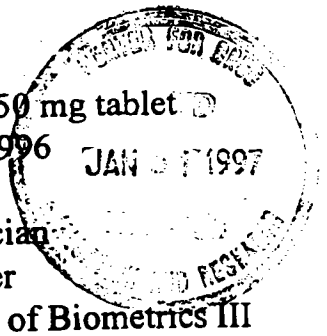
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020675

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION - STABILITY STUDY

JAN 27 1997



NDA#:	20-675
Applicant:	Axcan Pharma, Inc.
Name of Drug:	URSOFALK Ursodeoxycholic Acid 250 mg tablet
Document Reviewed:	Document received dated March 28, 1996
Statistical Reviewer:	
Primary:	Yi Tsong, PhD, Mathematical Statistician
Secondary:	Mohammad Huque, PhD, Team Leader
	Nancy Smith, PhD, Director, Division of Biometrics III
Review Chemist:	Michael Adams, PhD, HFD-180

I. INTRODUCTION:

In this NDA submission, Axcan Pharma, Inc., has requested an expiration dating period of 36 months for URSO tablets. Division of Biometrics III was requested to perform the statistical review and evaluation of the sponsor's stability data analysis.

II DESIGN

The study consists of the following three lots of URSO tablets manufactured by Shering Canada with the following configurations.

Lots: Lot # 1-SULK-01 manufactured on January 22, 1991, lot # 1-SULK-02 manufactured on January 23, 1991 and lot # 1-

Strength: Each URSOFALK tablet contains 250mg of Ursodeoxycholic acid and the following ingredients

INGREDIENT	MARKET FORMULATION	[redacted]
[redacted]	[redacted] (mg/tablet)	[redacted]
UDCA	[redacted]	
Microcrystalline cellulose		
[redacted]		
Polyethylene glycol		
Sodium starch glycolate		
Magnesium stearate		

	(b)(4) C/C
[redacted]	
[redacted]	
Dibutyl sebacate	
Polyethylene glycol	
Carnauba wax (polishing)	

Package configurations: Bottle of 100.

Tested Parameter: UDCA

Temperature: Room temperature at 25° C.

Specification Limits: 90% LC - 110% LC (Label Claim).

Sampling Times: Initial, 4, 6, 12, 18, 24, 30 and 36 months.

III. SPONSOR'S ANALYSES

III.a Statistical Methods

The sponsor analyzed the stability data using the SAS program developed by the Division of Biometrics, FDA. The procedure consists of the following steps:

Step 1: Model selection (testing for pooling of stability batch data)

An assessment is made as to whether or not the degradation curves, considering all individual batches separately, are of the same slope and/or intercept. If there is no statistical evidence that the degradating slopes of the three batches are different and/or no evidence that the intercepts of the three batches are different, it is desirable to pool the data across the batches in order to obtain a more precise estimate of degradating slope and/or intercepts. The equalness of the degradating slope and of the zero-time intercept are assessed by fitting linear regression models to the each batch data, and tested with statistical tests within the framework of analysis of covariate. The following two considerations must be satisfied to allow such pooling of the data.

a) The test for the hypothesis that the degradation lines of the three batches have separate intercepts and a common slope (H_{10}) versus the alternative hypothesis that all three degradation lines have separate intercepts and separate slopes (H_{1a}) should have a p-value of 0.25 or less to reject H_{10}, and

b) The test of the hypothesis that the three batches have degradation lines with a common intercept and a common slope (H_{20}) versus the alternative that the three degradation lines have the same slope but separate intercepts (H_{2a}).

At the end of Step 1, one of the following model is selected for the degradation model.

a) separate intercepts and separate slopes;
b) separate intercepts and common slope;
c) common intercept and common slope.

Step 2 Construct a 95% two sided confidence band for the mean degradation curve (as of the model selected in Step 1).

III.b Acceptance Criteria

In order to have an acceptable potency level of the assay under test, the 95% lower confidence bound should be above the lower specification limit (90% LC) and the 95% upper confidence bound should be below the upper specification limit (110% LC) are required. However, the estimated expiration date should be greater than the expiration date requested by the sponsor and in general, the requested expiration date should not be longer than 6 month beyond the data collected.

III.c Data analysis and results

The analysis and results were presented by sponsor in NDA 20-675 submission Volume 1.3, Section J, pages 297-309. The tests for H_{10} results in a p-value of 0.9156, for H_{20} results in a p-value of 0.9378. Hence a common intercept and common slope model is selected for the degradation line for the three batches. The degradation date estimate is 63 months, at which the upper limit of the confidence limit runs across the upper specification limit.

IV. REVIEWER'S COMMENTS

Since the sponsor employed the SAS program developed and used by the Divisions of Biometrics, FDA, to conduct the statistical analysis on this stability data, this reviewer did not repeat the analysis. Based on the sponsor's analysis and this reviewer's review, therefore, the sponsor's request of a 36-month (6 months beyond the last collection day of stability data) degradation dating was supported by the stability data.

[redacted] /S/

Yi Tsong, Mathematical Statistician

[redacted] /S/ 1/27/97

Concur: Mohammed Huque, PhD, Team Leader

[redacted] /S/ 1/27/97

Nancy Smith, PhD, Director, Division of Biometrics III

cc: Archival NDA 20675
HFD-180/Dr. Fredd/Dr. /Mr Strongin
HFD-720/Chron Copy/Dr. Smith/Dr. Huque/Dr. Tsong
YTsong/x3174/urso/ursostab.wpd/1/24/97

[redacted] APPEARS THIS WAY ON ORIGINAL

Statistical Review and Evaluation - NDA

Date: SEP 27 1996

NDA #:	20,675
Applicant:	AXCAN Pharma US Inc.
Name of Drug :	URSO™ (Ursodiol) Tablet 250 mg
Indication:	Treatment of Primary Biliary Cirrhosis.
Documents Reviewed:	NDA vol. 1.1-1.2, 1.34-1.43 received on March 22, 1996, vol. 1.44 received on May 14, 1996, Amendment #2 received on Jul 18, 1996, Amendment #9 received on Aug. 2, 1996
Primary Reviewer:	Yi Tsong, PhD
Secondary Reviewers:	Mohammad Huque, Ph.D., Nancy Smith, PhD
Medical Reviewer:	This review has been discussed with the medical official, Hugo Gallo-Torres, M.D., Ph.D.

