NKTR-358: A Selective Regulatory T Cell Inducing
Agent for the Treatment of Autoimmune and
Inflammatory Diseases

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Introduction

• A progressive imbalance of regulatory T cells (Tregs) relative to conventional T cells (Tcon) is shared by many autoimmune diseases

• Enhanced sensitivity of Tregs to IL-2 supports use of low-dose IL-2 therapy
  — Low-dose IL-2 therapy hampered by poor pharmacokinetics, AEs, short-lived effects
  — Magnitude of Treg mobilization ultimately limited by elicitation of Tcon
  — Clinical benefit demonstrated in GVHD, psoriasis, SLE and other indications
NKTR-358

- Preferential increase in number and activity of Tregs, minimal action on non-Tregs
  - Potential first-in-class therapeutic for direct manipulation of Tregs
- Biotherapeutic born from Nektar’s extensive development experience with IL-2 and polymer conjugation
- Utilizes the FDA-approved aldesleukin sequence
- Monthly or twice monthly self-administered subcutaneous product for the treatment of autoimmune, chronic inflammatory, and allergy indications

Nektar and Eli Lilly entered into a co-development agreement for NKTR-358 in August 2017
Design and Discovery of NKTR-358
NKTR-358 was Discovered by In Vivo Screening

- NKTR-358 discovered through an *in vivo* testing funnel
  - Subcutaneous injection
  - Blood Treg levels measured
    - Similar results in spleen
  - Assessment of Tconv and Teff to examine potential for broad-scale immune activation

- Design goals
  - Optimize IL-2 pathway activation for Treg specificity
  - Biological activity on both nTreg and iTreg populations
  - Improve margin of Treg/Tcon responses seen with IL-2
  - Reversible pharmacological effect to increase both Treg number and function
  - Utilize FDA approved aldesleukin amino acid sequence
  - Subcutaneous route of administration
  - Q2wk or Q4wk dosing
Calibrating the System with Native IL-2

C57Bl/6

Assess immune cell populations in blood using flow cytometry

IL-2 qdx5 SC

Treg, IL-2

- IL-2, 0.1mg/kg qdx5
- IL-2, 0.3mg/kg qdx5
- IL-2, 1mg/kg qdx5

1mg/kg qdx5 is near MTD and anti-tumor efficacious dose

0.1mg/kg qdx5 is an appropriate comparison to low-dose IL-2
Comparison of NKTR-358 and IL-2 by In Vivo Screening

Assess immune cell populations in blood using flow cytometry

NKTR-358

- NKTR-358, 0.3 mg/kg
- NKTR-358, 0.1 mg/kg
- NKTR-358, 0.03 mg/kg

IL-2

- IL-2, 0.1 mg/kg qdx5
- IL-2, 0.3 mg/kg qdx5
- IL-2, 1 mg/kg qdx5

C57Bl/6

Conjugate Single dose SC
NKTR-358 is Selective for Treg Populations

**Treg (blood)**
- NKTR-358, 0.3 mg/kg
- NKTR-358, 0.1 mg/kg
- NKTR-358, 0.03 mg/kg

**CD8 (blood)**
- NKTR-358 0.1 mg/kg
- NKTR-358 0.3 mg/kg
- NKTR-358 1 mg/kg

**Eosinophils**
- Total cells / μl

**Monocytes**
- Total cells / μl

**Total WBC**
- Total cells / μl

Days post dose: 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14

Fold change in Treg

Fold change in CD8
NKTR-358 Preferentially Expands Tregs in Monkeys

Cynomolgus monkey: 1M + 1F
25µg/kg: NKTR-358 single dose vs. qdx5 for IL-2
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
NKTR-358 Does Not Increase Eosinophil Levels in Monkeys

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

IL-5 Cytokine Levels in Serum

Eosinophils At Day 15
Molecular Pharmacology Characterization of NKTR-358
NKTR-358 has Attenuated Affinity to IL-2 Receptors

• PEG-conjugation reduces binding affinity of NKTR-358 relative to IL-2
• Relative to IL-2, NKTR-358 has:
  – Lower binding affinity to IL-2Rβ
  – Different binding bias for IL-2Rα & IL-2Rβ
NKTR-358 PK After Subcutaneous Administration to Mouse and Monkey

- **Half-life values are:**
  - ~2 days in mouse and rat
  - ~10 days in monkey
NKTR-358 Favors Activation of Treg Over Tcon

IL-2

NKTR-358

pSTAT5 MFI

Concentration (ng/mL, log scale)

Concentration (ng/mL, log scale)
NKTR-358 Favors Activation of Treg Over Other Subsets

