IMMUNOLOGY
The presentations for Eli Lilly’s investment community meeting contain forward-looking statements that are based on management’s current expectations, but actual results may differ materially due to various factors. The company’s results may be affected by factors including, but not limited to, the risks and uncertainties in pharmaceutical research and development; competitive developments; regulatory actions; the extent and duration of the effects of the COVID-19 pandemic; litigation and investigations; business development transactions; economic conditions; and changes in laws and regulations, including health care reform.

For additional information about the factors that affect the company’s business, please see the company’s latest Forms 10-K, 10-Q, and any 8-Ks filed with the Securities and Exchange Commission. In addition, certain financial information in this presentation is presented on a non-GAAP basis. Investors should refer to the reconciliations included in these presentations and should consider the company’s non-GAAP measures in addition to, not as a substitute for or superior to, measures prepared in accordance with GAAP.

The company undertakes no duty to update forward-looking statements except as required by applicable law.
Approximately 12 million people in U.S. have diagnosed auto-immune disorders, of which ~20% are treated with a biologic or novel oral medicine.

Lilly’s pipeline has the potential to impact a broad spectrum of autoimmune disorders with high prevalence and unmet need.

In addition to internal research, external opportunities help to develop differentiated assets as demonstrated with Dermira acquisition as well as Nektar and Rigel collaborations.
LATE-STAGE PIPELINE OPPORTUNITIES
POTENTIAL TO ADDRESS UNMET MEDICAL NEED IN KEY AREAS OF IMMUNOLOGY

MIRIKIZUMAB
- Anti-IL-23p19 monoclonal antibody
- Phase 3 induction and maintenance studies for people with moderately-to-severely active UC met primary and all key secondary endpoints; global submissions are planned for H1 2022
- Phase 3 study in Crohn’s disease includes head-to-head versus Stelara and is expected to read out in early 2024

LEBRIKIZUMAB
- Potential best-in-class IL-13 monoclonal antibody with competitive profile in atopic dermatitis
- Phase 3 induction study demonstrated more than half of people with moderate to severe atopic dermatitis had at least 75% skin clearance as measured by EASI
- Upcoming Phase 3 read outs include combination with topical corticosteroids expected late 2021/early 2022 and 52-week maintenance data expected H1 2022

OLUMIANT
- The first JAK-inhibitor to demonstrate hair regrowth for alopecia areata in a Phase 3 program; Submitted in the U.S., Europe and Japan
- Phase 3 studies in SLE to read out before end of the year
- Approved in the EU and Japan for atopic dermatitis with U.S. regulatory action expected early 2022

Well positioned to become a leader in immunology with growing presence in dermatology and rheumatology as well as emergence in gastroenterology

UC = ulcerative colitis; EASI = eczema area and severity index; JAK = Janus kinase Inhibitors; SLE = systemic lupus erythematosus;
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2021 INVESTMENT COMMUNITY MEETING
**IMMUNOLOGY DEVELOPMENT STRATEGY**

**CORE AREAS OF FOCUS**

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**ADAPTIVE IMMUNITY**
- Offers potential of efficacy across many diseases
  - T cell biology
  - B cell biology
  - Cellular Signaling
- Most industry attention focused here with multiple approved assets

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**IMMUNE RESOLUTION**
- Possibility of lasting remission
  - Checkpoints
  - Treg biology
  - Immunometabolism
  - Tolerance
- Key area of clinical focus for Lilly with industry-leading pipeline

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**INNATE IMMUNITY**
- Potential for efficacy in hard-to-treat targets
  - Myeloid cells/neutrophils
  - Dendritic cells
  - Fibrosis
- Emerging area of focus for Lilly

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**Taltz®**
- Mirikizumab (Ph 3)
- Olumiant®
- Lebrikizumab (Ph 3)
- RIPK1 SM (Ph 1)
- IL-2 conjugate (Ph 2)
- CD200R mAb (Ph 1)
- PD-1 mAb (Ph 2)
- BTLA mAb (Ph 1)
- CXCR 1/2 mAb (Ph 2)

mAb = monoclonal antibody; SM = small molecule

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2021 INVESTMENT COMMUNITY MEETING
Leukocyte FcγRIIB LAIR-1 PD-1 TIM-3 BTLA CD200R

HISTORICAL IMMUNOLOGY R&D

CHECKPOINT RECEPTOR STRATEGY
AGONIST ANTIBODIES (CD200R, BTLA, PD-1) INHIBIT IMMUNE RESPONSE AND PROMOTE A STATE OF RESOLUTION

CHECKPOINT RECEPTOR FOCUS

Gas

Activating receptors

CD28 OX40 GITR CD137 CD27 HVEM

Brakes

Inhibitory receptors

PD-1 CD200R TIM-3 BTLA FcγRIIB LAIR-1

Prior efforts focused on pro-inflammatory response, whereas checkpoint agonists are focused on resolution