A. Background

URSO™ (Ursodiol) tablets, 250 mg (tablet of UDCA, Ursodeoxycholic Acid), under development by the sponsor for the treatment of patients with primary biliary cirrhosis, was granted the Orphan Drug Status on June 20, 1991 for this indication. The sponsor has submitted two pivotal trials in support of the proposed claims. The first study (Mayo Clinical Study) began as a two year placebo-controlled, randomized, double-blind, parallel trial (double-blind phase) then continued as an open-label long-term follow-up study (open-label phase). The second study (Heathcote Study) was a two year placebo-controlled, randomized, double-blind, parallel trial,

The Mayo clinical trial was conducted in the U.S. The primary study objective of the double-phase was to show that the UDCA treatment would reduce the incidence rate of and prolong the time to treatment failure. The parameters of treatment failure in this study were death, liver transplantation, histologic progression by two stages or to cirrhosis, development of varices, ascites or encephalopathy, doubling of total bilirubin, marked worsening of fatigue or pruritus, inability to tolerate the drug and voluntary withdrawal.

The open-label phase of the Mayo study was conducted with the primary objective to show that the UDCA treatment (including patients treatment with UDCA after two placebo treatment) would reduce the incidence rate of, and prolonged the time to death and liver transplant. Another objective was to show that the UDCA treatment reduced the incidence rate of and prolong the time to treatment failure, using a definition that included all parameters except the doubling of bilirubin and voluntary withdrawal)..

The Heathcote Study was conducted in Canada with the primary objective to show that the UDCA treatment would reduce the incidence rate of and prolong the time to doubling of total bilirubin.

B. Overview of Sponsor's Analysis

In the double-blind phase of Mayo clinical trial, the sponsor showed that the UDCA treatment reduced the incidence rate of and prolong the time to treatment failure (including death, liver transplantation, histologic progression by two stages or to cirrhosis, development of varices, ascites or encephalopathy, doubling of total bilirubin, marked worsening of fatigue or pruritus, inability to tolerate the drug and voluntary withdrawal). This study provided adequate evidence to show the efficacy of UDCA for the objective. The sponsor also showed that the UDCA treatment significantly prolonged the time to treatment failure using a definition that included all parameters except the doubling of total bilirubin and voluntary withdrawal.

In the open-label phase of the Mayo study, the sponsor showed that the UDCA treatment (including patients treatment with UDCA after two placebo treatment) reduced the incidence rate of and prolonged the time to death and liver transplant. They sponsor also showed that the UDCA treatment reduced the incidence rate of and prolong the time to treatment failure, using a definition that included all parameters except the doubling of bilirubin and voluntary withdrawal.

In the Heathcote Study, the sponsor showed that the UDCA treatment reduced the incidence rate of and prolong the time to the doubling of total serum bilirubin.

The sponsor's results of these studies are summarized in the following table and Figures A-J. Details of the statistical analysis and review of each study are given in the following sections.

Table 1 Summary of Sponsor's Results

Mayo Study Double-Blind Phase		
SAMPLE SIZE	STUDY OUTCOMES	STAT SIG
UDCA 86 Placebo 86	Primary outcomes	
	1 - Treatment failure (including doubling of total bilirubin, voluntary withdrawal)	Incidence frequency - D[1]= -24%, p<0.01 Time (days) to incidence[2] - D=162.7, p = 0.0001
	2 - Death/liver transplant	Incidence freq - D = 6.3% Time (days) to incidence[2] - p = 0.11 p = 0.07(adjusted for baseline Mayo risk score)
	3 - Treatment failure (excluding doubling of total bilirubin, voluntary withdrawal)(post-hoc)	incidence freq) - D = -10% time (days) to incidence[2] - D = 110 days, p = 0.001
	Secondary Outcomes	
	1 - Hepatic biochemical parameters (alkaline phosphatase, SGOT, total bilirubin, prothrombin time, albumin, IgM, IgA, IgG, gamma globulin	All p-value are less than 0.05 in favor of UDCA except albumin
	2 - Development of symptoms (cirrhosis, ascites, varices, portal systemic encephalopathy, pruritus, fatigue)	Time (days) to any symptom[2] D = 74, p =0.01 Frequency of Cirrhosis- D = -16%, p =0.07 Frequency of Varices - D = -11%, p =0.28 Frequency of Ascites - D = -2%, p = 0.74 Frequency of PSE - D =-1%, p = 0.47 Mean changes in pruritus - D = -0.21, p=0.18 Mean changes in fatigue - D =-0.17, p=0.19
	3 - Biliary bile acids	Mean measurement change Ursodeoxycholic - D=34.15 p<0.001 Cholic - D = -23.77, p<0.001 Chenodeoxycholic - D =6.46, p<0.01 Deoxycholic - D =-6.45, NS Lethoho;ic - D = 0.56, p <0.01 Sulfa-lithocholic - D =-0.12, NS
	4 - Histologic stage	NS
	5 - Mayo risk score	Mean change - D =-0.6, p <0.001

