolizumab (Part C only; n=111)

- Chills, pyrexia & fatigue are most frequently (>30%) reported treatment-related AEs; anticipated effects of cytokine administration
  - Transient, all Grade ≤2 in severity
- Most frequent (>10%) Grade 3-4 TRAE was neutrophil count decrease
- Discontinuation due to treatment-related AEs included: fatigue, pneumonitis, infusion-related reaction, inanition
- Two deaths in pancreatic cancer patients (reported at ESMO 2020)
  - One death due to inanition and assessed by the investigator as related to nemvaleukin
  - One death due to underlying cancer and assessed as unrelated to treatment

---

Data as of December 2020
Monotherapy Responses in Melanoma
High Unmet Needs Remain for Treatment of Refractory Melanoma

### Melanoma Burden

- Fifth most common type of cancer in the U.S.\(^1\)
  - U.S. prevalence: ~100K new cases in 2020
  - ~7K estimated deaths in the U.S. in 2020 due to melanoma
- Melanoma patients with distant metastases have a 5-year survival rate of 27%\(^2\)
- Incidence has risen faster than almost any common cancer type in the last 50 years\(^3\)

### Mucosal Melanoma

- Rare and aggressive type of melanoma occurring in mucosal membranes that is often diagnosed late due to non-specific symptoms and anatomic location\(^4\)
- Poor prognosis when compared with cutaneous melanoma
  - 5-year survival rates as low as 14% for mucosal melanoma\(^5\)
- Mucosal melanoma is largely resistant to traditional therapies\(^5,6\)
  - Response rates with chemotherapy are poor and targeted therapies such as BRAF inhibitors are usually not an option for mucosal melanoma
  - Immune checkpoint inhibitors (nivolumab, ipilimumab) have lower response rates for mucosal melanoma than for cutaneous melanoma
- Nemvaleukin was recently granted Orphan Drug Designation for mucosal melanoma

---

ARTISTRY-1 Nemvaleukin Melanoma Monotherapy Cohort
Focused on Unmet Need

Key Inclusion Criteria

- Progressed on:
  - Immune checkpoint inhibitor (e.g., anti-PD-(L)1 with or without anti-CTLA-4)
  - Targeted agent as appropriate (e.g., BRAF inhibitor if BRAF-mut)

ARTISTRY-1 Monotherapy Study
Melanoma Cohort

- Protocol-defined efficacy response criteria achieved, triggered Simon Two-Stage expansion cohort
- Second stage of enrollment underway

<table>
<thead>
<tr>
<th>ARTISTRY-1 Simon Two Stage</th>
<th>Stage 1 N</th>
<th>Enroll more if</th>
<th>Stage 2 N</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory melanoma expansion</td>
<td>21</td>
<td>&gt;2 PR/CR</td>
<td>20</td>
<td>41</td>
</tr>
</tbody>
</table>
ARTISTRY-1: Nemvaleukin Monotherapy
Responses in CPI-Experienced Melanoma Patients

• Preliminary data (ongoing study):
  ° Out of 28 evaluable patients (with ≥ 1 scans):
    º Total 3 responses observed, with tumor shrinkage
    -- 2 mucosal melanoma and 1 cutaneous melanoma
  ° Majority of patients are ongoing as of March 15, 2021 data cut

CPI = Checkpoint Inhibitors, IV = Intravenous, PD = Progressive Disease, PR = Partial Response, RP2D = Recommended Phase 2 Dose, SD = Stable Disease.

†Reported after the data cut off and awaiting confirmation.
ARTISTRY-1 Monotherapy Dose Expansion Cohort

Case Study: 67-Year-old Male Cutaneous Melanoma Patient

Diagnosis
Melanoma
• Diagnosed December 13, 2016

Prior Treatment

<table>
<thead>
<tr>
<th>Line</th>
<th>Therapy</th>
<th>Duration (mos)</th>
<th>Best Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adj</td>
<td>Cobimetinb/atezolizumab</td>
<td>9</td>
<td>PD</td>
</tr>
<tr>
<td>1</td>
<td>Nivolumab</td>
<td>4</td>
<td>PD</td>
</tr>
<tr>
<td>2</td>
<td>Vaccine AGI-101H</td>
<td>1</td>
<td>PD</td>
</tr>
<tr>
<td>3</td>
<td>Paclitaxel/carboplatin</td>
<td>2</td>
<td>SD</td>
</tr>
</tbody>
</table>

Last dose of prior treatment November 3, 2020

On-Study Activity

Started Tx: December 2020 (Remains On treatment*):
Nemvaleukin monotherapy (6 µg/kg IV)

Change in Target Lesion from Baseline

<table>
<thead>
<tr>
<th>Target Lesion Size</th>
<th>Cycle 2</th>
<th>Cycle 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable Disease (SD)*:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27% reduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial Response (PR)*†:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>44% reduction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment-related AEs:
• Manageable with no dose modifications
• Anemia and fever, grade 2
• Intermittent neutropenia grade 3 and grade 4

*Patient continues on therapy as of March 15, 2021; † per RECIST criteria; † Reported after the data cut off and awaiting confirmation. PD=progressive disease, SD=stable disease.
# Nemvaleukin Monotherapy for Melanoma Advancing Toward Registration Stage

**Demonstrate monotherapy activity:**
- Mucosal monotherapy
- Cutaneous monotherapy

**Identify unmet need:**
- CPI-experienced patients
- Mucosal melanoma FDA orphan designation

**Advance clinical studies to support potential registration path in mucosal melanoma monotherapy**
- Engage with regulatory authorities on registration plans
Responses in Heavily Pre-treated Platinum-Resistant Ovarian Cancer Patients in Combination with Pembrolizumab
High Unmet Needs Remain for Treatment of Ovarian Cancer

**Ovarian Cancer Burden**
- Second most common gynecological cancer\(^1\)
  - U.S. prevalence: ~233K cases in 2017\(^2\)
  - Leading cause of gynecologic cancer-related deaths in the U.S.\(^1\)
  - 5-year survival rate for stage IV ovarian cancer of 29%\(^3\)
  - Median overall survival (mOS) for platinum-resistant ovarian cancer is less than 12 months\(^4\)
  - Standard of care median progression-free survival (mPFS) ~3.5 months\(^5\)

**Limited Treatment Options**
- 1L (Standard of Care)
  - Surgery + platinum-based chemotherapy +/- bevacizumab followed by bevacizumab and/or PARP inhibitor as maintenance\(^6\)
  - Many become platinum resistant (refractory) and progress < 6 months after completion of platinum-based chemotherapy\(^6\)
- Few treatment options post-platinum chemotherapy
  - In one study of non-platinum chemotherapy, objective response rate was 12% and median progression-free survival was 3.4 months\(^7\)
- Anti-PD-1 (e.g., pembrolizumab, atezolizumab) have been shown to be ineffective for treatment of ovarian cancer\(^8,9\)
  - Pembrolizumab efficacy in ovarian cancer is ~10% for high PD-1 expression\(^8\)

---
ARTISTRY-1: Nemvaleukin in Combination With Pembrolizumab
Responses in Heavily Pre-treated Ovarian Cancer

