A Phase I Single Ascending Dose Study of NKTT120 in Stable Adult SCD Patients

Joshua F. Field MD, Rosemary Mazanet MD, PhD, Cheryl Eaton, Robert Mashal MD, Robert Schaub PhD, Felix Scheuplein PhD, Abraham Thariath PhD, and David G, Nathan MD

Blood Center of Wisconsin, and Medical College of Wisconsin, Milwaukee WI; NKT Therapeutics, Waltheim MA, Dana-Farber Cancer Institute, Boston Children’s Hospital and Harvard Medical School, Boston

Abstract
Background: Multiple lines of evidence point to iNKT cells as critical mediators of the chronic inflammatory cascade in sickle cell disease (SCD). Increased numbers of activated iNKT cells are seen in both preclinical models of SCD, and in adult patients with the disease. In preclinical models, inhibition of iNKT cell function leads to improvement in organ function. NKTT120 is a humanized monoclonal antibody that specifically depletes iNKT cells. Preclinical studies show that NKTT120 has high affinity and specificity for iNKT cells, is very potent, depletes iNKT cells in vivo in a dose-dependent manner, and that once depleted, iNKT cells return to the peripheral circulation in a dose- and time-dependent manner. Objective: This ascending single dose Phase 1 study will evaluate the safety, maximum tolerated dose (MTD), pharmacokinetics, and pharmacodynamics of NKTT120 in adult patients with stable SCD. Clinical and laboratory markers of inflammation and the activity will also be measured. The primary objective is to determine the dose that allows periodic dosing in phase 2 studies in the same patient population. Methods: This phase 1 study will evaluate single doses that are escalated in a 3+3 design over a range from 0.001 mg/kg to 0.1 mg/kg (0.001, 0.003, 0.01, 0.03, and 0.10 mg/kg). For the purpose of this protocol, stable SCD is defined as not having experienced acute pVOC or ACS or other SCD-associated event requiring hospitalization or outpatient care within one month prior to dosing. In addition to determining the primary objectives, this study will also examine pain, analgesic use, Quality of Life (QoL), and pulmonary function. During the two-week screening run-in period and throughout the follow-up, subjects will keep a daily smartphone eDiary (eSCaP) for pain, fatigue, and analgesic and initiated SABA use. The ASCCoMe and PROMIS QoL questionnaires will be administered at clinic visits. The screening run-in outcomes will be used as baseline comparison for values obtained post-dosing. Results: The results from the early cohorts of patients enrolled will be presented at a later date. This study is currently enrolling. Conclusions: NKTT120 is being developed as a first in class agent for the treatment of chronic inflammation associated with SCD. The expected in vivo mechanism of action of NKTT120 is the dose dependent depletion of the pro-inflammatory iNKT cells in blood and tissues of SCD patients, and this reduction should result in a suppression of the inflammatory stimuli that promote many of the pathophysiological sequelae seen in SCD.

Background: NKTT120 Preclinical

– NKTT120 is an IgG1 humanized monoclonal antibody
– Concentrations decline in a bi-exponential manner and in parallel during the terminal phase
– Cmax and AUC0-Inf are proportional to dose
– Strict proportionality over the dose range of 0.01 to 0.3 mg/kg
– The mean clearance was 0.131 mL/hr/kg across doses
– The average volume of distribution at steady state (Vss) was 63.7 mL/kg
– The apparent terminal half-life was 420 hours (17.5 days) on average.

Repeat Dose Tox (Cynomolgus Monkeys)

5 doses (0.3, 3.0 and 10.0 mg/kg, weekly)
8-week recovery period for control and high dose groups

Findings
No adverse events during the dosing or recovery period
Gross necropsy showed no abnormalities
Histopathology showed no test article related abnormalities except for decreased thymiccellularity (reversed in 2 months)
Clinical chemistry and CBC analyses
CBC normal
Elevated BUN (40%) in 10 mg/kg/week males; resolved in 1 month
No elevation in cytokines (IL-1β, IL-2, IL-4, IL-6, IL-10, IL-13, TNFα, IFNγ)

NKT120 Toxicokinetics

Safety margin based upon a "No Observed Adverse Event Level" (NOAEL) of 10 mg/kg

<table>
<thead>
<tr>
<th>Human Dose (mg/kg)</th>
<th>AUC (mg/hr/mL)</th>
<th>Predicted Safety Factor Relative to NOAEL AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.001</td>
<td>0.06</td>
<td>0.0225</td>
</tr>
<tr>
<td>0.003</td>
<td>0.18</td>
<td>0.0674</td>
</tr>
<tr>
<td>0.01</td>
<td>0.6</td>
<td>0.0247</td>
</tr>
<tr>
<td>0.03</td>
<td>1.8</td>
<td>0.0774</td>
</tr>
<tr>
<td>0.1</td>
<td>6.0</td>
<td>2.2742</td>
</tr>
</tbody>
</table>

* Assumes a 60 kg subject
* The NOAEL AUC was 0.02 mg/hr/mL

Conclusion
A first in human phase I trial of an iNKT depleting antibody is enrolling adult patients with stable SCD. Safety, PK, PD (iNKT cell depletion and recovery) and biomarkers will be collected as well as QoL measures.

Contact
R. Mounesan, NKT Therapeutics Inc., 680 Winter Street, Suite 330, Waltham, MA rmounesan@NKTX.com

120-SCD1 Study Objectives
Phase 1b, First in Human study
Safety
Determination of the pharmacokinetic characteristics of the antibody NKTT120
Determination of the pharmacodynamic profile of iNKT cell depletion and recovery
Assess markers of SCD activity
Measure and assess biomarkers of inflammation, coagulation, and endothelial cell activation
Measure QoL and eDiary (eSCaPe)

Inclusion Criteria 120-SCD1
1. Adults 18-50 years of age
2. Willing and able to sign informed consent
3. Diagnosed with SCD, either HbSS or HbS/β0 thalassemia, based on hemoglobin analysis
4. Have baseline iNKT cell numbers above the lower limit of quantification as determined by recognition on FACS assay of circulating peripheral blood iNK T cells measured at screening pre-run-in visit and again at the screening-run-in visit
5. Have stable SCD defined as not having experienced acute pVOC, ACS or other major or significant SCD-associated event requiring hospitalization or outpatient medical care during the month prior to enrollment

NKT120 Projected Dosing Schema

The maximal dose to be used in this study will be the least of:
• A dose which shows a DLT in ≥ 2 out of 6 subjects in any cohort
• A dose 1.5 logs greater than the minimal dose required to result in complete peripheral iNKT cell depletion lasting at least 2 weeks, or
• 0.1mg/kg