SMC-101-1007, SMC-101-1008, and SMC-101-1009: Peripheral Vein Administration of Thymoglobulin® for Induction Therapy in Adult Renal Allograft Recipients

These results are supplied for informational purposes only.

Prescribing decisions should be made based on the approved package insert in the country of prescription.

.

NAME OF SPONSOR/COMPANY:

Genzyme Corporation, 500 Kendall Street, Cambridge, MA 02142
SangStat Medical Corporation, Menlo Park, CA 94025 (SangStat Medical Corporation was acquired by Genzyme Corporation September 2003)

TITLE OF STUDY:

SMC-101-1007, SMC-101-1008, and SMC-101-1009: Peripheral Vein Administration of Thymoglobulin® for Induction Therapy in Adult Renal Allograft Recipients

INVESTIGATORS AND STUDY CENTERS:

Each trial was conducted at a single center in the United States.
Note: The protocols were identical with minor exceptions (e.g., incidence of acute rejection and patient and graft survival rates were to be determined at 6 months for Protocol SMC-101-1008 and at 6 and 12 months for Protocols SMC-101-1007 and SMC-101-1009.)

STUDIED PERIOD:

11 November 1998 (First Patient Enrolled) To
25 December 1999 (Last Patient Completed)

PHASE OF DEVELOPMENT:

Phase 2

OBJECTIVES:

To evaluate peripheral venous infusion as a mode of administering Thymoglobulin® for induction therapy in adult renal transplant recipients.

METHODOLOGY:

Prospective, open-label, multicenter study with follow up at 6 months (SMC-101-1008) or 6 and 12 months (SMC-101-1007 and SMC-101-1009). Concomitant immunosuppression was prescribed per investigative center's standard care. Antiviral therapy was required and administered per investigative center's standard care.

NUMBER OF PATIENTS (PLANNED AND ANALYZED):

Sixty patients were allowed, and 39 were enrolled and analyzed. The smaller sample size was the result of limited availability of patients and cost.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Male and non-pregnant, non-lactating female patients ≥ 18 years of age receiving renal transplantation who were judged by the investigator to be candidates for Thymoglobulin® therapy. Patients were eligible if they could have an intravenous (IV) catheter placed in a peripheral vein in 1 of their arms.

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

Thymoglobulin® 1.5 mg/kg administered IV.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION:

Not applicable.

DURATION OF TREATMENT:

Patients were to receive Thymoglobulin® infusions once daily for 5 to 7 days.

CRITERIA FOR EVALUATION:

Criteria for Evaluation - Primary Endpoint:
The percentage of patients receiving Thymoglobulin® via peripheral administration 5 days after transplantation. Administration via either a central venous catheter or a dialysis access port was considered a failure

Criteria for Evaluation - Efficacy:
Incidence of the following was assessed 6 months (SMC-101-1008) or 6 and 12 months (SMC-101-1007 and SMC-101-1009) after transplant: Incidence of acute rejection episodes, along with severity and timing of the episodes; Patient and graft survival rates.

Criteria for Evaluation - Safety:
Drug-related adverse events (AEs), infections, and malignancy as well as a listing of all AEs.

STATISTICAL METHODS:

Statistical Methods - Patients:
Demographic information and baseline characteristics were summarized using descriptive statistics (mean, median, standard deviation, minimum, and maximum) for continuous variables, and counts and percents for categorical variables.

Statistical Methods - Primary Endpoint:
All patients who received at least 1 dose of Thymoglobulin® therapy (n=39) were analyzed for the primary endpoint. The number and percentage of patients receiving peripheral venous administration at 5 days post-transplant were calculated.

Statistical Methods - Efficacy:
The data set analyzed for efficacy assessments included all patients who received at least 5 Thymoglobulin® infusions (n=32). Severity and timing of acute rejection episodes and patient and graft survival rates at 12 months post-transplant were calculated and summarized descriptively using the Kaplan-Meier method. Two-sided 95% confidence intervals (CI) were generated.