Reasons to believe:
- Validated in immuno-oncology
- Associated with autoimmune side effects
- Agonists selectively impact activated cells
**CD200R AGONIST AB (LY3454738)**
LEAD CHECKPOINT AGONIST SHOWS POTENTIAL FOR EFFICACY AND DURABILITY

**MECHANISM OF ACTION**

- Expressed on both innate and adaptive immune cells
- Agonism of the receptor leads to decreased cytokine release and decreased cell proliferation
- Pre-clinical data using an agonist antibody demonstrate inhibition of inflammation

**PRECLINICAL DATA**

Long-term efficacy without measurable exposure suggest the potential for durable response after a single dose

Hapten-induced contact dermatitis*

Measured 24 Hours Post Challenge 1, 2, and 3

**Days Post Challenge #1**

<table>
<thead>
<tr>
<th>Days Post Challenge #1</th>
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<th>CD200R</th>
<th>Ruxolitinib</th>
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***p<0.0001 vs Isotype 2way ANOVA/Dunnett’s post hoc test

*Challenges are defined as hapten-induced dermatitis at predefined intervals

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Mean EASI Percent Change from Baseline by Treatment in Atopic Dermatitis*

EASI 75 of ~40% at week 12 established proof of concept for checkpoint agonists in Phase 1b study in atopic dermatitis

Exploring durability of effect and potential for less frequent subcutaneous dosing

Potential for enriching responses through biomarker-driven tailored approaches

*Interim analysis
EASI = eczema area and severity index; POC = proof of concept
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MECHANISM OF ACTION

Binds BTLa on B cells, T cells, and dendritic cells to suppress immune activation

POTENTIAL TARGETED THERAPY IN SLE

- HVEr, the BTLa ligand, is reduced in SLE patients
- BTLa agonist antibody may function as HVEr replacement therapy
Phase 1 MAD Study: Skin Disease Improvement in SLE Patients with CLASI ≥ 4 at Baseline

Patients were dosed for 10 weeks (last dose d71)

Mean Proportion CLASI Change

Days

Potential for durable response

- Placebo
- Dose 1
- Dose 2
- Dose 3

BTLA = B- and T-lymphocyte attenuator; MAD = multiple ascending dose; SLE = systemic lupus erythematosus; HEM = herpesvirus-entry mediator; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index

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**PD-1 AGONIST MAB (LY3462817)**
FIRST-IN-CLASS OPPORTUNITY TO AGONIZE A VALIDATED IMMUNE CHECKPOINT RECEPTOR

**FIRST IN CLASS OPPORTUNITY**

PD-1 agonism suppresses lymphocyte activation & expansion

- Cell Proliferation
- Cell Survival
- Protein Synthesis
- IL-2 Production


- First-in-class development program will test the hypothesis of durability / disease resolution through checkpoint agonism
- PD-1 inhibition broadly associated with autoimmune side effects including colitis, autoimmune diabetes and inflammatory arthritis

**ONGOING PHASE 2 POC IN RA**

- **Patient Population:** Insufficient responders to conventional, biologic, or targeted synthetic disease modifying anti-rheumatic drugs
- **Primary Endpoint:** DAS28 hsCRP change from baseline at 12 weeks

RA = rheumatoid arthritis; POC = proof of concept; LDA = Low Disease Activity; CDAI = Clinical Disease Activity Index; PBO = placebo; RAMRIS = Rheumatoid Arthritis Magnetic Resonance Imaging Score; DAS28 = Disease Activity Score-28; hsCRP = high-sensitivity C-reactive protein

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2021 INVESTMENT COMMUNITY MEETING
**IL-2 CONJUGATE (NKTR-358)**
NOVEL BIOLOGY & TREATMENT APPROACH IN PARTNERSHIP WITH NEKTAR

**Novel Biology:** IL-2 conjugate, An IL-2 Agonist biased for Treg expansion, affords a...

**...Novel Treatment Approach:** Resolution/Restoration of immune system

- **Current Marketed Products** (e.g., cytokine inhibitors) aim to reduce T-effector cells, leading to **Autoimmunity**.
- **NKTR-358** (Rebalance the immune system by increasing Treg population/function), leads to **Homeostasis**.

Differential expression of high and low affinity IL-2 receptors allows IL-2 to regulate both pro-inflammatory T-effector cells and anti-inflammatory Treg cells. NKTR-358 is a stable pegylated IL-2 conjugate composition that preferentially stimulates expansion of Tregs with minimal effects on T-effectors.
Phase 1 MAD data in SLE demonstrated dose-dependent increase in CD25^{bright} Tregs (up to 20-fold) with no appreciable impact on T-effectors and an acceptable safety profile.

