This presentation includes forward-looking statements regarding Nektar’s proprietary drug candidates, the timing of the start and conclusion of ongoing or planned clinical trials, the timing and outcome of regulatory decisions, and future availability of clinical trial data. Actual results could differ materially and these statements are subject to important risks detailed in Nektar's filings with the SEC including the Form 10-Q filed on May 9, 2019. Nektar undertakes no obligation to update forward-looking statements as a result of new information or otherwise.
Today’s Speakers

Dr. David Klatzmann
Professor of Immunology, Department of Inflammation-Immunopathology-Biotherapy, Pierre & Marie Curie Medical School

Dr. Jonathan Zalevsky
Chief Scientific Officer, Nektar Therapeutics

Dr. Brian Kotzin
SVP of Clinical Development, Nektar Therapeutics
Dr. David Klatzmann

Dr. David Klatzmann is a professor of Immunology at the Pierre & Marie Curie Medical School in Paris, France. He also serves as chairman of the Inflammation-Immunopathology-Biotherapy Department.

Klatzmann received his MD and PhD from the Pierre & Marie Curie Medical School. His research interests include translational Immunology with focus on Treg cells, for which he was awarded funding from the European Research Council (ERC Advanced Grant) in 2012. He jointly discovered the AIDS virus and pioneered research low-dose IL-2 immunotherapies.
Today’s Agenda

• T Regulatory Cell Biology and Experiences in Autoimmune Disorders with Low-Dose IL-2
  • David Klatzmann, M.D.

• "Selective Expansion of Regulatory T-Cells in Humans by a Novel IL-2 Conjugate T-Reg Stimulator, NKTR-358, Being Developed for the Treatment of Autoimmune Diseases”
  • Jonathan Zalevsky Ph.D., Nektar Therapeutics

• Q&A Expert Panel
T Regulatory Cell Biology and Experiences in Autoimmune Disorders with Low-Dose IL-2

David Klatzmann, MD
The discovery of Tregs has dramatically changed our understanding of autoimmune diseases

Experimental ablation of Tregs at any time in life leads to « catastrophic autoimmunity » and death in 2-3 weeks

✓ at any time, normal individuals harbor effector T cells that have the capacity to attack their normal tissues, but which are suppressed by Tregs

✓ thus, in health, there is a balance between Teff and Tregs
Autoimmune diseases intrinsically reflect a distorted Teff/Treg balance

The goal in autoimmune diseases is to restore a proper Treg/Teff balance
Goal of autoimmune disease therapy is to control the overactive immune system

Block the mechanisms of immune activation

Small Molecules
- Corticosteroids, cyclosporine, azathiporine, etc.

Large Molecules
- Anti-TNF, Anti-IL6, Anti-IL12/23, Anti-IL-17, Anti-CD25, etc.

Stimulate the mechanisms of immune resolution

Objective: Restore homeostasis in the immune system

Interleukine-2
- Grow your body’s own population of Tregs to restore balance in the immune system and treat the underlying disease pathology

Non-specific immune suppressants
- Infection, bleeding, cancer risks
- Many side-effects impact chronic use
- Symptomatic, do not treat underlying disease
IL-2 is the main cytokine promoting Tregs’ survival and function

Mice rendered deficient in IL-2 or IL-2R have no Tregs and develop severe inflammation and multiorgan autoimmunity

Many autoimmune disorders, including SLE, are associated with:
- Reduced Treg numbers
- Impaired Treg function
- Reduced systemic IL-2

IL-2 has the potential to regulate the Teff/Treg balance by promoting Tregs
Pregnancy is a physiological setting that requires an increase performance of Tregs driven by IL-2

Remarkable coordinated increase of IL-2 plasma levels and of Tregs all along pregnancy

An IL-2 increase during pregnancy emphasizes the likelihood of an excellent safety profile of IL-2
Treg activation by low-dose IL-2 reverses pregnancy loss in a spontaneous immune-induced abortion model
Interleukin-2 mechanisms of action are well understood

**IL-2 stimulates and expands Tregs**
- control of the effector T cell mediated autoimmune response

**IL-2 blocks the differentiation of Tfh cells**
- control of the effector antibody mediated autoimmune response

**IL-2 blocks the differentiation of pro-inflammatory Th17 cells**
- control of inflammation

These properties have contributed to positive pre-clinical results obtained in >30 experimental autoimmune and inflammatory diseases (including T1D, EAE and SLE)
Effector T cells and regulatory T cells show differential use of signaling pathways and differential sensitivity to interleukin-2
Promoting Treg expansion with ultra low-dose IL-2