Out of 14 patients with ≥1 scans:
- 4 patients experienced an objective response
  - 1CR, 3PRs confirmed and unconfirmed
- 5 patients remain on study as of March 15, 2021 data cut

Tumor Type (Line of Therapy)
- Ovarian Cancer (5)
- Ovarian Cancer (2)
- Ovarian Cancer (11)
- Ovarian Cancer (6)
- Ovarian Cancer (7)
- Ovarian Cancer (5)
- Ovarian Cancer (4)
- Ovarian Cancer (2)
- Ovarian Cancer (3)
- Ovarian Cancer (3)
- Ovarian Cancer (5)
- Ovarian Cancer (2)
- Ovarian Cancer (6)
- Ovarian Cancer (4)
- Ovarian Cancer (3)

Time on Study (Weeks)
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96 102 108 114

Nemvaleukin (IV 3 µg/kg) & Pembrolizumab (IV, 200 mg)
- Evaluation of SD
- Evaluation of PD
- Evaluation of PR
- Evaluation of CR
- Ongoing

IV=Intravenous, PD=Progressive Disease, PR=Partial Response, SD=Stable Disease, CR=Complete Response

Data cut off March 15, 2021
**ARTISTRY-1: Nemvaleukin in Combination With Pembrolizumab**

**Responses in Platinum-Resistant Ovarian Cancer**

<table>
<thead>
<tr>
<th>Age</th>
<th>Prior Therapies (Lines)</th>
<th>Max. Reduction of Target Lesions (%)</th>
<th>Overall Response (Investigator assessment)</th>
<th>CA125 (U/ml) Response From Baseline</th>
<th>Time on Therapy (Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC1</td>
<td>48 CBP/PAC/BEV, CDDP/GEM, CBP/PLD, PCA, CBP/DOC (5)</td>
<td>-70</td>
<td>CR†</td>
<td>Normalized from 282 to 24.5 at Cycle 4</td>
<td>112 ➤</td>
</tr>
<tr>
<td>OC2</td>
<td>83 CBP/PAC/DOC, CBP/DOC/NIR/TAM (2)</td>
<td>-95</td>
<td>PR</td>
<td>Normalized from 125 to 16 at Cycle 4</td>
<td>56 ➤</td>
</tr>
<tr>
<td>OC3</td>
<td>60 CBP/PAC, CBP/PLD, CBP/BEV, PAC/BEV, BEV, PLD (7)</td>
<td>-45</td>
<td>uPR</td>
<td>Reduced from 1400 to 766 at Cycle 11</td>
<td>38</td>
</tr>
<tr>
<td>OC4</td>
<td>75 CBP/PAC, PLD/BEV, CBP/GEM, TOP, NIR (6)</td>
<td>-34</td>
<td>PR, awaiting confirmation*</td>
<td>Reduced from 493 to 191 at Cycle 14</td>
<td>46 ➤</td>
</tr>
<tr>
<td>OC5</td>
<td>83 CBP/PAC, CBP, CBP/PAC/CAP, CBP/PLD, CBP/PLD (11)</td>
<td>-28</td>
<td>SD</td>
<td>Normal at baseline at 10.6</td>
<td>52 ➤</td>
</tr>
</tbody>
</table>

BEV=bevacizumab, CAP=capecitabine, CBP=carboplatin, CDDP=cisplatin, DOC=docetaxel, GEM=gemcitabine, NIR=niraparib, PAC=paclitaxel, PCA=paclitaxel albumin, PLD=pegylated liposomal doxorubicin hydrochloride, TAM=tamoxifen, TOP=topotecan, CR=complete response, PR=partial response, uPR=unconfirmed PR, SD=stable disease

†CR due to node shrinkage to <10 mm short axis, *per RECIST criteria

Table: Patient Experience in Reduction of Tumor Burden

Data cut off March 15, 2021
ARTISTRY-1: Nemvaleukin in Combination With Pembrolizumab
Case Study: 75-Year-Old Ovarian Cancer Patient

Diagnosis
High-Grade Serous Ovarian Cancer
- PD-L1 status: unknown
- BRCA status: wild-type
- Platinum-resistant

Prior Treatment

<table>
<thead>
<tr>
<th>Line</th>
<th>Therapy</th>
<th>Duration (mos)</th>
<th>Best Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CBP/paclitaxel</td>
<td>4</td>
<td>Not evaluable</td>
</tr>
<tr>
<td>1M</td>
<td>ZEJULA*</td>
<td>4</td>
<td>SD</td>
</tr>
<tr>
<td>2</td>
<td>DOXIL*/AVASTIN*</td>
<td>3</td>
<td>PD</td>
</tr>
<tr>
<td>3</td>
<td>Carboplatin/gemcitabine</td>
<td>4</td>
<td>PR</td>
</tr>
<tr>
<td>4</td>
<td>Topotecan</td>
<td>2</td>
<td>SD</td>
</tr>
<tr>
<td>5</td>
<td>ZEJULA* last dose 3/6/20</td>
<td>5.5</td>
<td>SD</td>
</tr>
</tbody>
</table>

On-Study Tumor Shrinkage

<table>
<thead>
<tr>
<th>Change in Target Lesions from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 2: Stable Disease (SD): 22% reduction</td>
</tr>
<tr>
<td>Cycle 4: Stable Disease (SD): 22% reduction</td>
</tr>
<tr>
<td>Cycle 6-12: Stable Disease (SD): 28% reduction</td>
</tr>
<tr>
<td>Cycle 14: Partial Response (PR)*: 34% reduction</td>
</tr>
</tbody>
</table>

Patient has remained on treatment for 11 months

Treatment-related AEs:
- Manageable with no dose modifications
- Majority AEs grade 1 and 2
- Grade 3 elevated ALT and grade 3 anemia

Notes:
*Continues on therapy as of March 15, 2021, †per RECIST criteria, ‡Reported after the data cut off and awaiting confirmation, PD = Progressive Disease, PR=Partial Response, SD=Stable Disease
Advancing Fast-to-Market Opportunity in Platinum-Resistant Ovarian Cancer (PROC)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advance discussions on registration plans with regulatory agencies</td>
<td>Initiated</td>
</tr>
<tr>
<td>Initiate study with intravenous nemvaleukin in combination with pembrolizumab</td>
<td>H2 2021</td>
</tr>
<tr>
<td>Complete enrollment - subcutaneous nemvaleukin dose expansion PROC cohort</td>
<td></td>
</tr>
</tbody>
</table>

Ongoing studies designed to accumulate additional data:

- **ARTISTRY-1**
  - Intravenous
  - Phase 1/2

- **ARTISTRY-2**
  - Subcutaneous
  - Phase 1/2

- **ARTISTRY-3**
  - Tumor Microenvironment
  - Phase 2

- **ION**
  - Head and Neck
  - Phase 2
Clinical Update for ARTISTRY-2
Selection of Recommended Phase 2 Dose (RP2D)
ARTISTRY-2: RP2D Determined