Mayo Study Open Label Phase		
SAMPLE SIZE	STUDY OUTCOMES	STAT SIG
UDCA 89 placebo 91	Primary outcomes 1 - Death/liver transplant	Time (days) to incidence[2] D(freq of incidence) = 8% D(time to incidence) = 40 days Life table - p =0.06 Cox (cov Mayo risk score at baseline) - p= 0.007
	2 - Treatment failure (excluding doubling of total bilirubin, voluntary withdrawal)	Time (days) to incidence[2] D(freq of incidence) = -18% D(time to incidence) = 268 days, p = 0.001
	Secondary - time to varices	Time (days) to incidence[2] D(freq of incidence) = -18% D(time to incidence) = 201 days, p =0.003
Heathcote Study		
SAMPLE SIZE	STUDY OUTCOMES	STAT SIG
UDCA 106 Placebo 104	Primary - Rise of total bilirubin	D(Freq of doubling) = -17.5%, p <0.0001 D(mean % change) = -60.7%, p = 0.0001
	Secondary outcomes 1 - Clinical chemistry including total serum bile acids, alkaline phosphatase (ALP), AST, ALT, gamma-glutamyl transferase (γGT), total serum bilirubin, immunoglubin level, hemoglobin, platelet count, prothrombin times	Sig. More reduction in UDCA than placebo in ALP, AST, ALT, Total cholesterol, IgM
	2 - Signs and symptoms and hepatic histological progression	No sig. difference in percentage of clinical symptom or in hepatic pathology progression
	3 - Death/liver transplant	Time (months) to incidence D(freq of incidence) = -6.3% Life table[2] p =0.22
	4 - Post-hoc definition of treatment failure (including discontinued study, doubling of total bilirubin, total bilirubin ≥ 1.5 mg/dl, development of ascites, encephalopathy	Time (months) to incidence D(freq of incidence) = -24.4% Life table[2] p <0.0001

1: UDCA - Placebo
2: See the corresponding figures

Figure A. Time to Treatment Failure - All Patients Included (MAYO study)

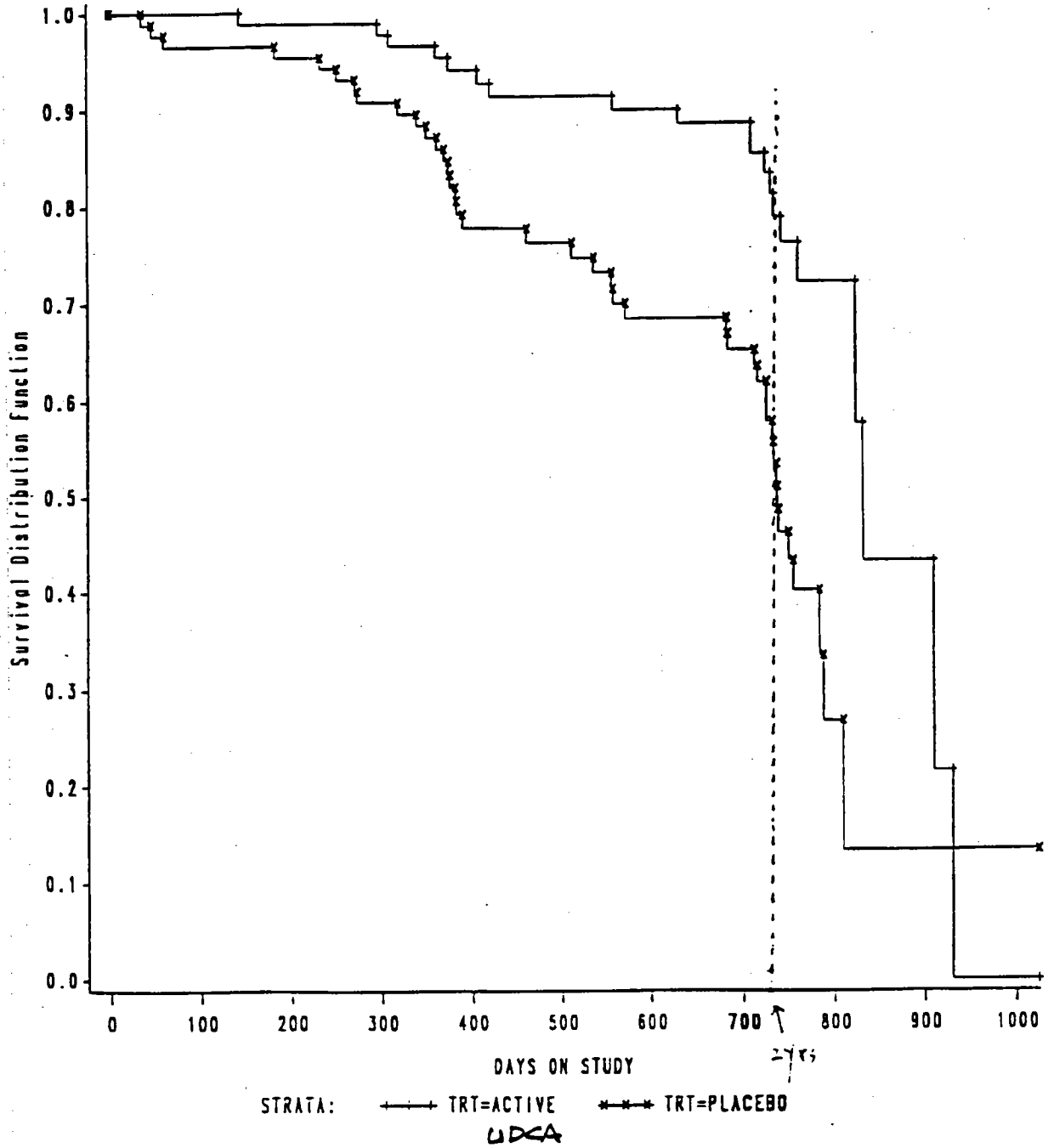


Figure B. Time to Death/Transplant - All Patients Included (Mayo Study)

