CONFIDENTIAL

The Safety, Pharmacokinetics, and Pharmacodynamic Effects of TNX-832 (Sunol-cH36) in Subjects with Acute Lung Injury/Acute Respiratory Distress Syndrome

TNX-832 **Active Ingredient:** TNX-832 (Sunol c-H36)

Indication: Acute Lung Injury/Acute Respiratory Distress Syndrome

Study TNX-832.201 **Phase I/IIa**

Study Initiation Date: December 16, 2004

Date of Early Termination: July 26, 2006

Abbreviated Clinical Study Report

Prepared for Genentech, Inc.

by XTrials Research Services

265 Davidson Ave, Suite 202

Somerset, NJ 08873

Report Issue Date: 11 February, 2008

Sponsor Signatory: Alex Bajamonde
Director, DATA Group, Genentech, Inc.

Medical Director: Sean Bohen, M.D., Genentech, Inc.

This study was performed in compliance with good clinical practice (GCP), including the archiving of essential documents.

Sponsor Signature Page

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Study TNX-832.201

I, the undersigned, have reviewed this report, including Appendices, and confirm that, to the best of my knowledge, it accurately describes the conduct and results of the study.

Sponsor Signatory	Alex Bajamonde
Title	Director, DATA Group, Genentech, Inc.

Signature: Alex C Bajamonde

Date: 20 February 2008

Medical Director Signature Page

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Sponsor Signatory Sean Bohen, M.D.

Title Medical Director, Genentech, Inc.

Signature: 

Date: 15 Feb. 2008

Sponsor Signature Page

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Sponsor Signatory	Alex Bajamonde
Title	Director, DATA Group, Genentech, Inc.

Signature: Alex C Bajamonde

Date: 20 February 2008

2. Synopsis

Sponsor Name:	Study Drug:	Active Ingredient:
Genentech	TNX-832	TNX-832 (Sunol-cH36)
Title: The Safety, Pharmacokinetics, and Pharmacodynamic Effects of TNX-832 (Sunol-cH36) in Subjects with Acute Lung Injury/Acute Respiratory Distress Syndrome		
Investigators/Study Centers: This study was conducted at 12 sites in the United States and 5 sites in Canada.		
Publications: None		
Study Period: 16 Dec 2004 to 30 July 2006	Phase of development: I/IIa	
Objectives: The objectives of this study were: • To evaluate the safety and pharmacokinetics of six dose levels of TNX-832 (0.06 mg/kg, 0.08 mg/kg, 0.1 mg/kg, 0.2 mg/kg, 0.3 mg/kg, and 0.4 mg/kg) in subjects with suspected or proven bacteria-induced ALI/ARDS. • To evaluate the pharmacodynamic effects of six dose levels of TNX-832 (0.06 mg/kg, 0.08 mg/kg, 0.1 mg/kg, 0.2 mg/kg, 0.3 mg/kg, and 0.4 mg/kg) in subjects with suspected or proven bacteria-induced ALI/ARDS.		
Methodology: This multi-center, randomized, placebo-controlled, single-blinded dose-escalation study was to evaluate TNX-832 in subjects with suspected or proven bacteria-induced acute lung injury (ALI)/acute respiratory distress syndrome (ARDS). Five cohorts of at least six subjects each were originally planned. Subjects were to be randomized in a 5:1 ratio to receive TNX-832 or placebo, respectively, administered as a single bolus infusion over 15 minutes. In November, 2005, a Data Safety Monitoring Board (DSMB) review of adverse events in the 0.1 mg/kg in led to an observation of probably-related hematuria in all subjects who received TNX-832 at 0.1 mg/kg. This review required the studying of TNX-832 at a lower dose cohort than previously planned. One additional cohort (0.08 mg/kg) of at least 6 subjects was planned. Additionally, the DSMB recommended administering study drug through a slow IV infusion (over 2 hours; 50 cc/hr). In September, 2006, upon a subsequent DSMB review of adverse events in the 0.08 mg/kg dose group, a decision was made to prematurely discontinue the study.		
Subject Population: Eligible subjects were 18 years of age or older with a suspected or proven bacterial infection. Subjects were also required to: 1). Have a diagnosis of acute lung injury/acute respiratory distress syndrome ALI/ARDS; 2). be receiving positive pressure ventilation through an endotracheal tube; and 3). provide signed informed consent, authorization in accordance with the Health Inisurance Portability Accountability Act of 1996 (HIPAA) and agree to comply with all protocol-specified procedures and evaluations.		

