NKTR-358: a selective, first-in-class IL-2 pathway agonist which increases number and suppressive function of regulatory T cells for the treatment of immune inflammatory disorders

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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, SLE and other indications
NKTR-358

• Potential first-in-class therapeutic for direct manipulation of Tregs
• Biotherapeutic born from Nektar’s extensive development experience with IL-2 and polymer conjugation
• Preferential increase in number and activity of Tregs, minimal action on non-Tregs
• Utilizes the FDA-approved aldesleukin sequence
• Monthly or twice monthly self-administered subcutaneous product
• In development for autoimmune and allergy indications
NKTR-358 was identified by an *in vivo* screen

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
NKTR-358 promotes Treg proliferation and activation

- Single subcutaneous NKTR-358 administration in mice
- Induction of proliferation and activation markers
  - Helios, GITR, CTLA-4, CD39, CD73, OX40, and PD-1 (not shown)
  - Similar effect in blood and spleen
Preferential Treg expansion in non-human primates

**Treg, CD8 in blood**

- NKTR-358, Treg
- NKTR-358, CD8

- IL-2, Treg
- IL-2, CD8

Cell number fold change (mean ± SEM)

Days

- 0 7 14 21
- 0 5 10 15 20 25

**Treg activation**

- Treg proliferation (Ki67)
  - NKTR-358
  - IL-2

- %Ki67+ of Treg (mean ± SEM)

Days

- 0 7 14 21
- 0 1 2 3

- Treg activation (CD25)
  - NKTR-358
  - IL-2

Fold-change in MFI (mean ± SEM)

Days

- 0 7 14 21
- 0 1 2 3

**Cynomolgus monkey**: 1M + 1F

25µg/kg : NKTR-358 single dose vs. qdx5 for IL-2
NKTR-358 suppresses antigen-driven inflammation

Primary efficacy

Rechallenge: Antigen-specific Treg memory

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

OVA

- Vehicle
- 0.1 mg/kg

KLH

- Vehicle
- 0.1 mg/kg

Sensitization
KLH, flank

Elicitation
KLH, ear

Measure ear

Day 0

Day 5

3 – 4 weeks, no treatment

NKTR-358 s.c. q3d; CsA qd

Day 0

Day 5

0 24 48 72 96 120 144 168

0 2 4 6 8 10 12 14 16

0 24 48 72 96

0 2 4 6 8 10 12 14 16

0 24 48 72 96 120 144 168

0 2 4 6 8 10 12 14 16

0 24 48 72 96 120 144 168
NKTR-358 suppresses antigen-driven inflammation in a primate model of cutaneous hypersensitivity

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

TT Sensitization
TT Sensitization
TT Sensitization
TT Elicitation
Measure CHS

Week -6
Week -4
Week -2
Week 0

Naive
CHS
0.003
0.015

Naive
CHS
0.003
0.015

Naive
CHS
0.003
0.015

*
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 naïve mouse parameters
- Efficacy is consistent with Treg elevation
Summary

• Nektar’s immune-regulatory cytokine drug NKTR-358 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
  – Prolonged activation and proliferation of Treg in higher species

• Phase I Single Ascending Dose trial initiated March 2017
  – Primary readouts are Treg mobilization, functional activity, PK and safety
  – Goal is to establish a range of dose levels to be advanced into a Multiple Ascending Dose trial in patients with SLE