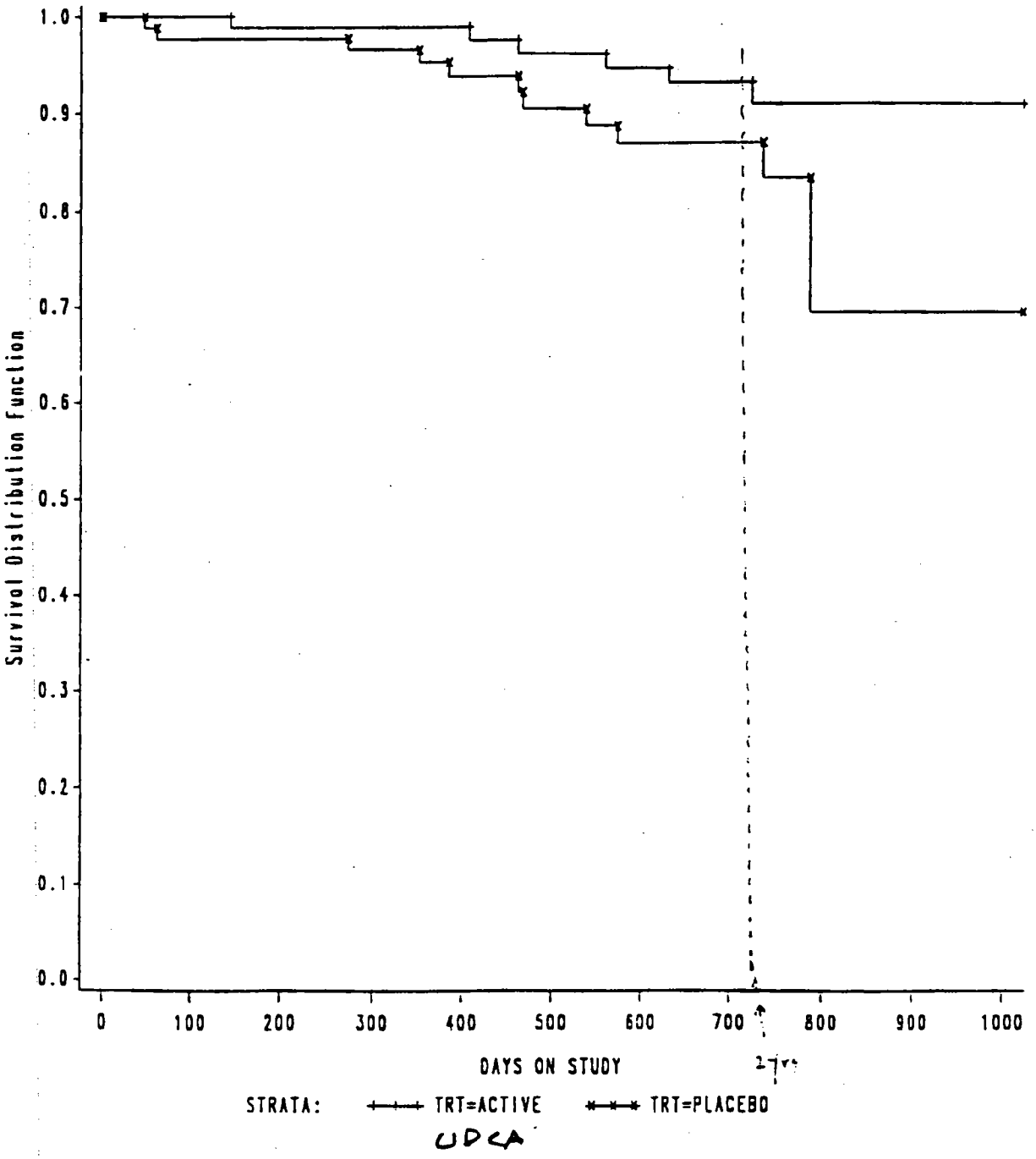


FIGURE ~~A~~ ~~B~~ C (MAYO study)

TIME TO DEATH/TRANSPLANT
DOUBLE – BLIND PORTION (TWO – YEAR CUTOFF)