- SC 3 mg q7d nemvaleukin selected as recommended phase 2 dose (RP2D) for ARTISTRY-2 efficacy expansion stage
- Selection of RP2D based on totality of data including PK/PD, safety and efficacy during dose escalation phase
  - Acceptable safety and tolerability profile consistent with the anticipated pharmacological effect and that observed with intravenous nemvaleukin
  - Dose-dependent increases in NK cell and CD8+ T cell activation and minimal increase in immunosuppressive $T_{\text{regs}}$
  - Clinical benefit (stable disease) observed
- Additional ARTISTRY-2 data to be presented at future medical meeting
- Phase 2 efficacy expansion initiated based on totality of dose escalation data

$T_{\text{regs}}$ = regulatory T cell, NK = Natural Killer, PK/PD = Pharmacokinetic/Pharmacodynamic
### Safety Profile of SC Nemvaleukin Consistent With Mechanism of Action and IV Nemvaleukin

#### RP2D Regimens Selected

<table>
<thead>
<tr>
<th>SC 3 mg q7d declared as RP2D based on totality of data</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 6 mg q21d dose may offer additional flexibility in treating certain tumor types and/or in combination settings in the future</td>
</tr>
<tr>
<td>• Maximum tolerated doses (MTD) for SC nemvaleukin were determined to be 6 mg q7d and 10 mg q21d</td>
</tr>
</tbody>
</table>

#### Most Commonly Reported TEAEs at RP2D Monotherapy

<table>
<thead>
<tr>
<th>3 mg q7d (n=7):</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chills, pyrexia, fatigue, nausea, lymphopenia, injection site reactions, AST/ALT increase are most frequently (&gt;30%) reported treatment-related adverse events (AEs); majority anticipated effects of cytokine administration</td>
</tr>
<tr>
<td>◦ Transient, majority Grade ≤2 in severity</td>
</tr>
<tr>
<td>• Most frequent (&gt;10%) Grade 3-4 TRAE was neutropenia</td>
</tr>
<tr>
<td>• No treatment-related SAE, discontinuations or deaths</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6 mg q21d (n=8):</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Safety profile was consistent with 3mg q7</td>
</tr>
<tr>
<td>• Most frequent (&gt;10%) Grade 3-4 TRAE was AST/ALT increase (1 patient)</td>
</tr>
<tr>
<td>• No treatment-related SAE, discontinuations or deaths</td>
</tr>
</tbody>
</table>

### DLTs at MTD

Three DLTs reported at MTDs 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)
  - Injection site reaction (Grade 3)
  - Transient fatigue, nausea, vomiting (Grade 3)

No additional toxicities were reported in combination with pembrolizumab

---

TRAEs = Treatment-related adverse events; DLTs = Dose-limiting-toxicities; MTD = Maximum tolerated dose, RP2D = Recommended phase 2 dose, SAE = Serious Adverse Event, SC = Subcutaneous, IV = Intravenous

Data as of 02 Mar 2020
SC Nemvaleukin Induced Dose-Dependent, Selective Expansion of Circulating NK and CD8+ T Cells

CD8+ T Cells
Nemvaleukin Fold Change from Baseline

NK Cells
Nemvaleukin Fold Change from Baseline

Tregs
Nemvaleukin Fold Change from Baseline

3 mg q7d SC nemvaleukin provided greater expansion of CD8+ T cells and NK cells relative to IV nemvaleukin

SC = Subcutaneous, IV = Intravenous, Q7D = Once Every 7 Days, Q21D = Once Every 21 Days, NK = Natural Killer, Tregs = Regulatory T cells
ARTISTRY-2: Phase 2 Efficacy Expansion Initiated Following SC RP2D Determination

**Phase 1: Dose Escalation, 6-Week Monotherapy Lead-in**
Followed by combination of 200 mg pembrolizumab q21d and either SC nemvaleukin q7d or q21d

| Cohorts A2 to A5 (0.6 mg – TBD) | SC nemvaleukin q7d | Dose Escalation + pembrolizumab
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RP2D SELECTED</strong></td>
<td><strong>3.0 mg q7d</strong></td>
<td></td>
</tr>
</tbody>
</table>

| Cohorts B2 to B5 (1.0 mg – TBD) | SC nemvaleukin q21d | Dose Escalation + pembrolizumab

**Phase 2: Efficacy Expansion in Solid Tumors INITIATED at RP2D**
Combination nemvaleukin + pembrolizumab

Efficacy expansion in select solid tumors where previous responses were observed

**Primary Objectives**
- Safety and Efficacy
- 3.0 mg q7d in combination with pembrolizumab q21d

SC = Subcutaneous; RP2D = Recommended phase 2 dose; q7d = Administered once weekly; q21d = Administered once every three weeks

*Secondary objectives include clinical pharmacokinetic profile and immunogenicity, clinical pharmacodynamic effects (all parts), anti-tumor activity (phase 1) and ORR (objective response rate), and DOR (duration of response) (phase 2)
ARTISTRY-2: Nemvaleukin in Combination With Pembrolizumab
Case Study: 69-Year-Old Female With High-Grade, Serous PROC

**Diagnosis**

High-Grade Serous PROC
- Diagnosed December 29, 2019
- PD-L1 status: positive
- BRCA status: negative
- TMB Status: Low

**Prior Treatment**

<table>
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<th>Line</th>
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<th>Best Response</th>
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<td>CBP/PAC</td>
<td>6</td>
<td>PR</td>
</tr>
<tr>
<td>2</td>
<td>OLP/BEV</td>
<td>2</td>
<td>PD</td>
</tr>
<tr>
<td>3</td>
<td>BEV/DOX</td>
<td>&lt;1</td>
<td>PD</td>
</tr>
</tbody>
</table>

Last dose of prior treatment December 30, 2020

**On-Study Activity**

Started Tx: January 2021 (remains on treatment):
Nemvaleukin (3 mg q7d) subcutaneous + pembrolizumab IV

**Change in Target Lesion and CA-125 Levels from Baseline**

<table>
<thead>
<tr>
<th></th>
<th>Total Target Lesions Size</th>
<th>CA-125 Level (Unit/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>207 mm</td>
<td>1920</td>
</tr>
<tr>
<td>Cycle 2</td>
<td>~100 mm (50% reduction)</td>
<td>300 (84% reduction)</td>
</tr>
</tbody>
</table>

**Partial Response (PR)**

**Treatment-related AEs:**
- Manageable with no known dose modifications
- Hypotension and dehydration, Grade 1 and 2 multiple events
- Multiple injection site reactions, Grade 1

Data as of March 1, 2021

*Patient continued on therapy as of March 1, 2021; ** per RECIST Criteria, awaiting confirmation, PD = Progressive Disease, PR = Partial Response
PROC = Platinum-Resistant Ovarian Cancer; TMB = tumor mutational burden; BEV = bevacizumab; CBP = carboplatin; DOX = Doxorubcin; HRD = homologous recombination deficiency; OLP = olaparib; PAC = paclitaxel
Advancing Nemvaleukin Across Key Domains

• Submission of data for presentation at upcoming congresses
  ◦ ARTISTRY-1: Updated safety and efficacy data
  ◦ ARTISTRY-2: Dose escalation and initial efficacy and safety data
• Advance ongoing studies
• Advance interactions with regulatory authorities
• Initiate studies in mucosal melanoma and platinum-resistant ovarian cancer to support potential registration
• Pursue strategic collaborations to expand development program
Nemvaleukin Alfa: Preclinical Research Paving the Clinical Development Path