MAD = multiple ascending dose; SLE = systemic lupus erythematosus

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IL-2 CONJUGATE (NKTR-358)
PHASE 1B POC DATA IN ATOPIC DERMATITIS SUPPORTS CLINICAL PROGRAM EXPANSION

PHASE 1B DATA FOR PATIENTS
WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

EASI: Percentage Change from Baseline*

<table>
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<tr>
<th></th>
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<th>Placebo (Q2W)</th>
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Sustained disease control for at least 6 months after last dose demonstrates potential for NKTR-358 to differentiate from standard of care

POC data demonstrated dose dependent reduction in EASI

* Interim analysis; SLE = systemic lupus erythematosus; EASI = eczema area and severity index; POC = proof of concept

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CLINICAL STATUS

Phase 2 trial recruiting [NCT04433585]; Encouraging Phase 1b data (NCT03556007)

Phase 2 trial recruiting [NCT04677179]

Encouraging Phase 1b data [NCT04081350]; Plan to initiate Phase 2 clinical study in 2022
CXCR1/2L (LY3041658)
NOVEL NEUTROPHIL-TARGETED MAB BEING STUDIED IN HIDRADENITIS SUPPURATIVA

MECHANISM OF ACTION

- Neutralizing all ELR+ chemokines acts as a dual CXCR1/CXCR2 antagonist, impacting the ability of neutrophils to migrate to sites of inflammation
- Due to the interplay between the innate and adaptive immune system, reducing neutrophil infiltration may result in downregulation of the adaptive autoimmune response

PHASE 1 MAD DATA IN HS

- LY doses [Q2W]: Potential application in neutrophil-driven autoimmune diseases including HS, ulcerative colitis and other neutrophilic skin diseases
- Full Phase 2 HS data expected H1 2022

HS = Hidradenitis Suppurativa; MAB = monoclonal antibody
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**BIOLOGIC RATIONALE**

Orally available, potent and selective inhibitor of RIP1 kinase, recently in-licensed from Rigel

RIP1 kinase plays a key role in TNF signaling and in the induction of pro-inflammatory necroptosis, which could support indications in psoriasis, RA and IBD

R552/LY3871801 could achieve best-in-class status relative to competition based on current Phase 1 data

**DOWNSTREAM SIGNALING**

Adapted from Yuan J. & Kroemer G., Genes & Dev 2010

RIP1 = receptor-interacting serine/threonine-protein kinase 1; TNF = tumor necrosis factor; RA = rheumatoid arthritis; IBD = inflammatory bowel disease

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SELECT NME AND NILEX PIPELINE AS OF OCTOBER 22, 2021

TAU siRNA
Alzheimer’s

P2X7 INHIBITOR
Pain

NRG4 AGONIST
Heart Failure / Obesity

RIPK1 INHIBITOR
Immunology

DACR A
Diabetes / Obesity

GIPR AGONIST LA II
Diabetes

LAARA
Diabetes / Obesity

CD200R MAB AGONIST
Immunology

GLUCOSE SENSING
Insulin / Diabetes

PHASE 1

GIPR AGONIST
Diabetes

ANGPTL3 siRNA
CVD

P2X7 INHIBITOR
Diabetes / Obesity

PHASE 2

PYY ANALOG
Gastroenterology

RELAXIN-LA
Heart Failure

PI3Kα SELECTIVE INHIBITOR
Cancer

NOT DISCLOSED
Cancer

PHASE 3

NLRP3 INHIBITOR
Cancer

IDH1/2 INHIBITOR
Cancer

BARICITINIB
Alopecia Areata

BARICITINIB
Diabetes

LEGEND

NME
NILEX
Commercial Collaboration
Rolling submission in the U.S. initiated
Discussed in Dec 15 Investment Community Meeting

Note: select pre-clinical assets listed, most of which were discussed at the Lilly Investment Community meeting on December 15, 2021; NME = new molecular entity; NILEX = new indication or line extension
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2021 INVESTMENT COMMUNITY MEETING
IMMUNOLOGY SUMMARY

Marketed products and late-stage assets, including Taltz, Olumiant, mirikizumab and lebrikizumab, support potential for continued growth and competitiveness in immunology.

Over the last decade, Lilly has built a deep early- and mid-stage portfolio with several potential first-in-class or best-in-class assets addressing improved efficacy, durability and formulations from both internal and external innovation.

Lilly is a leader in key areas of emerging science, including checkpoint agonism and Treg biology, and we are starting to deliver promising early phase data to validate these approaches.
AJAY NIRULA, M.D., PH.D.
Vice President, Immunology, Lilly Research Laboratories

DAN SKOVRONSKY, M.D., PH.D.
Chief Scientific and Medical Officer, and President of Lilly Research Laboratories

LOTUS MALLBRIS, M.D., PH.D.
Vice President, Immunology Development and Medical Affairs

PATRIK JONSSON
President, Lilly Immunology and Lilly USA, and Chief Customer Officer

2021 INVESTMENT COMMUNITY MEETING