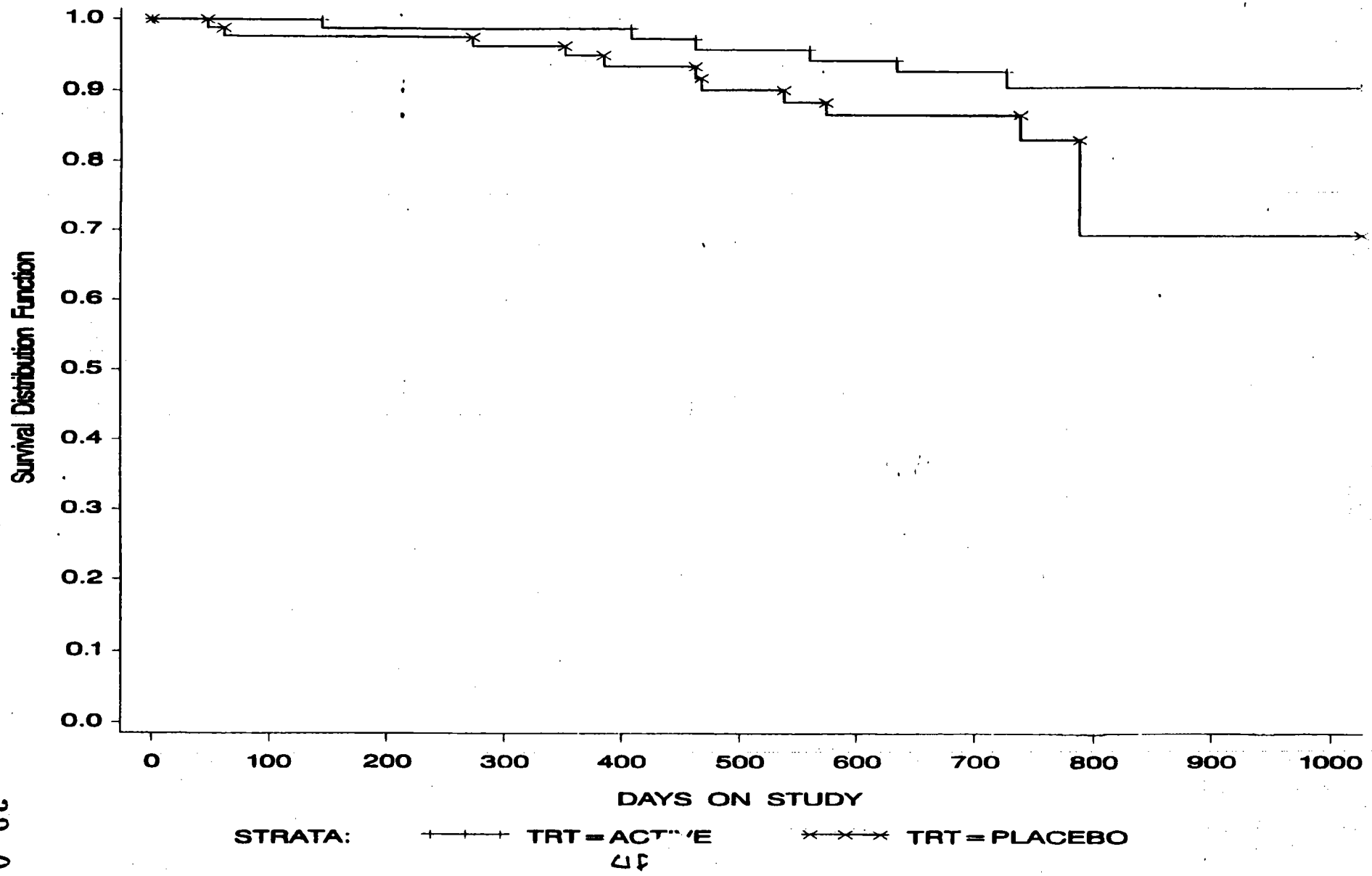


FIGURE 2B D (MAYO STUDY)
TIME TO DEATH/TRANSPLANT
EXTENDED FOLLOW-UP

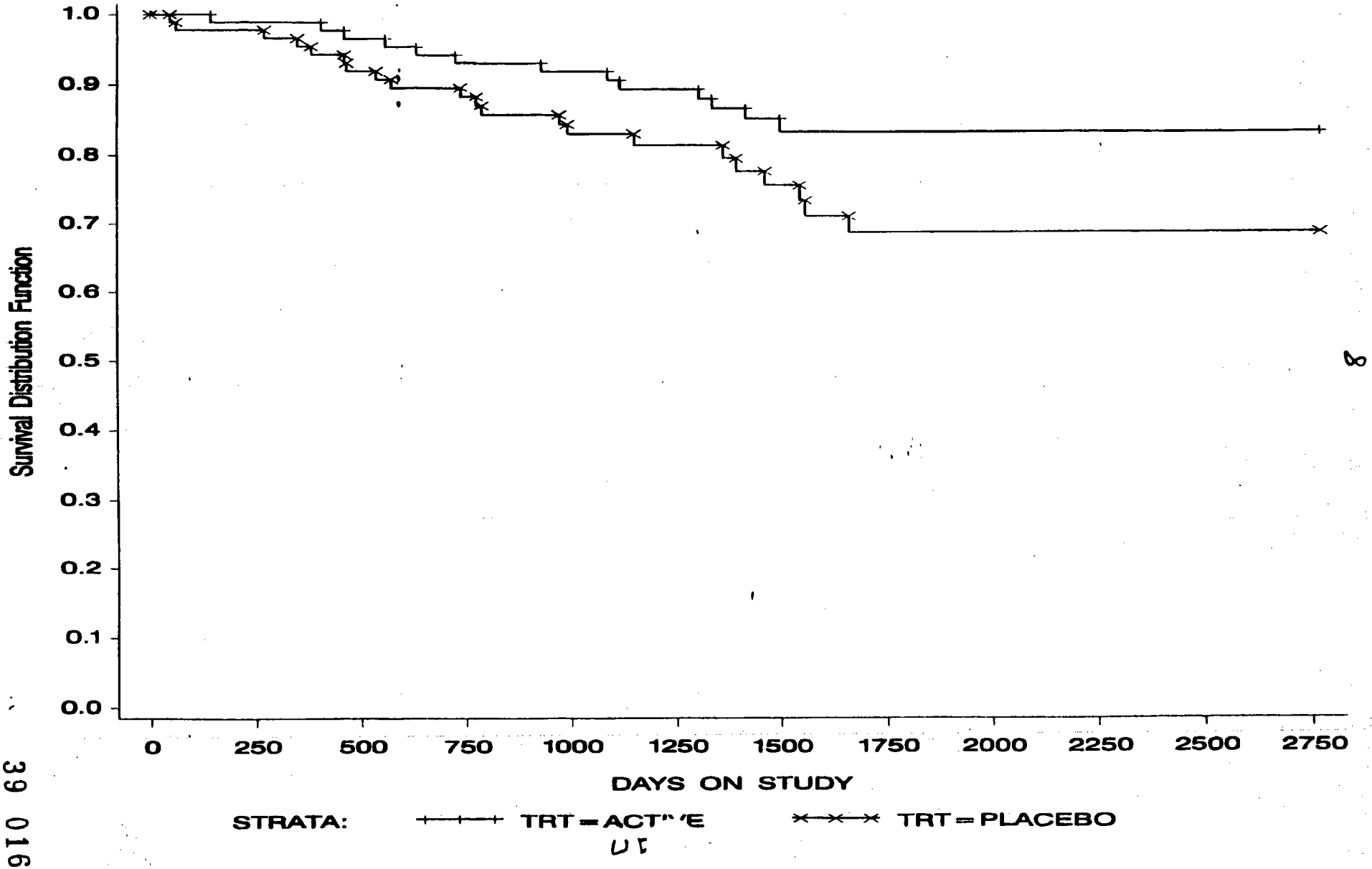


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FIGURE E (MAYO Study)
TIME TO TREATMENT FAILURE (REVISED DEFINITION)
DOUBLE-BLIND PORTION (TWO-YEAR CUTOFF)