Heather Losey, Ph.D.
Sr. Director, Research Program Lead, Oncology
# Immune Modulation Portfolio of Engineered Cytokines

<table>
<thead>
<tr>
<th>Nemvaleukin alfa</th>
<th>Tumor-Targeted Split IL-12</th>
<th>Enhanced Efficacy IL-18</th>
</tr>
</thead>
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<tr>
<td><strong>Technical challenge</strong></td>
<td>• Efficacy of rhIL-2 limited by expansion of immunosuppressive T\textsubscript{reg} cells and other undesirable effects</td>
<td>• rhIL-12 has low tolerability when given systemically</td>
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<td><strong>Alkermes’ protein engineering solution</strong></td>
<td>• Fusion of circularly permuted IL-2 with the IL-2\textsubscript{R\alpha} subunit resulting in only activating intermediate-affinity IL-2R</td>
<td>• Separate inactive tumor-targeted IL-12 subunits assemble and activate in the tumor</td>
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<td><strong>Key anti-tumor mechanisms</strong></td>
<td>• Expansion of CD8\textsuperscript{+} T cells and NK cells</td>
<td>• Drive proinflammatory responses at the tumor site through potent activation of CD8\textsuperscript{+} T and NK cells</td>
</tr>
<tr>
<td></td>
<td>• Minimal expansion of T\textsubscript{reg} Cells</td>
<td></td>
</tr>
<tr>
<td><strong>Potential cancer types</strong></td>
<td>• Solid tumors, including melanoma, platinum-resistant ovarian cancer</td>
<td>• Solid tumors, including pancreatic, breast, colon and ovarian cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Immuno-oncology Goal: Activate Innate and Adaptive Immune Responses to Drive Tumor Cell Death

- **Antigen Identification and Presentation**
- **Immune System Activation**
- **Immune Cell-mediated Tumor Cell Death**

**Recognition by Immune System**
Endogenous IL-2
Other Cytokines

- Dendritic cell presenting antigen
- Activated CD8+ T cells and NK cells
- Activated cells attacking tumor
- Tumor killing and release of antigens
**Immuno-oncology Goal: Activate Innate and Adaptive Immune Responses to Drive Tumor Cell Death**

**Enhanced Antigen Identification and Presentation, Cell Death**

Chemotherapy  
Radiation  
Checkpoint Inhibitors  
Targeted Agents  
Growth Factor Inhibitors

**Immune System Activation**

Endogenous IL-2  
Other Cytokines

**Immune Cell-mediated Tumor Cell Death**

Dendritic cell presenting antigen  
Activated CD8⁺ T cells and NK cells  
Activated cells attacking tumor  
Tumor killing and release of antigens
Immuno-oncology Goal: Activate Innate and Adaptive Immune Responses to Drive Tumor Cell Death

- **Antigen Identification and Presentation**
- **Amplified Immune System Activation**
- **Immune Cell-mediated Tumor Cell Death**

**Recognition by Immune System**

- **Nemvaleukin**
- **Dendritic cell presenting antigen**
- **Activation and expansion CD8+ T cells and NK cells**
- **Activated cells attacking tumor**
- **Tumor killing and release of antigens**

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Immuno-oncology Goal: Activate Innate and Adaptive Immune Responses to Drive Tumor Cell Death

Enhanced Antigen Identification and Presentation, Cell Death
Chemotherapy
Radiation
Checkpoint Inhibitors
Targeted Agents
Growth Factor Inhibitors

Amplified Immune System Activation
Nemvaleukin

Enhanced Immune Cell-mediated Tumor Cell Death
Activated cells attacking tumor
Tumor killing and release of antigens

Dendritic cell presenting antigen
Activation and expansion CD8+ T cells and NK cells
Nemvaleukin: Preclinical Efforts Inform the Clinical Development Strategy

### Preclinical Research

<table>
<thead>
<tr>
<th>Molecular design</th>
<th>Confirmed selectivity</th>
<th>Demonstrated efficacy</th>
<th>First-in-human studies</th>
<th>Signal-seeking studies</th>
<th>Pivotal studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptor selectivity</td>
<td>CD8+ T cell &amp; NK cell expansion</td>
<td>Monotherapy</td>
<td>Determined Recommended Phase 2 Dose from safety, PK and PD data</td>
<td>Responses in multiple tumor types (monotherapy and in combination with anti-PD-1)</td>
<td>Monotherapy</td>
</tr>
<tr>
<td>Maintained potency</td>
<td>Minimal expansion of Tregs</td>
<td>Combination with anti-mouse PD-1</td>
<td></td>
<td></td>
<td>Combination with pembrolizumab</td>
</tr>
</tbody>
</table>

### Clinical Research

- Demonstrate efficacy with complementary mechanisms
  - CPIs
  - Growth Factor Pathway Inhibitors
  - Chemotherapy / Radiation Other agents
Agents That Induce Immunogenic Cell Death (ICD) May Offer Synergistic Advantages in Combination With Nemvaleukin

Agents that induce immunogenic cell death include:

- Immune Checkpoint Inhibitors
- Growth Factor Pathway Inhibitors
- Cytotoxic Chemotherapies / Radiation
Agents That Induce Immunogenic Cell Death (ICD) May Offer Synergistic Advantages in Combination With Nemvaleukin

Immune Checkpoint Inhibitors
- Anti-PD-1/L1 (Ongoing clinical trials)
- Anti-CTLA-4

Growth Factor Pathway Inhibitors
- Multi-tyrosine kinase inhibitors
- Anti-VEGF/VEGFR antibodies

Cytotoxic Chemotherapies / Radiation
Inhibition of Growth Factor Pathways Induces Immunogenic Cancer Cell Death

- Growth factors support several mechanisms that promote cancer cell survival and metastasis\(^1\)
- Inhibition of tumor growth factor pathways is a validated therapeutic approach in oncology\(^1,2\)
- T cell mediated immune responses emerging from inhibition of tumor growth factors may be augmented by nemvaleukin’s ability to activate cancer fighting immune cells

Growth Factor Receptors

\(\uparrow\) activity of immune suppressive cells
\(\downarrow\) tumor cell survival/growth
\(\downarrow\) tumor cell metastasis
\(\downarrow\) tumor angiogenesis

Growth Factor Pathway Inhibitors
(e.g. multi-TKIs, anti-VEGF/VEGFR)

\(\uparrow\) immune cell trafficking to tumor tissue

Immunogenic Cancer cell death
Release of cancer antigens

T cell activation and expansion

Ref. 3

Nemvaleukin in combination with either lucitanib or lenvatinib (not shown) resulted in increased immune activation and decreased immune suppression in tumors.
Nemvaleukin in combination with either lenvatinib or lucitanib (not shown) resulted in enhanced angiogenesis blockade and activated multiple immune pathways.