IL-2 receptor subunit expression

<table>
<thead>
<tr>
<th>Cell type</th>
<th>CD25 (IL-2Rα)</th>
<th>CD122 (IL-2Rβ)</th>
<th>CD132 (IL-2Rγ)</th>
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<tbody>
<tr>
<td>Naïve T cell</td>
<td>-</td>
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<td>+</td>
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<tr>
<td>Effector T cell</td>
<td>+++</td>
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<td>+</td>
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<tr>
<td>Treg cell</td>
<td>+++</td>
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In vitro responses to IL-2

- Regulatory immune cells respond to very low levels of IL-2
- Effector cells require higher IL-2 levels

Adapted from Boyman and Sprent, Nat Rev Immunol 2012

Klatzmann and Abbas, Nat Rev Immunol 2004
Treg boosting and potential role in autoimmune states

Potential adverse effects

- Mild to moderate constitutional symptoms such as asthenia, myalgia, fever and arthralgia

Potential beneficial effects

- **Atherosclerosis**
  By boosting T<sub>reg</sub> cells, IL-2 could help to control local inflammation to reduce plaque formation

- **Type 1 diabetes**
  By boosting T<sub>reg</sub> cells, IL-2 could suppress effector T cell-mediated killing of insulin-producing cells

- **Systemic lupus erythematosus**
  By blocking T<sub>reg</sub> cells and stimulating T<sub>eff</sub> cell differentiation, IL-2 could reduce autoantibody formation and immune complex deposition

- **Rheumatoid arthritis**
  By boosting T<sub>reg</sub> cells, blocking T<sub>17</sub> cells and favouring iT<sub>reg</sub> cells, IL-2 could help to control inflammation-dependent joint destruction
Low-dose IL-2 PoC in an autoimmune disease: vasculitis

Tregs

Clinical response

We also showed that low-dose IL-2 has anti-inflammatory effects

- 10 patients treated: 1.5 - 3 million IU/day
- Very well tolerated
- Excellent Treg induction
- Clinical improvements in 8/10 patients
Low-Dose IL-2 PoC in an allo-immune inflammatory disease: chronic graft-versus-host disease (cGVHD)

- Daily s.c. IL-2 delivery of 1 MIU/m2
  - patients following stem-cell transplant, median age of 49.5 years
  - 20/35 patients demonstrate (incomplete) clinical response
  - Reduction in steroid usage, improved skin pathology, liver function
- Continued administration does not lead to further Treg expansion
  - Continued IL-2 administration required for Treg increase
  - Responders have higher baseline Treg:Tcon ratios

3-5x increase in blood Treg cells

3.5x increase in blood Treg cells

3-5x increase in blood Treg cells

Treg, NK expansion following IL-2 treatment

Before

After

Koreth, NEJM 2011; Koreth, Blood 2016
Clinical remission in refractory SLE patient treated with low-dose IL-2

- 36-year-old female patient with SLE with high disease activity at baseline
  - Active arthritis with clinical and laboratory signs of myositis, rash, hypocomplementaemia and elevated anti dsDNA antibodies (SELENA-SLEDAI 14).

- First treatment cycle with low-dose IL-2:
  - Signs of arthritis, active skin eruptions and laboratory signs of myositis disappeared (figure 1A–C) and myalgia also improved 3 weeks later.

- Following three cycles:
  - Organ manifestations remained absent, disease activity remained low (SELENA-SLEDAI 4) (figure 1A–C)
  - Daily dose of glucocorticosteroids could be reduced step by step (figure 1E).
  - Clinical response associated with cyclic and treatment-related increases of the CD25++Foxp3+CD127lo Treg population (figure 1F).
Low-dose IL-2 in alopecia areata: IL-2 stimulated Tregs migrate to the pathological sites
Low-dose IL-2 in alopecia areata: IL-2 stimulated Tregs migrate to the pathological sites

CD25

Doxp3

CD8

Baseline  | End of the treatment  | 2 months after the end of the treatment
---|---|---
A | B | C
D | E | F
G | H | I
Low-dose IL-2 in alopecia aerate: IL-2 stimulated Tregs migrate to the pathological sites
Universal effects of IL-2 across 11 autoimmune diseases