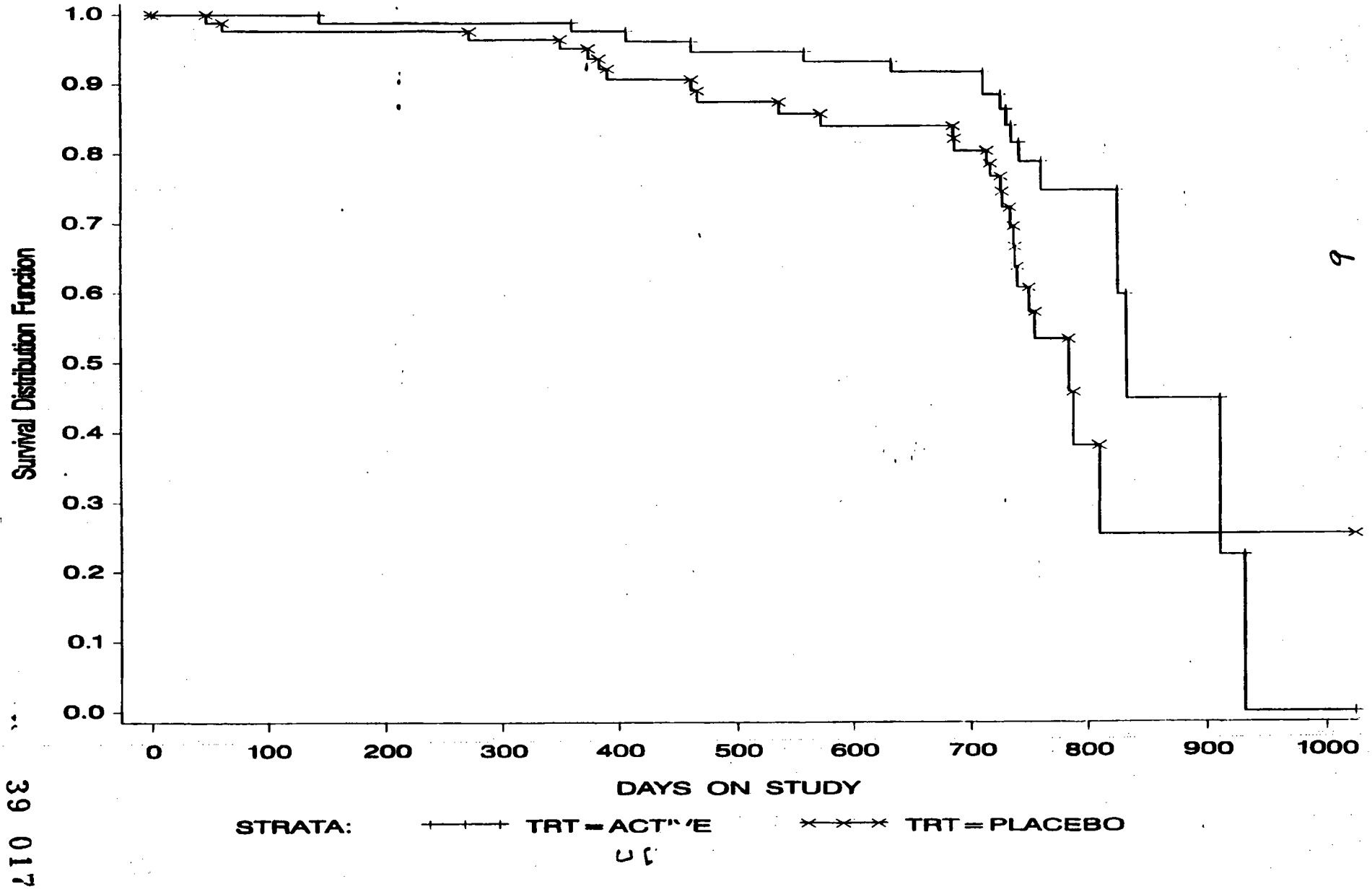

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FIGURE 2B F (Mayo study)

TIME TO TREATMENT FAILURE (REVISED DEFINITION)
EXTENDED FOLLOW – UP

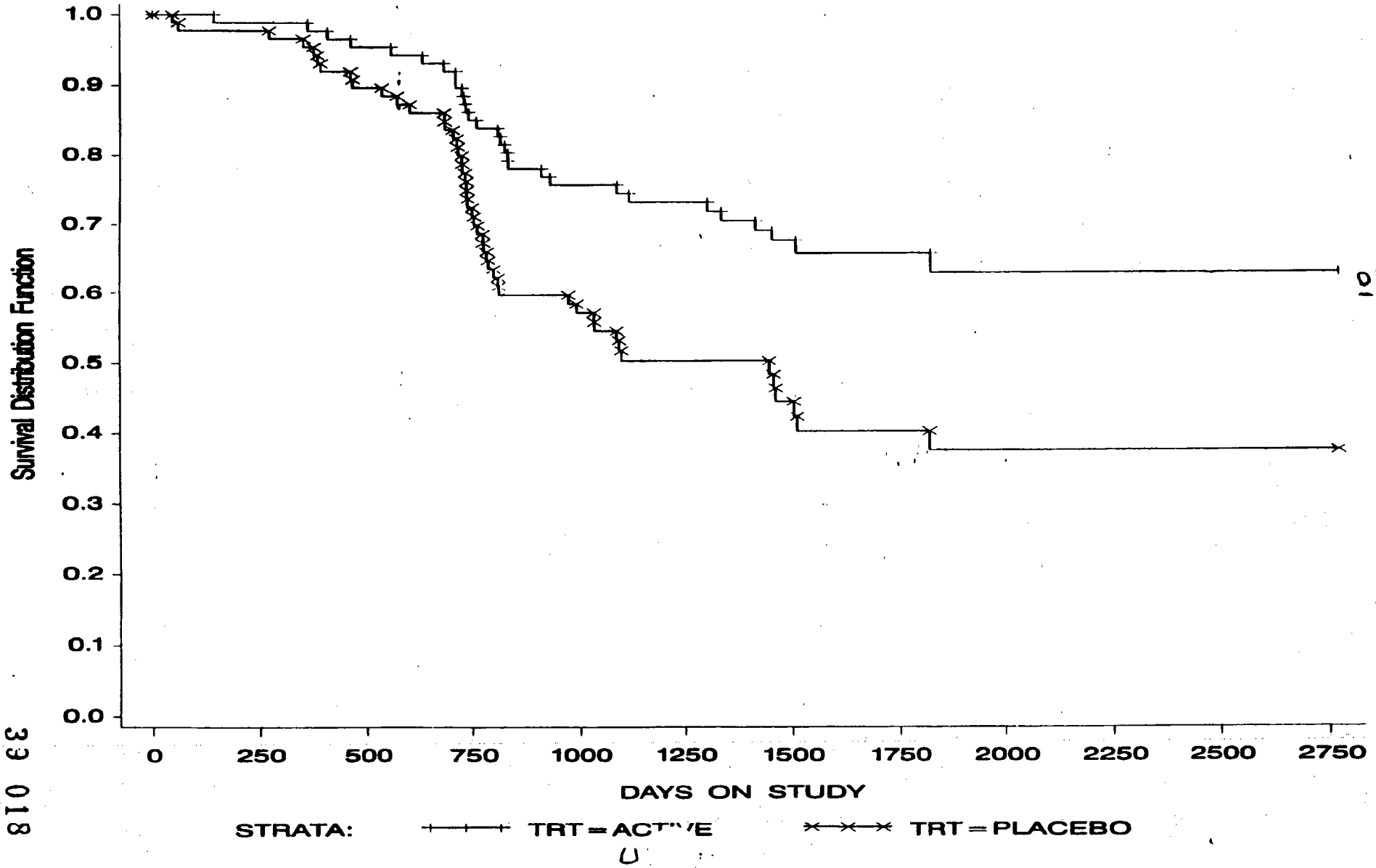

FIGURE 6 (Mayo study)