Alkermes internal data on file; *The mouse ortholog of nemvaleukin, RDB 1462, was used in mouse MC38 tumor model.
Nemvaleukin Enhanced the Anti-Tumor Efficacy of Lenvatinib in Mouse Tumors

• Nemvaleukin* in combination with either lenvatinib or lucitanib (not shown) resulted in enhanced tumor suppression and survival relative to monotherapy groups

• Similar results observed with a mouse surrogate of bevacizumab, which is a selective inhibitor of the angiogenesis factor VEGF

Alkermes internal data on file; *The mouse ortholog of nemvaleukin, RDB 1462, was used in mouse MC38 tumor model
Agents That Induce Immunogenic Cell Death (ICD) May Offer Synergistic Advantages in Combination With Nemvaleukin

**Immune Checkpoint Inhibitors**
- Anti-PD-1/L1 (Ongoing clinical trials)
- Anti-CTLA-4

**Growth Factor Pathway Inhibitors**
- Multi-tyrosine kinase inhibitors
- Anti-VEGF/VEGFR antibodies

**Cytotoxic Chemotherapies / Radiation**

(Pharmacotherapy 2016;36(3):317–334)
Exploring Nemvaleukin’s Potential Synergistic Benefits to Chemotherapy or Radiation Mediated Mechanisms

• Chemotherapy and radiation can have positive effects on anti-cancer immunity
  o Both can directly induce tumor cell lysis and lead to immunogenic cancer cell death\(^1\)
  o Chemotherapy and radiation can enhance innate anti-tumor immune responses\(^2,3\)

• However, chemotherapy and radiation can also have negative effects on the immune system
  o Decreased lymphocyte and leukocyte counts, which can negatively impact response to therapy\(^4\)
  o Immune suppression due to increased \(T_{\text{regs}}\) in the tumor microenvironment\(^5\)

• Ongoing preclinical collaborations leverage specialized translational models to explore nemvaleukin’s ability to augment chemotherapy/radiation driven anti-cancer mechanisms, while countering the negative impacts

Research Collaborations With Leading Institutes Explore Further Potential Clinical Utility of Nemvaleukin

<table>
<thead>
<tr>
<th>Principal Investigator and Institute</th>
<th>Research Collaborations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Brian Gastman</td>
<td>Preclinical collaboration to study combinations of nemvaleukin with <strong>multiple immune checkpoint inhibitors</strong> in individualized, humanized melanoma xenograft models</td>
</tr>
<tr>
<td>Cleveland Clinic Lerner College of Medicine</td>
<td></td>
</tr>
<tr>
<td>Dr. Kwok-Kin Wong</td>
<td>Preclinical collaboration to study novel combinations of nemvaleukin with SOC <strong>chemotherapy</strong>, in mouse lung tumor models</td>
</tr>
<tr>
<td>NYU Langone Health</td>
<td></td>
</tr>
<tr>
<td>Dr. James Welsh</td>
<td>Preclinical collaboration to study combinations of nemvaleukin with <strong>novel radiation</strong> approaches in mouse models of <strong>immune checkpoint inhibitor resistance</strong></td>
</tr>
<tr>
<td>The University of Texas</td>
<td></td>
</tr>
<tr>
<td>MD Anderson Cancer Center</td>
<td></td>
</tr>
<tr>
<td>Dr. Tullia Bruno and Dr. Lan Coffman</td>
<td>Preclinical collaboration to study the effects of nemvaleukin on the human <strong>tumor microenvironment</strong> in multiple solid tumor types <strong>in vitro</strong></td>
</tr>
<tr>
<td>University of Pittsburgh Medical Center</td>
<td></td>
</tr>
</tbody>
</table>

**SOC:** Standard of Care
Nemvaleukin: Preclinical Efforts Inform the Clinical Development Strategy

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<td>Chemotherapy / Radiation Other agents</td>
<td></td>
</tr>
<tr>
<td>Potential expansion of clinical program</td>
<td>New combinations / New indications New collaborations</td>
</tr>
</tbody>
</table>
Tumor-Targeted Split IL-12 Fusion Protein Program

Joshua Heiber, Ph.D.
Principal Scientist, Research, Oncology
# Immune Modulation Portfolio of Engineered Cytokines

## Technical challenge
- Efficacy of rhIL-2 limited by expansion of immunosuppressive $T_{reg}$ cells and other undesirable effects
- rhIL-12 has low tolerability when given systemically
- Efficacy of rhIL-18 limited by a checkpoint protein that binds to IL-18 (IL-18BP)

## Alkermes’ protein engineering solution
- Fusion of circularly permuted IL-2 with the IL-2R$\alpha$ subunit resulting in only activating intermediate-affinity IL-2R
- Separate inactive tumor-targeted IL-12 subunits assemble and activate in the tumor
- Engineered IL-18, for which activity is not blocked by suppressive mechanisms

## Key anti-tumor mechanisms
- Expansion of CD8$^+$ T cells and NK cells
- Minimal expansion of $T_{reg}$ cells
- Drive proinflammatory responses at the tumor site through potent activation of CD8$^+$ T and NK cells
- Enhance IL-18 mediated anti-cancer immune responses
- Reduce T cell exhaustion
- Immunosuppressive tumor microenvironment
- Checkpoint inhibitor-resistant tumors

## Potential cancer types
- Solid tumors, including melanoma, platinum-resistant ovarian cancer
- Solid tumors, including pancreatic, breast, colon and ovarian cancer
- Checkpoint inhibitor-resistant tumors

### Nemvaleukin alfa
- Expansions of CD8$^+$ T cells and NK cells
- Minimal expansion of $T_{reg}$ cells

### Tumor-Targeted Split IL-12
- Drives proinflammatory responses at the tumor site through potent activation of CD8$^+$ T and NK cells

### Enhanced Efficacy IL-18
- Enhances IL-18 mediated anti-cancer immune responses
- Reduces T cell exhaustion
- Immunosuppressive tumor microenvironment
- Checkpoint inhibitor-resistant tumors
IL-12 is a Highly-Potent Proinflammatory Cytokine With Diverse Anti-Tumor Effects

IL-12 is a heterodimeric protein consisting of two covalently linked subunits p35 and p40\(^1\)

- Individual components are non-functional

Anti-tumor activity is driven through activation of both innate and adaptive immune compartments and production of IFN-\(\gamma\)\(^1\)

- Robust anti-tumor efficacy observed in preclinical studies\(^2\)

---


NKT= Natural killer T cell, NK= Natural Killer cell, CD4 = CD4+ T cell, CD8= CD8+ T cell
IL-12 Potential Clinical Utility Limited by Severe Toxicities

Clinical evaluation limited due to severe toxicities associated with systemic exposure to IL-12 and its narrow therapeutic index\(^1\,^2,\,^3\)

- Systemic administration associated with the potential for rapid development of lethal inflammatory syndrome

Ongoing efforts in biopharma seeking to develop strategies for tumor-localized IL-12 delivery\(^1\,^2\)

- Gene therapy, viral delivery, electroporation, nanoparticles
- Primarily based on intratumoral (IT) administration

**Alkermes design intentions for engineered IL-12:**

- Harness the therapeutic potential of IL-12
- Address delivery challenges associated with IT approaches
- Avoid toxicity associated with systemic exposure to IL-12

---

Alkermes’ Design Approach: Build Functional IL-12 in the Tumor Through Engineered Tumor-Targeted IL-12 Subunits

Key design considerations and challenges:

• **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
  - Certain proteins exhibit increased expression in tumors relative to normal tissue and can be leveraged to target payloads to tumors with high specificity

