2. JZAD Synopsis

Clinical Study Report Synopsis: Study H8K-MC-JZAD

Title of Study: A Phase 2 Study of LY573636-sodium as Second Line or Third-Line Treatment for Patients with Unresectable or Metastatic Soft Tissue Sarcoma

Number of Investigators: This multicenter study included 19 principal investigators.

Study Centers: This study was conducted at 19 study centers in 3 countries.

Publications Based on the Study: None at this time.

Length of Study:	**Phase of Development:** 2
Date of first patient enrolled: 10 September 2007 Date of last patient completed: 09 October 2009	

Objectives:

Primary Objective

The primary objective of this study was to estimate median progression-free survival for patients who had received LY573636 (tasisulam) after 1 or 2 prior systemic treatment regimens for unresectable or metastatic soft tissue sarcoma (STS), one of which must have been doxorubicin-based.

Secondary Objectives

The secondary objectives were:

- to characterize the progression-free survival distribution
- to estimate the objective response rate (complete response [CR] + partial response [PR]) and clinical benefit rate (CR+PR+stable disease [SD])
- to evaluate the pharmacokinetics (PK) of tasisulam using a limited sampling methodology in this population
- to estimate time-to-event variables, such as overall survival time, duration of overall objective response, and duration of SD
- to evaluate the safety of tasisulam in this patient population

Study Design: This is a nonrandomized, single-arm, open-label, multicenter Phase 2 study of tasisulam in patients with unresectable or metastatic STS who had failed no more than 2 prior systemic treatment regimens.

Number of Patients:

Planned: Approximately 60 patients were to be enrolled, with half assigned to approximately equal-sized cohorts of 2 groups of different STS subtypes.

Enrolled: 63 in the 420 µg/mL target C_{max} group (420/75 group), 38 in the 360 µg/mL target C_{max} group (360/90 group).

Treated (at least 1 dose): All 63 in the 420/75 dose group and 38 in the 360/90 dose group received at least 1 dose.

Diagnosis and Main Criteria for Inclusion:

- At least 18 years of age
- Histologically or cytologically documented STS that was unresectable or metastatic
- Must have received 1 or 2 previous systemic treatment regimens for metastatic STS, one of which must have been doxorubicin-based
- Must have had measurable disease as defined by the RECIST guidelines and have a performance status of 0 to 1 on the Eastern Cooperative Oncology Group (ECOG) Scale

Test Product, Dose, and Mode of Administration:
Tasisulam was administered as a 2-hour (±10 minutes) intravenous (IV) infusion on Day 1 of a 21-day cycle. Patients were given a loading dose calculated to achieve a C_{max} of 420 µg/mL followed by chronic dosing intended to maintain blood levels at 75% of the loading dose. The protocol was amended to lower the dose to a loading dose of 360 µg/mL followed by chronic dosing intended to maintain blood levels at 90% of the loading dose. The protocol was amended again to increase the duration of the 360/90 regimen from a 21-day cycle to a 28-day cycle to allow more bone marrow recovery time.
The tasisulam lot numbers used in this study were: [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted].

Duration of Treatment:
Patients were allowed to remain on study treatment until disease progression.

Variables:
Efficacy: Sarcomas were evaluated using RESICT criteria to measure tumor response. The following measures were used to assess efficacy: progression-free survival; objective response rate and clinical benefit rate; PK of tasisulam; and time-to-event variables such as overall survival time, duration of overall objective response, and duration of SD.
Safety: All patients treated with 1 dose of study drug were evaluated for safety. The safety information is summarized and listed in preferred terms of MedDRA, Version 12 and CTCAE, Version 3.
Bioanalytical: Plasma samples were analyzed by liquid chromatography-tandem mass spectrometry.
Pharmacokinetic/Pharmacodynamic: Blood samples for plasma PK analyses were collected using a limited sampling scheme. Clearance, intercompartmental clearance, volume of distribution, and C_{max} were evaluated.

Statistical Evaluation Methods:
Efficacy: No hypothesis tests were planned for this study. Parameter estimates and their 90% confidence intervals are reported. Preliminary efficacy signals were investigated using a Kaplan-Meier analysis on the observed progression-free survival distributions. RECIST criteria were used to measure tumor response. The secondary efficacy endpoints for the study were to characterize the progression-free survival distribution, the objective response rate (CR+PR), and the clinical benefit rate (CR+PR+SD) overall. No sample size calculation was done to establish statistical robustness.
Safety: All patients who receive at least 1 dose of tasisulam were evaluated for safety and toxicity.
Pharmacokinetic: No hypothesis testing were planned for PK parameters. PK parameters are reported as mean values.

Summary:

Patient Disposition:

- A total of 101 patients were enrolled in this study: 63 in the 420/75 dose group and 38 in the 360/90 dose group.
- The most common reasons for discontinuation, regardless of causality, were disease progression (87 patients, 86.1%), AE (6 patients, 5.9%), and death (4 patients, 4.0%). Other reasons included patient decision (2 patients, 2.0%), investigator decision (1 patient, 1.0%), and protocol violation (1 patients, 1.0%). Of the four deaths leading to discontinuation, two were identified by the investigator as being possibly related to study treatment.