TIME TO VARICES
AMONG PATIENTS WITHOUT VARICES AT BASELINE
DOUBLE-BLIND PORTION (TWO-YEAR CUTOFF)
BASEVAR = NO VARICES

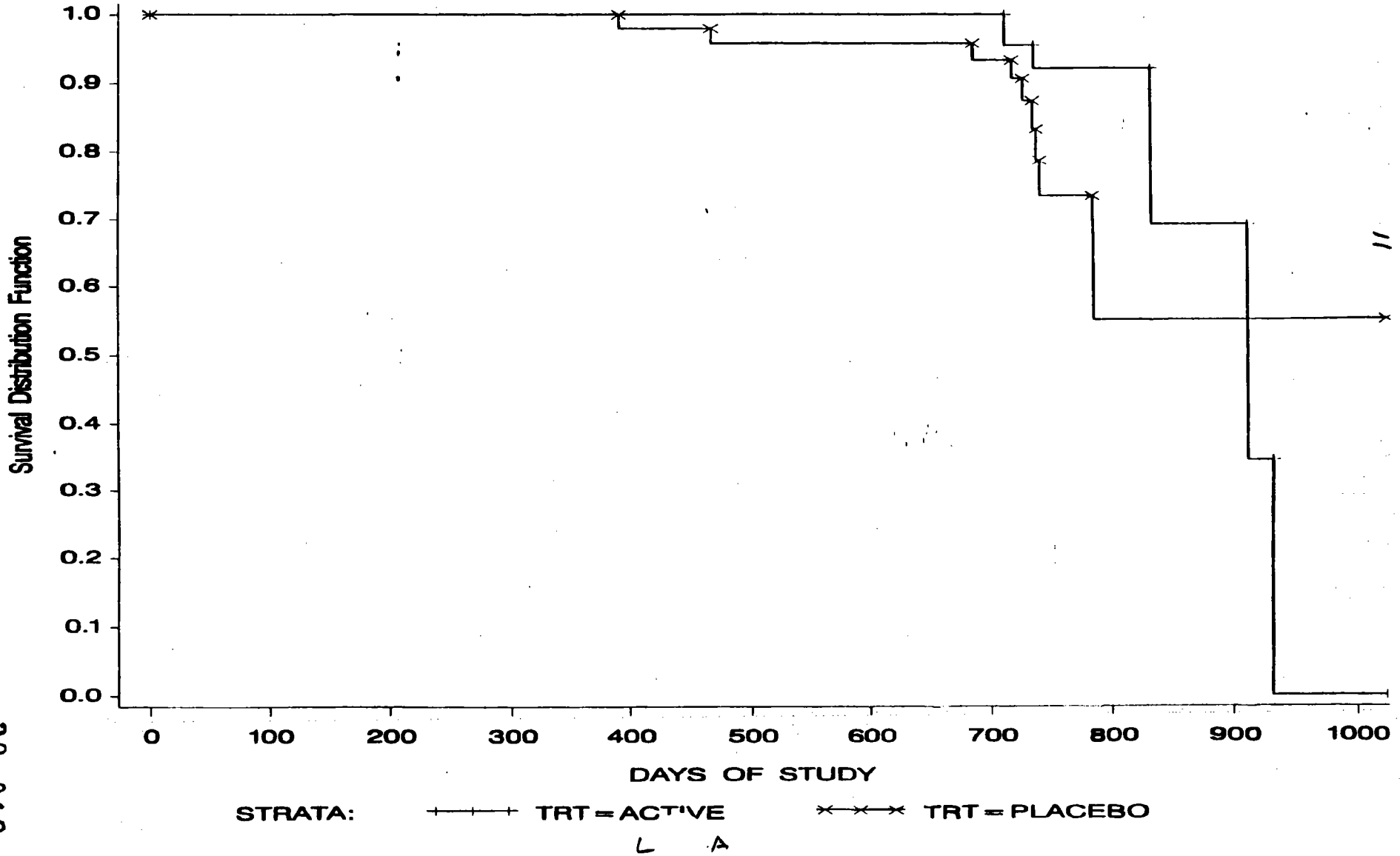

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FIGURE 4B H (Mayo study)