• **Produce** novel engineered tumor-targeted fusion proteins using proprietary antibodies
Tumor Site-Specific Assembly of Functional IL-12 Designed to Avoid Systemic IL-12 Exposure

- Sequentially-timed injections of tumor-targeted subunits reduce systemic exposure to functional IL-12, thereby potentially reducing associated toxicities
- Targeted accumulation of functional IL-12 in the tumor may improve anti-tumor activity
Tumor clearance of targeted IL-12 subunits was slower than serum clearance, facilitating tumor-specific assembly

*Alkermes internal data on file
Preclinical Data Demonstrated Accumulation of Tumor-Targeted Split IL-12 Subunits in the Tumor

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

Radiolabeled IL-12 molecules in tumor

* = p<0.05, ** = p<0.01, *** = p<0.001

*Alkermes internal data on file; Murine CT-26 tumors in Balb/c mice; %ID/g = percent of injected dose per gram of tissue
Sequential Administration of Split IL-12 Subunits Resulted in Dose-Dependent Pharmacodynamic Response in Preclinical Study

Alkermes internal data on file; PBMC humanized NCG mice
## Tumor-Targeted Split IL-12: Advancing Toward Preclinical Proof-of-Concept and Cell Line Development

<table>
<thead>
<tr>
<th>Status</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓</td>
<td>Engineer tumor-targeted IL-12 subunits (fused to proprietary tumor-targeting antibody)</td>
</tr>
<tr>
<td>✓</td>
<td>Demonstrate that tumor-targeted IL-12 subunits are retained in tumors with expected kinetics</td>
</tr>
<tr>
<td>✓</td>
<td>Demonstrate that sequentially-administered IL-12 subunits combine to form functional IL-12 and drive dose-dependent IFN-γ production in humanized mice</td>
</tr>
<tr>
<td>✓</td>
<td>Complete humanization of tumor-targeting antibodies</td>
</tr>
<tr>
<td>Ongoing</td>
<td>Characterize lead candidates and preclinical proof-of-concept studies</td>
</tr>
<tr>
<td>Planned</td>
<td>Initiate cell line development</td>
</tr>
</tbody>
</table>
Neuroscience
Selective HDAC Inhibitors in Synaptic Dysfunction

Markus Haeberlein, Ph.D.
Senior Vice President, Research
Alkermes’ HDAC Inhibitor Portfolio

• Introduction to synaptogenesis and synaptic dysfunction

• Biological rationale for the program:
  o Established epigenetic control of synapse formation and function modulated by HDAC inhibitors
  o Limitations of first-generation HDAC agents as CNS therapeutics

• Alkermes’ novel chemotypes: Rationally designed to selectively target the HDAC1/2 CoREST complex

• ALKS 1140: First nominated development candidate from HDAC inhibitor portfolio

• Leveraging proprietary chemistry and insight to other potential compounds and indications, including Frontotemporal Dementia with Granulin Precursor Mutations (FTD-GRN)

HDAC: histone deacetylase
CoREST: co-repressor of repressor element-1 silencing transcription factor
Synapses Play a Vital Role in Brain Function, Learning and Memory

**synapse**: points of communication between neurons

**synaptogenesis**: formation of synapses occurring throughout a healthy person's lifespan

- normal dendritic spines
- reduced dendritic spine density
Synaptopathies Span Multiple Neurological Diseases Independent of Underlying Pathology

• Many neurological disorders are characterized by synaptic pathology, which includes:
  o Synapse loss
  o Abnormal density of dendritic spines
  o Aberrant synaptic signaling and plasticity
• Targeting the synapse may slow progression and preserve cognitive and functional abilities in a range of diseases

<table>
<thead>
<tr>
<th>Neuropsychiatric</th>
<th>Neurodegenerative</th>
<th>Neurodevelopmental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar Spectrum Disorder</td>
<td>Frontotemporal Dementia</td>
<td>Epilepsy</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Huntington’s Disease</td>
<td>Autism spectrum disorders:</td>
</tr>
<tr>
<td>Major Depressive Disorder</td>
<td>Alzheimer’s Disease</td>
<td>Phelan-McDermid Syndrome</td>
</tr>
<tr>
<td>Retinal</td>
<td></td>
<td>Fragile X Syndrome</td>
</tr>
<tr>
<td>Dementia in Down Syndrome</td>
<td>Cochlear</td>
<td>Tuberous Sclerosis Complex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rett Syndrome</td>
</tr>
</tbody>
</table>
Epigenetic Control of Synaptogenesis

- Knockout or inhibition of histone deacetylases, HDACs, increases the number of synapses. Conversely, overexpression reduces the number of synapses.

- HDAC inhibitors function by enhancing the acetylation of histones. This opens up the chromatin and increases accessibility of DNA for transcription of multiple genes associated with synaptogenesis.

Class I HDACs Function in Association With Multi-Protein Complexes That Determine Their Activity

HDAC family consists of 18 HDAC enzymes

Class III
- SIRT6
- SIRT5
- SIRT3
- SIRT1
- SIRT2

Class IIa
- HDAC7
- HDAC5
- HDAC9
- HDAC10
- HDAC11
- HDAC8
- HDAC3

Class IIb
- HDAC4
- HDAC6
- HDAC1
- HDAC2

Class IV
- HDAC10
- HDAC8

Class I
- HDAC1
- HDAC2
- HDAC3

Complexes with HDAC1/2
- Sin3
- MIER
- RERE
- CoREST
- MiDAC
- NuRD

CoREST complex is directly involved in repression of prosynaptic genes in neuronal tissue

HDAC family consists of 18 HDAC enzymes

Class I HDACs Function in Association With Multi-Protein Complexes That Determine Their Activity
Alkermes’ Novel Chemotypes Selectively Target HDAC1/2 Bound in the CoREST Complex

Alkermes has designed HDAC inhibitors binding to HDAC1/2 specifically in the CoREST complex

Selectivity achieved by exploiting a key pocket present in HDAC1/2

Alkermes’ Proprietary HDAC Inhibitors: Design Goals

**Selectivity:**
Selectively inhibit HDAC-CoREST complex

**Safety:**
Demonstrate favorable hematological safety

**Brain penetration:**
Exhibit desired brain exposure
ALKS 1140: A Novel CoREST-Selective Inhibitor Candidate for the Treatment of Neurodegenerative and Neurodevelopmental Disorders
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/C\textsubscript{plasma, unbound} ratio in rat/dog/NHP = 0.6-1.5*

CSF: cerebrospinal fluid
*Alkermes data on file
Rational Assessment of HDAC Inhibitors via Molecular, Structural and Functional Assays

**Molecular**
Gene and/or protein modification

**Structural**
Synapse formation

**Functional**
Long-term potentiation (LTP)

Target engagement, histone acetylation

Increases in synaptic genes and proteins

Synaptogenesis, Spine morphology changes

Increased LTP, Increased brain function in disease model
ALKS 1140 Increased Proteins Related to Number of Synapses and Activated Dendritic Spines

Increase in Number of Synapses

\[ SV2A/PSD-95 \text{ coincidence} \]

Increase in Activated Dendritic Spines

\[ PSD-95/pTrk \text{ coincidence} \]