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Study Medication: Subjects were to be randomized in a 5:1 ratio to receive TNX-832 or placebo, respectively, administered as a single bolus infusion over 15 minutes. The TNX-832 dose for each cohort dosed was:

- Cohort 1: 0.06 mg/kg TNX-832
- Cohort 2: 0.1 mg/kg TNX-832
- Cohort 3: 0.08 mg/kg TNX-832

The original planned dose in Cohort 3 was .2 mg/kg. This was lowered to 0.08 mg/kg following a recommendation by the DSMB upon a review of adverse events in Cohort 2.

Criteria for Evaluation:

Pharmacokinetics: The following PK parameters were to be determined: C_{max} (maximum serum concentration), T_{max} (time to maximum serum concentration), AUC_{last} (area under the serum concentration-time curve from the time of dosing to the time of the last observed concentration), AUC_{∞} (area under the serum concentration-time curve from the time of dosing extrapolated to infinity), CL (serum clearance), V_d (apparent volume of distribution at elimination phase), V_{ss} (apparent volume of distribution at steady state), $t_{1/2}$ (terminal elimination phase half life).

Pharmacodynamics: Sample for the following inflammatory markers were collected but not analyzed: C-reactive protein [CRP], IL-6, IL-8, IL-1β, and TNF-α.

Safety: Safety assessments performed during this study included adverse events, clinical laboratory parameters (hematology, chemistry, coagulation, urinalysis, hematoccult), vital signs measurements (body temperature, heart rate, respiratory rate, blood pressure), physical examinations and electrocardiograms. Additional assessments included arterial blood gases, ventilation assessments, chest radiograph, hospital indices, and immunogenicity.

Statistical Methods: Serum concentration and pharmacokinetic parameters were to be summarized by and compared among dosing cohorts using descriptive statistics. Parametric and/or non-parametric statistical comparisons were to be done if suggested by the data, but were not performed. Continuous data variables were summarized by sample size, mean and its standard error, median, standard deviation , minimum, and maximum values. PD samples were not analyzed as the data were not anticipated to provide any meaningful information about the action of the study drug. Safety evaluations were based on the incidence, intensity and type of AEs and clinically significant changes in the subject's physical examination findings, vital signs, and

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clinical laboratory results. Safety variables were tabulated and presented for all subjects who received TNX-832 or placebo. Subjects who received TNX-832 were grouped by cohort. Subjects who received placebo were treated as one group.

Summary:

Number of Subjects: Eighteen subjects were assigned to study treatment. Two subjects were withdrawn from the study following administration of study drug. Subject 10-005 died during the study. The death occurred after removal of respiratory support for acute hypoxia; the death was determined by both the Investigator and the Sponsor to be not related to study drug administration. Subject 08-002 withdrew consent 48 days after administration of 0.06 mg/kg TNX-832.

Demographics: Demographics and baseline characteristics are summarized in the table below.

	Placebo N=3	**0.06 mg/kg TNX-832 N=5**	**0.1 mg/kg TNX-832 N=5**	**0.08 mg/kg TNX-832 N=5**
Age, [Mean (SD)]	49.67 (24.3)	40.40 (18.2)	54.60 (13.7)	54.00 (16.9)
Gender, [N (%)]				
-Male	1 (33.3)	1 (20.0)	0 (0.0)	2 (40.0)
-Female	2 (66.7)	4 (80.0)	5 (100.0)	3 (60.0)
Race, [N (%)]				
-Caucasian	1 (33.3)	4 (80.0)	3 (60.0)	2 (40.0)
-Black	1 (33.3)	0 (0)	2 (40.0)	2 (40.0)
-Hispanic	1 (33.3)	1 (20.0)	0 (0.0)	1 (20.0)

Pharmacokinetic: Pharmacokinetic results are provided as an appendix to this report.