TIME TO VARICES
AMONG PATIENTS WITHOUT VARICES AT BASELINE
EXTENDED FOLLOW-UP
BASEVAR = NO VARICES

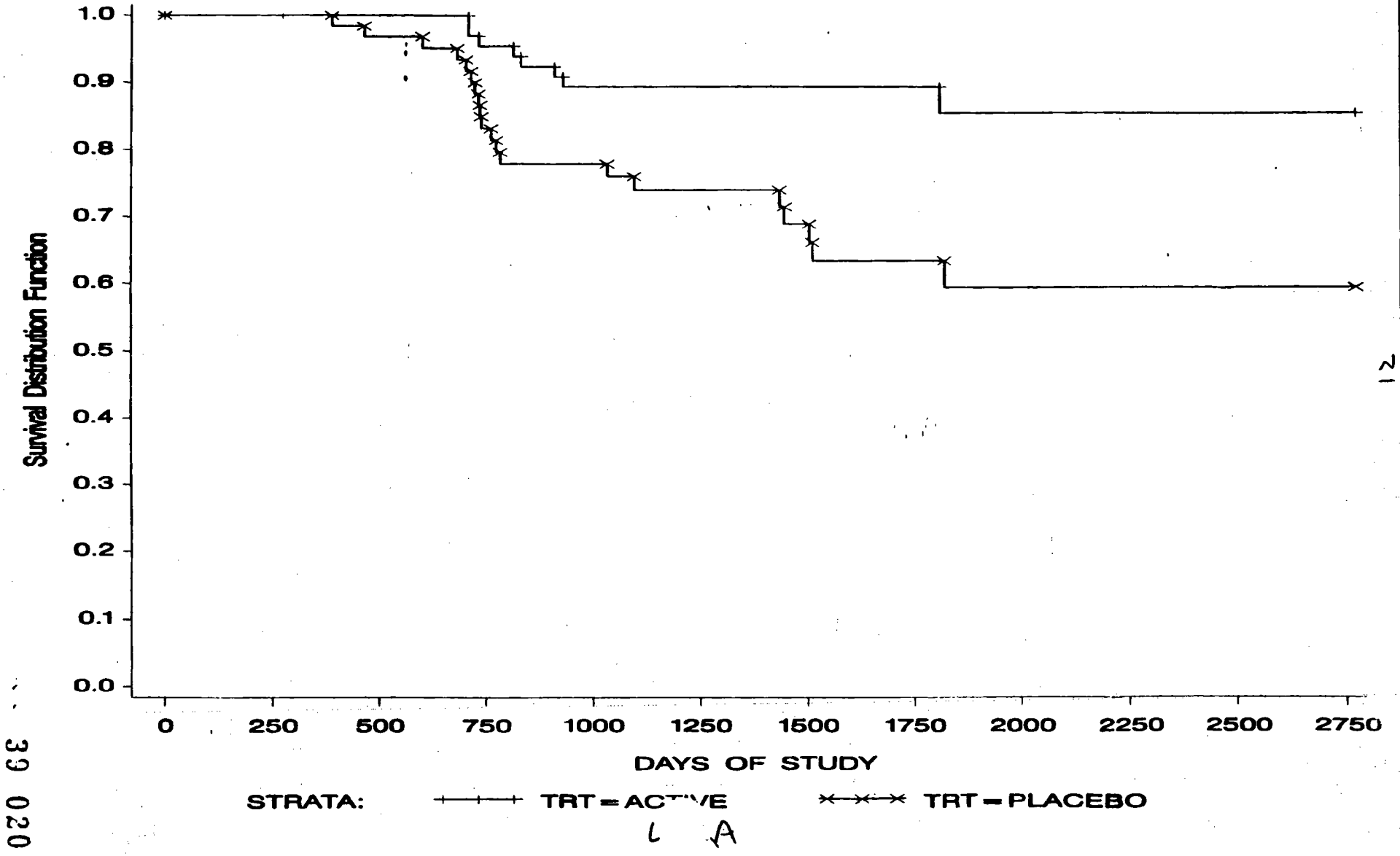

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Figure 1 **Median Serum Bilirubin Values Over Time by Treatment Group** (Heathcote study)

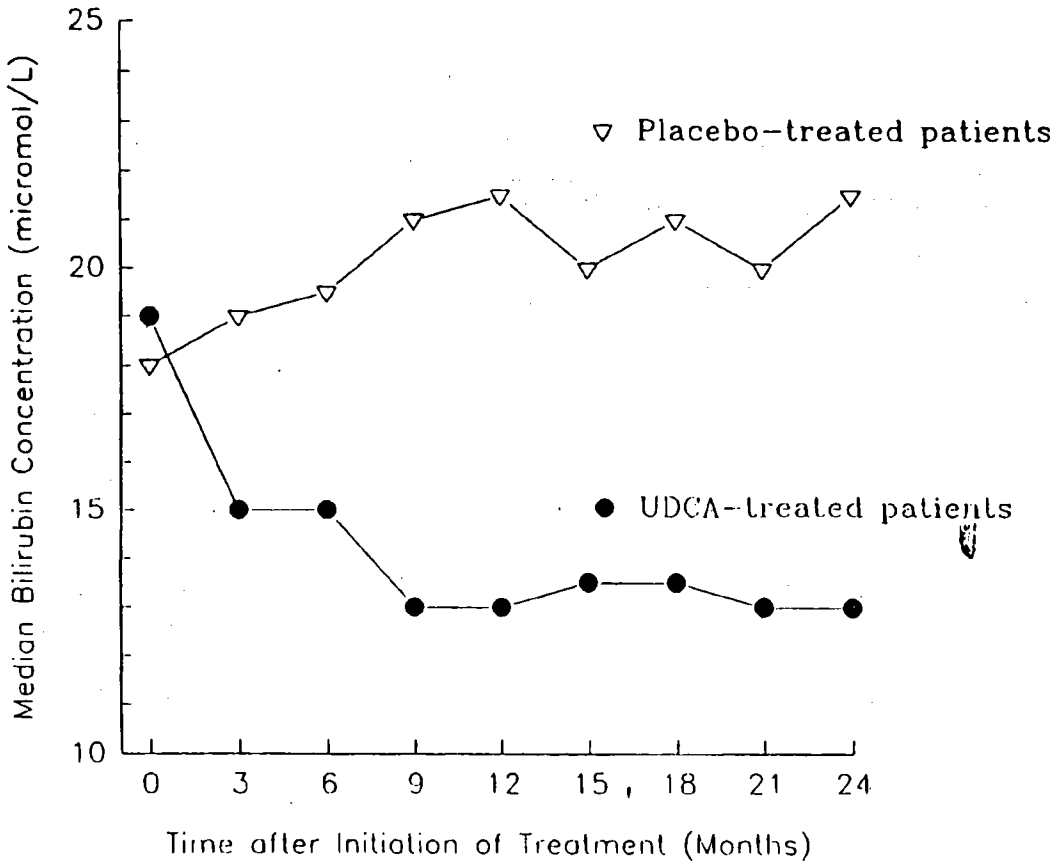

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Figure 7: Death and/or Transplant as Trial Endpoints Over Time by Treatment Group

(Heathcote Study)