‡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**

- Days of administration (3mg/kg/day)
- Spine density (% of vehicle)

**Persistence of Dendritic Spines**

- Total spines/10 μm Dendrite
- Days after last dose

†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**

<table>
<thead>
<tr>
<th></th>
<th>Normalized last 10 min fEPSP slope (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>120</td>
</tr>
<tr>
<td>ALKS 1140 3 mg/kg</td>
<td>140</td>
</tr>
<tr>
<td>ALKS 1140 6 mg/kg</td>
<td>160</td>
</tr>
</tbody>
</table>

* Ordinary one-way ANOVA, Holm Sidak post hoc

*p<0.05; **p<0.01; ***p<0.001

Alkermes data on file

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

- Vehicle in Wild Type Model
- Vehicle in 5xFAD Model
- ALKS 1140 6 mg/kg in 5xFAD Model

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

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Potential Indications in Neurodegenerative and Neurodevelopmental Disorders With Cognitive Deficits

• Indications that share common pathophysiology of synaptic dysfunction in hippocampus with deficits in cognition
  o Includes certain autism spectrum disorders with reduced synaptic density

• Initial clinical focus on rare and orphan diseases with potential expedited development pathways

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

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
## 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*

<table>
<thead>
<tr>
<th>Early Clinical Development Plan</th>
<th>Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 0 Biomarker Study</td>
<td>• Identify differences in synaptic biomarkers between healthy volunteers and patients with neurodegenerative/neurodevelopmental diseases and inform indication selection</td>
</tr>
<tr>
<td>Planned initiation: 2021</td>
<td></td>
</tr>
<tr>
<td>Phase 1 SAD/MAD</td>
<td>• Determine PK/PD relationship and MTD in healthy volunteers</td>
</tr>
<tr>
<td>Planned initiation: 2021</td>
<td>• Determine ALKS 1140’s effects on select biomarkers</td>
</tr>
<tr>
<td><strong>Phase 1b: Basket studies in neurodevelopmental and neurodegenerative disorders</strong></td>
<td><strong>• Confirm ALKS 1140’s effect on biomarkers of synaptopathy and neurocognitive function</strong></td>
</tr>
<tr>
<td></td>
<td><strong>• Prioritize indications and biomarkers for proof-of-concept studies</strong></td>
</tr>
</tbody>
</table>

SAD: single-ascending dose; MAD: multiple-ascending dose; PK: pharmacokinetic; PD: pharmacodynamic; MTD: maximum tolerated dose
Leveraging Alkermes’ HDAC Chemistry Expertise in New Indications: Frontotemporal Dementia With Granulin Precursor Mutations (FTD-GRN)
Treatment Options Needed for Frontotemporal Dementia With Granulin Precursor Mutations (FTD-GRN)

• Frontotemporal Dementia (FTD) is caused by degeneration of the frontal and/or temporal lobes
  o FTD patients demonstrate severe synaptic deficits\(^1\)
  o ~60,000 people in U.S. have FTD\(^2\)
  o No currently available therapies

• FTD-GRN is caused by mutation in granulin (GRN) gene
  o Carriers exhibit low levels of the progranulin protein
  o ~6,000 people in U.S. have FTD-GRN\(^3,4\)
  o Average age of onset is ~56 years with a ~6-year survival rate\(^4\)

• Specific HDAC inhibitors have increased progranulin \textit{in vitro}\(^6\)

---

Alkermes’ HDAC Inhibitors Increased Both Progranulin Levels and Dendritic Spine Density

- Studies in human neuronal cultures and transgenic animal models suggest that increasing levels of progranulin protein in FTD-GRN model systems can help rescue pathology\(^1,2\)
- Alkermes’ HDAC inhibitors increased GRN gene expression and progranulin protein \textit{in vitro}
- Demonstrated ability to increase synaptic density presents opportunity for additional therapeutic benefits to FTD patients


[^p<0.05]: adjusted for multiple testing by false discovery rate

[^p<0.01]: **p<0.01; ***p<0.001; VEH: Vehicle

Alkermes data on file
Alkermes’ Pipeline of Selective HDAC Inhibitors

- **Target Evaluation**
  - ALKS 1140
    - Neurology (Orphan)
  - HDAC Inhibitors
    - Neurology/Neuropsychiatry (Non-Orphan)
  - HDAC Inhibitors
    - Frontotemporal Dementia
  - HDAC Inhibitors
    - Oncology

- **Lead Generation**
- **Lead Optimization**
- **Clinical Development**

- Discovery Project Start
- Research POC
- Candidate Nomination

POC: proof-of-concept
Orexin 2 Receptor Agonists for the Treatment of Narcolepsy and Other Sleep Disorders

Brian Raymer, Ph.D.
Senior Director, Research Project Leadership and Strategy
Abnormal Neurotransmission of Orexin in the Brain Seen in Patients With Sleep Disorders

• Orexin, also known as hypocretin, is a neuropeptide produced in the hypothalamus

• Orexin controls sleep and arousal by stimulating the release of neurotransmitters that promote alertness, such as histamine, serotonin and norepinephrine

• Orexin acts on two receptors:
  o Orexin 2 receptor (OX2R): Wakefulness
  o Orexin 1 receptor (OX1R): Reward

• In narcolepsy and other sleep disorders, low orexin levels lead to inconsistent neurotransmitter release, resulting in sleep lapses and poor regulation of REM sleep

Figure from: Scammell, T E, and Saper, C B. Nature medicine. 2007;13:126-8

Orexin neurons promote wakefulness and modulate reward pathways

Narcolepsy: A Chronic Neurological Disorder

• Chronic neurological disorder characterized by daytime sleepiness and sudden transitions into sleep\(^1\)

• Affects ~200,000 people in U.S. and 3M people globally\(^2\)

• 70% of narcolepsy patients have narcolepsy type 1\(^3\), 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

\(^2\) Global Narcolepsy Drugs Market, Forecast 2019-2025. Allied Market Research
\(^3\) Swick TJ. Treatment paradigms for cataplexy in narcolepsy: past, present, and future. *Nat Sci Sleep*. 2015;7:159-169
Recent Identification of Orexin 2 Receptor Agonists Presents Opportunity for New Sleep Disorder Therapies

- OX2R agonists may have utility as replacement therapy for low or no levels of orexin by stimulating downstream release of wake-promoting neurotransmitters
- Potential applicability in narcolepsy and other indications with excessive daytime sleepiness (EDS), fatigue and attention issues
- Selective OX2R agonists may provide improved safety over currently available therapies

“Genetic and pharmacologic evidence suggests that orexin receptor agonists, especially OX2R agonist, will be useful for mechanistic therapy of the sleep disorder narcolepsy/cataplexy.”