Pharmacodynamic: Pharmacodynamic samples were not analyzed.

Safety Results: There was one death during the study. Subject 10005 died after removal of respiratory support for acute hypoxia. The subject died 10 days after administration of 0.08 mg/kg TNX-832. The death was considered unrelated to study medication by the Investigator. Four subjects experienced non-fatal SAEs during the study, including bilateral pulmonary embolism, hypoxic respiratory failure secondary to hospital-acquired pneumonia, worsening acute renal failure, and worsening anemia and empyema. Of these SAEs, the hypoxic respiratory failure secondary to hospital-acquired pneumonia in one subject was considered possibly related to study medication. The worsening anemia and empyema in one subject were considered possibly related to study medication, with empyema considered unrelated at the time of resolution. Of the

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18 subjects enrolled in this study, 16 subjects reported a total of 87 AEs during the study. Of the 87 treatment-emergent AEs in this study, 48 (55%) AEs were moderate in intensity, 35 (40%) AEs were mild in intensity, and 4 (5%) AEs were severe in intensity. Of the 87 treatment-emergent AEs, 16 AEs were considered by the Investigator to be related to study medication. Two AEs were considered related to placebo administration; 3 AEs were considered related to 0.06 mg/kg TNX-832 administration; 5 AEs were considered related to 0.1 mg/kg TNX-832 administration; 6 AEs were considered related to 0.08 mg/kg TNX-832 administration. A summary of treatment-emergent AEs is presented in the table below.

	Placebo	**0.06 mg/kg TNX-832**	**0.1 mg/kg TNX-832**	**0.08 mg/kg TNX-832**	**Total**
Dosed	3	5	5	5	18
Number of AEs	20	18	20	29	87
Subjects with AEs	3	4	5	4	16
Subjects with SAEs	0	1	2	2	5
Subjects with severe AEs	2	0	1	0	3
Subjects who discontinued due to AEs	0	0	0	1	1

Seven subjects had 16 laboratory values that were reported as AEs. None of these laboratory values reported as Aes were assessed as related to study medication by the Investigator, with the exception of decreased hemoglobin which resolved one day after onset with red blood cell transfusion. There were no clinically significant trends in vital signs during the study. Three subjects had changes in vital signs that were reported as AEs during the study. None of these changes in vital signs reported as Aes were assessed as related to study medication by the Investigator. Four subjects had ECG findings reported as Aes, none of which were assessed as related to study medication by the Investigator. There were no clinically significant trends in any ventilation evaluation during the study. Two subjects had clinically significant findings on chest x-ray following administration of study medication. One subject experienced pulmonary oedema, which resolved 22 days after onset. One subject experienced empyema and right pleural effusion, which resolved 8 days and 2 days after onset, respectively.

Conclusions:

This study was prematurely discontinued due to the high incidence of hematuria (nine occurrences) during the study. All instances of hematuria were experienced by patients who received study drug. In this study, the most frequent AEs were hematuria (n=9) and anemia (n=6). At the highest dose level of TNX-832 administered during this study (0.1 mg/kg), all five subjects dosed had AEs of hematuria. Hematuria was considered

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related to study medication by the Investigator in four of the five subjects. After the dose level was reduced to 0.08 mg/kg in Cohort 3, 2 subjects experienced hematuria (1 related to study medication). Based upon the bleeding related AEs of hematuria, the DSMB decided to discontinue the study. In conclusion, the study was prematurely discontinued due to the high incidence of treatment-related hematuria reported during the study, and the continued observation of hematuria in spite of the lowered dose in the third cohort . • Although there was one death during the study, the death was considered unrelated to study medication and was not the cause for discontinuation of the study.		
Date of Report: 11 February 2008		