- phase IIa, open label
- 132 patients with one of 11 autoimmune diseases
  - Rheumatoid Arthritis
  - Ankylosing Spondylitis
  - Systemic Lupus Erythematosus
  - Psoriasis
  - Behcet's Disease
  - Wegener's Granulomatosis
  - Takayasu's Disease
  - Crohn's Disease
  - Ulcerative Colitis
  - Autoimmune Hepatitis
  - Sclerosing Cholangitis

- same IL-2 treatment
- common + specific criteria for inclusion and evaluation
- **mild to moderate disease activity** (because of treatment issues)
- cognitive objectives: deep phenotyping for biomarkers discovery

clinicaltrials.gov: NCT01988506
Universal effects of IL-2 across 11 autoimmune diseases

- phase IIa, open label
- 132 patients with one of 11 autoimmune diseases

Will the effects on Tregs be specific and similar across diseases?
Will treatment be safe across diseases and concomitant treatments?
Will clinical benefits be similar across disease?
Universal effects of IL-2 on Tregs across 11 autoimmune diseases

✓ multidimensional analyses of CD4⁺ T cells (vs. Baseline) with unsupervised method confirms high Treg selectivity of Id-IL-2
Universal effects of IL-2 on NK and eosinophils across 11 autoimmune diseases
Clinical efficacy evaluation across 11 autoimmune diseases

Disease Activity

Disease Severity
Clinical efficacy of low-dose IL-2 assessed with disease specific scores

Psoriasis: BSA
N=5

Psoriasis: PASI
N=5
Clinical efficacy of low-dose IL-2 assessed with disease specific scores

Baseline

End of treatment

Rosenzwajg et al., Annals of Rheumatic Disease 2018
Low-dose IL-2 on fatigue & arthralgia

- **Fatigue**
  - Baseline
  - 3M
  - 6M

- **Arthralgia**
  - Baseline
  - 3M
  - 6M

**Significance Levels:**
- **n° patients**
  - 0
  - 10
  - 20
  - 30

**Statistical Notations:**
- ****
- ***
Conclusion

- IL-2 is the natural cytokine that controls inflammation and autoimmunity through Treg stimulation
- IL-2 physiologically increases during pregnancy to help protect the fetus from immune attack
- Autoimmune diseases consubstantially denote a Treg insufficiency
- Low-dose IL-2 is safe and selectively activates Tregs across multiple autoimmune diseases
- Low-dose IL-2 has a broad therapeutic potential for autoimmune and inflammatory diseases
"Selective Expansion of Regulatory T-Cells in Humans by a Novel IL-2 Conjugate T-Reg Stimulator, NKTR-358, Being Developed for the Treatment of Autoimmune Diseases”

Jonathan Zalevsky, PhD
NKTR-358: PEG-conjugated rhIL-2 Selectively Induces Regulatory T Cells (Tregs) and Their Suppressive Activity

**PEG-conjugation:**
- Increases half life (vs IL-2)
- Alters binding profile of NKTR-358 (relative to IL-2) with lower binding affinity to IL-2Rβ and different binding bias for IL-2Rα & IL-2Rβ
- Imparts selectivity for effect on Tregs over Tcons

NKTR-358 has shown activity in animal models of SLE and cutaneous hypersensitivity

*Stimulates Immune Response to Kill Tumor Cells*

*Down-Regulates Proliferation of conventional T-cells*

*Stimulated Tregs with potential for long term control of immune response*
Comparison of NKTR-358 and IL-2 by In Vivo Screening

Single NKTR-358 administration in mouse leads to superior Treg induction

Source: 13th Annual World Congress on Inflammation 2017, Langowski et. al.
NKTR-358 Preferentially Expands Tregs in non-Human Primates

Cynomolgus monkeys administered:
- NKTR-358 (25 μg/kg) single dose, or,
- recombinant human IL-2 (5 μg/kg) daily on 5 consecutive days

Source: 13th Annual World Congress on Inflammation 2017, Langowski et. al.
NKTR-358 Promotes Greater Treg Proliferation and Activation than IL-2

Cynomolgus monkey: 1M + 1F
25µg/kg: NKTR-358 single dose vs. qdx5 for IL-2

Source: 13th Annual World Congress on Inflammation 2017, Langowski et. al.
NKTR-358 Promotes Selective Treg Proliferation and Activation In Vivo