Efficacy:

- Median progression-free survival was 2.64 months (90% CI: 1.41, 3.38) in the 420/75 dose group and 1.38 months (90% CI: 1.38, 1.54) in the 360/90 dose group.
- Secondary objectives included characterization of the progression-free survival distribution; estimation of the objective response rate and the clinical benefit rate; evaluation of the PK of tasisulam; estimation of time-to-event variables, such as overall survival time, duration of overall objective response and duration of SD; and evaluation of the safety of tasisulam in this patient population.

- The median overall survival time was 8.71 (90% CI: 7.39, 16.23) months for patients in the 420/75 dose group and 12.25 (90% CI: 7.79, 15.64) months for patients in the 360/90 dose group.
- The objective response rate was 3.2% for patients in the 420/75 dose group and 2.6% for patients in the 360/90 dose group.
- The clinical benefit rate was 46.0% for patients in the 420/75 dose group and 26.3% for patients in the 360/90 dose group.
- The median duration of SD was 4.44 (90% CI: 4.14, 5.42) months for patients in the 420/75 dose group and 5.91 (90% CI: 2.76, 7.89) months for patients in the 360/90 dose group.
- A larger AUC_{alb} (AUC above albumin-corrected threshold) is correlated with an increased risk of Grade 4 hematological toxicity.

Safety:

- Ninety-seven (97; 96.0%) of the 101 patients experienced treatment-emergent adverse events (TEAEs). Of these, 87 (86.1%) experienced events that were possibly related to study drug. The most common TEAEs possibly related to study drug included thrombocytopenia (38; 37.6%), fatigue (35; 34.7%), and anaemia (34; 33.7%).
- The most common adverse events (AEs) possibly related to tasisulam were hematologic events and included thrombocytopenia, anaemia, febrile neutropenia, and neutropenia. Thirty-one (31; 30.7%) patients experienced 1 or more serious adverse event (SAE) while on therapy, including 21 (33.3%) in the 420/75 dose group and 10 (26.3%) in the 360/90 dose group. Of these, 21 (20.8%) were related to tasisulam. The incidence of thrombocytopenia and neutropenia were lower in the 360/90 dose group than in the 420/75 dose group.
- The most common SAEs (incidence of ≥5.0% regardless of causality) were thrombocytopenia, anaemia, febrile neutropenia, and neutropenia.
- Thirteen patients died on study or within 30 days of discontinuation: 8 were due to study disease, and 5 were due to AEs. Two of the deaths due to AEs were considered by the investigator as possibly related to study drug toxicity.
- Ten (10; 9.9%) patients in this study discontinued due to AEs, including 6 (9.5%) in the 420/75 dose group and 4 (10.5%) in the 360/90 dose group. Of these, 8 (7.9%) patients discontinued due to AEs that were possibly related to study drug (4 [6.3%] in the 420/75 dose group and 4 [10.5%] in the 360/90 dose group). Five (5.0%) patients discontinued due to thrombocytopenia, and 1 patient each due to multi-organ failure, myocardial infarction, and neutropenia.
- The most common non-laboratory toxicities were fatigue (35; 34.7%), constipation (24; 23.8%), diarrhoea (24; 23.8%), and nausea (20; 19.8%).

Conclusions:

- The median progression-free survival was 2.64 months for the 420/75 dose group and 1.38 months for the 360/90 dose group. Median progression-free survival tended to be lower for STS Group 2 patients.
- The median overall survival time was 8.71 months for patients in the 420/75 dose group and 12.25 months for patients in the 360/90 dose group. Median overall survival time tended to be lower in STS Group 2 patients.
- The objective response rate (CR+PR) was 3.2% for patients in the 420/75 dose group and 2.6% for patients in the 360/90 dose group.
- The clinical benefit rate (CR+PR+SD) was 46.0% for patients in the 420/75 dose group and 26.3% for patients in the 360/90 dose group.
- The median duration of SD was 4.44 months for patients in the 420/75 dose group and 5.91 months for patients in the 360/90 dose group.
- The primary toxicity was bone marrow suppression, most commonly thrombocytopenia and/or neutropenia.
- The relationship between Grade 4 hematological toxicity and AUC_{alb} is consistent with that which has been observed in other ongoing Phase 2 studies. A larger AUC_{alb} is correlated with an increased risk of Grade 4 hematological toxicity. Patients with a low predose albumin level will have less study drug bound to albumin and therefore a lower threshold (drug concentration) for hematological toxicity secondary to unbound tasisulam.

JZAD Clinical Study Report Amendment Summary

Changes are described in the following table:

Description of and Rationale for Change	Location of Change
• The original study report mistakenly reported that 13 patients died on study, and that of those, 8 were due to study disease, 4 to AEs, and 1 to study drug toxicity. This was corrected to read that 13 patients died on study or within 30 days of discontinuation: 8 were due to study disease, and 5 were due to AEs. Two of the deaths due to AEs were considered by the investigator as possibly related to study drug toxicity. • Minor editorial changes for clarity	Section 2: Synopsis
• Table JZAD.8.2 of the original study report mistakenly reported that Patient [redacted] died on study or within 30 days of discontinuation due to disease progression. Patient [redacted] discontinued the study due to disease progression but died within 30 days of discontinuation due to an AE of respiratory failure that was secondary to disease progression. This has been clarified in Table JZAD.8.2.	Section 8.2.1: Deaths and Serious Adverse Events
• Minor editorial changes for clarity	Section 5