J. Med. Chem. 2015;58:7931–7937
Leveraging Alkermes’ Molecular Design Capabilities to Target Orexin Dysfunction in Narcolepsy

• Working to develop a best-in-class molecule designed to:
  o Mimic potency and performance of endogenous peptide OX2R agonist with orally-bioavailable therapy
  o Possess favorable half-life
  o Have PK/PD profile that mirrors natural wake cycle
  o Avoid safety risks associated with stimulant medications

PK: pharmacokinetic; PD: pharmacodynamic
Figure adapted from: Hong, Chuan, et al. Nature communications. 2021;12; 3. PDB ID: 7L1U
Design Goals: Differentiated Orexin 2 Receptor Agonist to Address Unmet Patient Needs

<table>
<thead>
<tr>
<th>Robust Efficacy</th>
<th>Convenient Dosing</th>
<th>Favorable Tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Increased wakefulness duration</td>
<td>• Once-daily, oral medication</td>
<td>• Reduced risk of heart rate and blood pressure effects seen</td>
</tr>
<tr>
<td>• Improved cataplexy control</td>
<td>• Dose to allow for 8-12 hours wakefulness with no later insomnia</td>
<td>with stimulants</td>
</tr>
</tbody>
</table>
Alkermes’ Lead Orexin Candidate, RDC-264177, Demonstrated Potency Superior to Orexin Peptide in Preclinical Studies

- Application of RDC-264177 (‘177) induced robust concentration-dependent increases in neuronal excitability in rodent brain tissue
- RDC-264177 demonstrated greater potency compared to an orexin-B synthetic peptide

<table>
<thead>
<tr>
<th>OX2R Activity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>[Ala^{11},D-Leu^{15}]-Orexin B</td>
<td>381.0 nM</td>
</tr>
<tr>
<td>RDC-264177</td>
<td>47.4 nM</td>
</tr>
</tbody>
</table>

nM: nanomolar
Alkermes data on file
RDC-264177 Promoted Prolonged Wakefulness in Preclinical \textit{In Vivo} Studies

RDC-264177 via oral dosing demonstrated dose-dependent wake duration (shown by red gamma bands and dark blue theta and delta bands)

\textit{PharmacoEEG: Pharmaco-electroencephalography}
\textit{Alkermes data on file}
RDC-264177 Demonstrated Dose-Dependent Increases in Exposure and Wakefulness

- Strong PK/PD relationship demonstrated in rat EEG model suggests potential for low human dose
- RDC-264177 did not adversely elevate heart rate and blood pressure in a rat hemodynamic model at pharmacologically-relevant plasma exposures

Alkermes data on file
RDC-264177 Demonstrated Dose-Dependent Increased Wakefulness and Reduced Cataplexy in Predictive Model

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


\textsuperscript{2}In collaboration with SRI International
Moving Forward in Development: Potential for Meaningfully Differentiated Orexin Agonist

Nomination of lead candidate, RDC-264177, planned for 2021 based on data that demonstrated potential for:
- Robust efficacy
- Convenient dosing
- Favorable tolerability

Developing efficient clinical strategy with early stage-gates based on known biomarkers
- EEG biomarkers to determine sleep/wake states in animal models, with direct translation to humans

Prioritizing study of additional potential indications based on orexin biology, clinical feasibility, association with excessive daytime sleepiness and unmet need
- Obstructive sleep apnea
- Idiopathic hypersomnia
- Parkinson’s disease
- Traumatic brain injury
Appendix
Alkermes plc and Subsidiaries

GAAP to Non-GAAP Adjustments (Unaudited)

An itemized reconciliation between net loss according to generally accepted accounting principles in the U.S. (GAAP) and net income on a non-GAAP basis is as follows:

<table>
<thead>
<tr>
<th>(In millions, except margin %)</th>
<th>Year ended December 31, 2019</th>
<th>Year ended December 31, 2020</th>
<th>Year ending December 31, 2021 Projected*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Revenues</td>
<td>$1,170.9</td>
<td>$1,038.8</td>
<td>$1,135.0</td>
</tr>
<tr>
<td>Net Loss — GAAP</td>
<td>$(196.6)</td>
<td>$(110.9)</td>
<td>$(105.0)</td>
</tr>
<tr>
<td>Net Loss Margin — GAAP</td>
<td>-17%</td>
<td>-11%</td>
<td>-9%</td>
</tr>
<tr>
<td>Adjustments:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Share-based compensation expense</td>
<td>101.0</td>
<td>90.2</td>
<td>93.0</td>
</tr>
<tr>
<td>Depreciation expense</td>
<td>40.1</td>
<td>42.4</td>
<td>46.0</td>
</tr>
<tr>
<td>Amortization expense</td>
<td>40.4</td>
<td>39.5</td>
<td>40.0</td>
</tr>
<tr>
<td>Income tax effect related to reconciling items</td>
<td>5.8</td>
<td>10.1</td>
<td>5.0</td>
</tr>
<tr>
<td>Non-cash net interest expense</td>
<td>0.7</td>
<td>0.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Change in the fair value of contingent consideration</td>
<td>22.8</td>
<td>(3.9)</td>
<td>-</td>
</tr>
<tr>
<td>Change in the fair value of warrants</td>
<td>(1.8)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Acquisition of IPR&amp;D</td>
<td>86.6</td>
<td>0.7</td>
<td>-</td>
</tr>
<tr>
<td>Restructuring expense</td>
<td>13.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Non-GAAP Net Income</td>
<td>$112.2</td>
<td>$68.6</td>
<td>$80.0</td>
</tr>
<tr>
<td>Non-GAAP Net Income Margin</td>
<td>10%</td>
<td>7%</td>
<td>7%</td>
</tr>
</tbody>
</table>

* Projected GAAP and non-GAAP measures for the year ending December 31, 2021 reflect the mid-point of the ranges of the financial expectations provided, along with the assumptions and risks underlying such expectations, in Alkermes plc's (the "Company") Current Report on Form 8-K filed with the SEC on February 11, 2021. The Company expressly disclaims any obligations to update or affirm these forward-looking statements.

The non-GAAP measures that the Company presents, including non-GAAP net income and non-GAAP net income margin (non-GAAP net income/total revenues), are not based on any standardized methodology prescribed by GAAP and are not necessarily comparable to similar measures presented by other companies. Non-GAAP net income adjusts for one-time and non-cash charges by excluding from GAAP results: share-based compensation expense; amortization; depreciation; non-cash net interest expense; certain other one-time or non-cash items; and the income tax effect of these reconciling items. The Company's management and board of directors utilize these non-GAAP financial measures to evaluate the company's performance. The Company provides these non-GAAP measures of the Company's performance to investors because management believes that these non-GAAP financial measures, when viewed with the Company's results under GAAP and the accompanying reconciliations, are useful in identifying underlying trends in ongoing operations. However, non-GAAP net income and non-GAAP net income margin are not measures of financial performance under GAAP and, accordingly, should not be considered as alternatives to GAAP measures as indicators of operating performance.

The Company has not provided financial expectations for time periods after the year ending December 31, 2021 and therefore is not providing reconciliations of, or comparable GAAP financial measures for, non-GAAP financial measures, including non-GAAP net income margin or EBITDA margin (EBITDA/total revenues), for time periods after the year ending December 31, 2021 (EBITDA: Earnings before interest, tax, depreciation, amortization). Reconciliations of such forward-looking non-GAAP financial measures to GAAP are not provided as they are not determinable without unreasonable efforts due to the inherent difficulty in forecasting and quantifying certain amounts that would be necessary for such reconciliations, which amounts could have a significant impact on the Company’s future financial results, including such the non-GAAP financial measures and the comparable GAAP financial measures.