- Single dose NKTR-358 SC
- Induction of proliferation and activation markers
  - Helios, GITR, CTLA-4, CD39, CD73, OX40, and PD-1 (not shown)
  - Similar effect in blood and spleen (not shown)

Source: 2018 American College of Rheumatology Annual Meeting, Langowski et. al.
NKTR-358 Increases Treg Suppressive Activity

*In vivo / Ex vivo T suppressor assay in mice*

Source: 2018 American College of Rheumatology Annual Meeting, Langowski et. al.
NKTR-358 Suppresses Antigen-Driven Inflammation in a Mouse Model of Cutaneous Hypersensitivity (CHS)

Sensitization with KLH in flank

Elicitation with KLH in ear

Day 0

NKTR-358 s.c. q3d; CsA qd

Day 5

Measure ear swelling

Source: 2018 American College of Rheumatology Annual Meeting, Langowski et. al.

Med = 0.01 mg/kg

BW Loss for CsA at 10 mg/kg

MED = 0.01 mg/kg
NKTR-358 is Efficacious in a Mouse Model of SLE

- NKTR-358 demonstrated dose-dependent efficacy on multiple parameters in mouse SLE
- 0.3 mg/kg (q3d, week 8-20) reduces urine protein and blood urea nitrogen to naive mouse parameters
- Efficacy is consistent with Treg elevation
Selective Expansion of Regulatory T-Cells in Humans by a Novel IL-2 Conjugate T-reg Stimulator, NKTR-358, Being Developed for the Treatment of Autoimmune Diseases

C. Fanton, S. Siddhanti, N. Dixit, L. Lu, T. Gordi, D. Dickerson, J. Zalevsky, B. Kotzin
Disclosures

• C. Fanton, S. Siddhanti, N. Dixit, L. Lu, T. Gordi, J. Zalevsky, B. Kotzin are employees of Nektar Therapeutics and own shares of the company

• D. Dickerson is an employee of PRA Healthsciences
Many autoimmune disorders, including SLE, are associated with:

- Reduced Treg numbers
- Impaired Treg function
- Reduced systemic IL-2
NKTR-358: PEG-conjugated rhIL-2 Selectively Induces Regulatory T-cells (Tregs) and Their Suppressive Activity

NKTR-358

PEG-conjugation:
- Alters binding profile of NKTR-358 (vs IL-2) with lower binding affinity to IL-2Rβ and different binding bias for IL-2Rα & IL-2Rβ
- Imparts selectivity for effect on Tregs over Tcons (vs IL-2)
- Increases half life (vs IL-2)

NKTR-358 has shown activity in animal models of SLE and cutaneous hypersensitivity

Stimulates Immune Response to Kill Tumor Cells

Stimulated Tregs with potential for long term control of immune response
NKTR-358: Single Ascending Dose Study Objectives

Assess the effects of subcutaneous administration of single-ascending doses of NKTR-358 in healthy volunteers on:

**Primary**
- Safety and tolerability in subjects as evaluated by:
  - Adverse events
  - Vital signs
  - Clinical laboratory
  - Cytokine levels

**Secondary**
- Time course and extent of changes in the numbers and activity of Tregs, Tcons, and NK cells and subsets
- Pharmacokinetics (PK) of NKTR-358
- Other immunological effects: cytokine levels, peripheral blood cell populations, serum proteins and gene expression
Study Design: Randomized Double-blind Study of Subcutaneous Single Ascending Doses of NKTR-358 in Healthy Volunteers

Healthy Volunteers (N=100)
Age: 18 – 54 yrs.
Males: 60%
Females: 40%

Cohort 1
NKTR-358 0.3 μg/kg (n=9)
Placebo (n=3)

Cohort 2
NKTR-358 1.0 μg/kg (n=9)
Placebo (n=3)

Cohort 3
NKTR-358 3.0 μg/kg (n=9)
Placebo (n=3)

Cohort 4
NKTR-358 6.0 μg/kg (n=9)
Placebo (n=3)

Cohort 5
NKTR-358 9.0 μg/kg (n=9)
Placebo (n=3)

Cohort 6
NKTR-358 13.5 μg/kg (n=9)
Placebo (n=3)

Cohort 7
NKTR-358 20.0 μg/kg (n=13)
Placebo (n=3)

Cohort 8
NKTR-358 28.0 μg/kg (n=9)
Placebo (n=3)