- Healthy human PBMCs
  - IL-2 or NKTR-358 for 15 min
  - Analysis by CyTof
- IL-2 and NKTR-358 had primary effect on pSTAT5
  - No effect on pAKT, pERK, pS6, and pSTAT3 (save IL-2 on CD56+++ NK)
NKTR-358 Promotes Selective Treg Activation In Vivo

CD8 T cells

NK cells

CD4 Treg, CD25 MFI

CD4 Treg, FoxP3 MFI

Ki67+ Treg

ICOS+ Treg

Helios, GITR, CTLA-4, CD39, CD73, OX40, and PD-1 (not shown)
NKTR-358 Promotes Treg Suppressive Function In Vivo
NKTR-358 Expands Both nTreg and iTreg Populations In Vivo

NKTR-358 treated mice, day 4 post dose

- nTreg: Helios<sup>+</sup> 74.3%
- iTreg: Helios<sup>+</sup> 10.3%
NKTR-358 Suppresses Inflammation in Mouse DTH

- Sensitization: KLH, flank
- Elicitation: KLH, ear
- Measure ear

△ ear thickness (mm x 10^-2, mean ± SEM)

Time post KLH challenge (h)

- Vehicle
- 0.003 mg/kg
- 0.01 mg/kg
- 0.03 mg/kg
- 0.1 mg/kg
- 0.3 mg/kg
- Cyclosporin A, 10 mg/kg
NKTR-358 Promotes Treg Infiltration in Mouse DTH

**Figure:**

- **Graph:**
  - X-axis: Time post-KLH challenge (24hr, 48hr)
  - Y-axis: % FOXP3+ / mm² (± SEM)
  - Legend:
    - Vehicle
    - NKTR-358 0.1mg/kg
    - NKTR-358 0.3mg/kg
    - Cyclosporin-A 10mg/kg

**Statistical Notes:**

- *p<0.05, ****p<0.0001 vs Vehicle w.r.t. same timepoint
- One-way ANOVA (Bonferroni’s post-test)
- *p<0.001, unpaired t-test vs Vehicle w.r.t. same timepoint
Combination of NKTR-358 + Anti-Inflammatory: Synergy of Non-Overlapping MOAs
NKTR-358 Promotes Antigen-Specific Treg Memory

**Primary efficacy**

- Sensitization: KLH, flank
- Elicitation: KLH, ear
- Measure ear

Day 0 to Day 5

3 – 4 weeks, no treatment

**Rechallenge: Antigen-specific Treg memory**

- **OVA**
  - Vehicle
  - 0.003 mg/kg
  - 0.01 mg/kg
  - 0.03 mg/kg
  - 0.1 mg/kg
  - 0.3 mg/kg
  - Cyclosporin A, 10 mg/kg

- **KLH**
  - Vehicle
  - 0.1 mg/kg

Time post KLH challenge (h) | Time post OVA challenge (h) | Time post KLH challenge (h)
NKTR-358 Suppresses Inflammation in Monkey DTH

CHS: Cutaneous Hypersensitivity
TT: Tetanus Toxoid
Arrows: NKTR-358 s.c., 0.003 & 0.015 mg/kg q2w
*: p < 0.05 vs CHS, ANOVA

Skin Spot Area

Erythema

Edema

Naive CHS 0.003 0.015

Naive CHS 0.003 0.015

Naive CHS 0.003 0.015
NKTR-358 Efficacy in OVA-Induced Food Allergy in Mice

Clinical Score

- OVA
- OVA + CsA 10 mg/kg
- OVA + NKTR-358 0.1 mg/kg

MCPT1

- Serum MCPT1 (ng/mL)

Anti-OVA IgE

- Serum IgE (ng/mL)
NKTR-358 Efficacy in Mouse 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 naïve mouse parameters
- Efficacy is consistent with Treg elevation
Development Status of NKTR-358

- **Phase I Single Ascending Dose trial initiated March 2017**
  - Primary readouts are Treg mobilization and activity, Treg/Tcon selectivity ratio, PK and safety
- **Phase I Multiple Ascending Dose trial in SLE Patients initiated May 2018**
  - Primary readouts are Treg mobilization, Treg/Th17 ratio, B cell analysis, SLE biomarkers, disease activity
- **Nektar and Lilly plan multiple indications in Phase II**
Summary of NKTR-358

• NKTR-358 is an immune-regulatory cytokine drug being developed by Nektar and Lilly that induces profound Treg effects
  – Greater magnitude of total Treg cell increase than IL-2
  – Highly selective for Tregs with limited effects on non-Treg cells
  – Increased Treg suppressive capacity and induction of long-lived Treg memory
  – Prolonged activation and proliferation of Treg in higher species

• Clinical development ongoing for the treatment of autoimmune and chronic inflammatory indications