Statistical Methods - Safety:
The safety population included all patients who received at least 1 dose of Thymoglobulin® (n=39). AEs, coded by the COSTART dictionary, were summarized by body system, relationship to study drug, and severity. Drug-related AEs, infections and malignancies, assessed 12 months post-transplant, were presented separately. Serious adverse events (SAEs), AEs leading to discontinuation, and deaths were summarized.

SUMMARY / CONCLUSIONS

Summary / Conclusions - Patients:
A total of 39 patients were studied.
Most patients were male (26 of 39 subjects or 67%) and most were Caucasian (26 of 39 or 67%). The mean age of patients at the time of transplantation was 45 years (range: 22 to 63 years). Approximately 54% of transplants used cadaveric donor

organs.
Four patients failed to complete the study: one discontinued at the Sponsor's request, 2 had graft loss, and 1 died.

Summary / Conclusions - Primary Endpoint:
In all, 36 of 39 subjects (92%) successfully received their Thymoglobulin® infusions via peripheral venous infusion. Three of 39 (8%) patients had peripheral venous administration failure because of infiltrates, and they received their remaining doses through their existing central venous catheters. The time to failure ranged from 6 to 7 days.

Summary / Conclusions - Efficacy Results:
Four of 32 patients (13%) had at least 1 episode of acute rejection; the rejection episode(s) for 3 of these patients were confirmed by kidney biopsy. All rejection episodes were mild or moderate in severity. Median time to onset first acute rejection was 81 days (range: 9 to 164 days).

The 12-month patient survival rate was 97% (CI: 76 to 99%), and the graft survival rate was 94% (CI: 75 to 98%).

Variable	Result as n (%)	Confidence Interval (%)
Patients with at least 1 episode of acute rejection	4 (13)	not available
Patient survival at 12 months*	31 (97)	76 - 99
Graft survival at 12 months*	30 (94)	75 - 98
*Kaplan-Meier estimate based on 32 subjects who received at least 5 Thymoglobulin® infusions.		

Summary / Conclusions - Safety Results:
All but 7patients received at least 5 doses of Thymoglobulin®. One patient's Thymoglobulin® was discontinued after the first dose when it was discovered that the patient had also received OKT3. Details about the reasons the other patients received fewer than 5 doses are not available. The median number of infusions administered was 6 (range: 1 to 10). Patients received a median total dose of 560 mg of Thymoglobulin® (range: 150 to 1010 mg). A total of 229 peripheral vein infusions were administered, and information about dose adjustment was recorded for 206. Most infusions (158 of 206 or 77%) were administered without any dose adjustment. Dose reductions (by one-half) were made for 37 of 206 (18%) infusions, and 7 of 206 (3%) infusions were interrupted.

Thirty-two of 39 patients (82%) reported 884 AEs during the study. Five patients had 6 SAEs, and 1 of those patients died.

Most of the AEs were mild or moderate and most were judged as unlikely or not related to study drug.

The SAEs, including the death, are briefly summarized below.

One patient had transplant rejection and interstitial nephritis (relationship not reported), 1 had acute tubular necrosis after transplant (unlikely related) and later had pyelonephritis and urinary tract infection (relationship not reported), 1 had pneumonia (possibly related), 1 had a viral infection (relationship not reported), and 1 died 84 days after transplantation surgery as a result of *Aspergillus* infection in the lungs (possibly related).

Most patients (≥ 60%) did not have infusion-related AEs (e.g., redness, pain).

In all, 27 of 39 patients (69%) had 107 AEs that were considered possibly, probably, or definitely related to study treatment. The most common related AEs included leukopenia, thrombocytopenia, fever, and thrush. These events generally occurred within 3 to 5 days after transplantation. Additionally, some patients had pancytopenia or decreased platelets that were considered related to study drug.

In all, 9 of 39 patients (23%) had at least 1 infectious episode during the study. As described above, 1 patient died as a result of infection.

No malignancies were reported during the study.

Based on Report Prepared on: 10 March 2004
Synopsis Prepared on: 05 June 2006