Each cohort followed for 50 days

Study Enrolled and Follow-up Complete
NKTR-358 SAD Study Results: NKTR-358 was Safe and Well Tolerated in Healthy Volunteers

- No dose-limiting toxicities, deaths, or AEs leading to study discontinuation
- No clinically significant vital sign, ECG, or physical examination abnormalities
- Adverse events primarily limited to mild or moderate (Grade 1 or 2) injection site reactions
- 4 subjects experienced Grade 1 mild events of headache
- 1 subject at the highest dose tested (28.0 µg/kg) experienced mild (Grade 1) signs and symptoms of vomiting, diarrhea, anorexia, tachycardia, and myalgia attributed to elevated cytokine levels
- No anti-drug antibodies detected
NKTR-358 Concentration Curves Indicate Dose Proportional Pharmacokinetics*

- NKTR-358 Cmax and AUC values exhibited a dose proportional increase
- NKTR-358 concentrations reached maximum levels in 4-6 days
- NKTR-358 has an estimated elimination half-life of 8-9 days

*PK analyses preliminary and in progress
NKTR-358 Leads to Sustained, Dose-dependent Increases in CD25\(^{\text{bright}}\) Tregs

**Median peak effect of CD25\(^{\text{bright}}\) Tregs**

**Absolute numbers of CD25\(^{\text{bright}}\) Tregs**

- At 28 μg/kg NKTR-358:
  - 17-fold mean peak increase in numbers of CD25\(^{\text{bright}}\) Tregs above predose value
  - Treg levels peak at Days 10-12 and do not return to baseline until Days 20-25 following administration
- Increase in Treg activation markers ICOS and CTLA4 were observed at doses \(\geq 13.5\) μg/kg

Not all cohorts are shown for clarity
NKTR-358: No Changes in Numbers of Tcon Cells and Low-level Increases in Numbers of CD56+ NK Cells

Mean fold change of CD4+ cells

- Placebo
- 1.0 μg/kg
- 3.0 μg/kg
- 6.0 μg/kg
- 13.5 μg/kg
- 20.0 μg/kg
- 28.0 μg/kg

Mean fold change from predose

Day of administration

Mean fold change of CD8+ cells

Mean fold change of CD56+ NK cells

Not all cohorts are shown for clarity
NKTR-358 Selectively Induces Tregs in a Dose-Dependent Manner

Median peak effect of CD25\textsuperscript{bright} Treg/Tcon ratio

Mean Fold change in CD25\textsuperscript{bright} Tregs/Tcon cell ratio

- NKTR-358 administration leads to 15-fold increase in mean peak Treg:Tcon ratio over baseline at 28 μg/kg

In this analysis Tcon cells are defined as CD8\textsuperscript{+} Tcells; Not all cohorts are shown for clarity
• Safe and well tolerated in this first in human study
• Preliminary data suggest dose proportional pharmacokinetics and prolonged exposure with a half-life of 8-9 days
• Marked and selective dose-dependent expansion of CD25\textsuperscript{bright} Treg cells
• No measurable changes in numbers and percentages of CD4+ and CD8+ Tcons at all doses and low-level increases of NK cell numbers at highest doses tested
• Data provide strong support for studying NKTR-358 in autoimmune and inflammatory diseases
• NKTR-358 is currently being studied in a multiple ascending dose clinical trial in patients with SLE and additional studies in other inflammatory diseases are planned
Ongoing Phase 1b Study of Subcutaneous Multiple Ascending Doses of NKTR-358 in Patients With Mild to Moderate SLE Disease Activity

Patients with SLE* (N=48)
Age: 18-70 yrs

Each cohort followed for 79 days

Primary
- Safety and tolerability of NKTR-358

Secondary
- Pharmacokinetics of NKTR-358
- Pharmacodynamics: Time course and extent of changes in Tregs, Tcons, NK cells and cytokines
- Change in Disease Activity based on SLEDAI and CLASI scores

#Diagnosis of adult SLE according to 1997 ACR criteria for at least 6 months; Minimal to moderate disease activity
Q&A Session

Dr. David Klatzmann
Professor of Immunology, Department of Inflammation-Immunopathology-Biotherapy, Pierre & Marie Curie Medical School

Dr. Jonathan Zalevsky
Chief Scientific Officer, Nektar Therapeutics

Dr. Brian Kotzin
SVP of Clinical Development, Nektar Therapeutics