

Pharmacokinetics

Pharmacokinetics of ACTOS™

- Two major metabolites (M-III, M-IV) are pharmacologically active, peak concentrations 12-16 hours after dosing, half lives 26-30 hours
- No interactions with glipizide, metformin, digoxin or warfarin
- No appreciable effect of age
- Females have slightly higher serum levels

Pharmacokinetics of ACTOS™

- Extent of exposure to pioglitazone and active metabolites (AUC values) were similar for normal subject and subject moderate hepatic impairment
- Similar kinetics for normal subjects and subjects with renal impairment

Takeda America Research and Development Center, Inc.

Clinical Safety Assessment

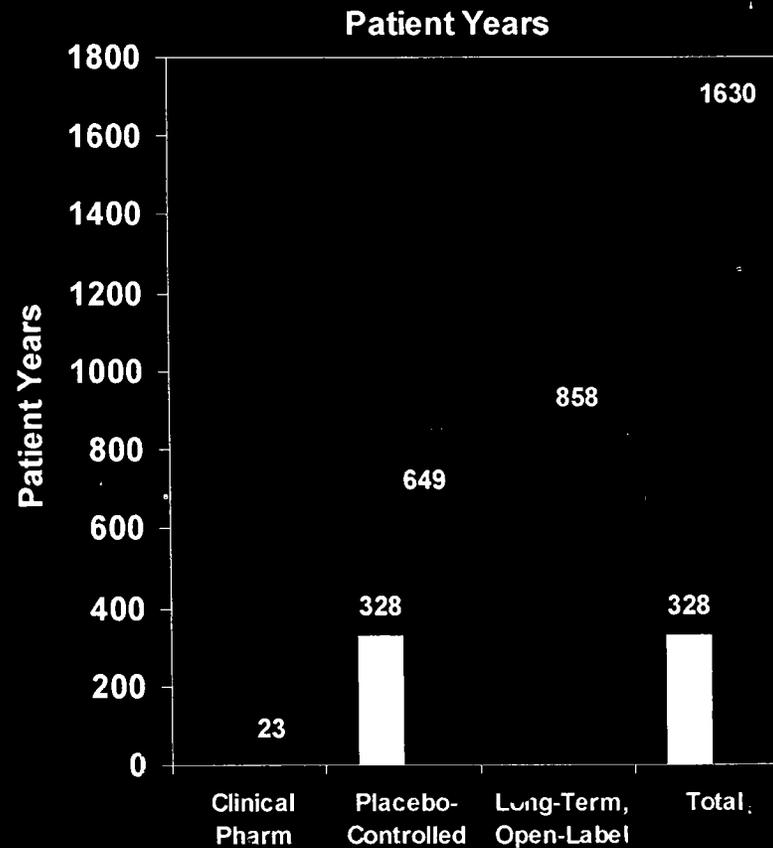
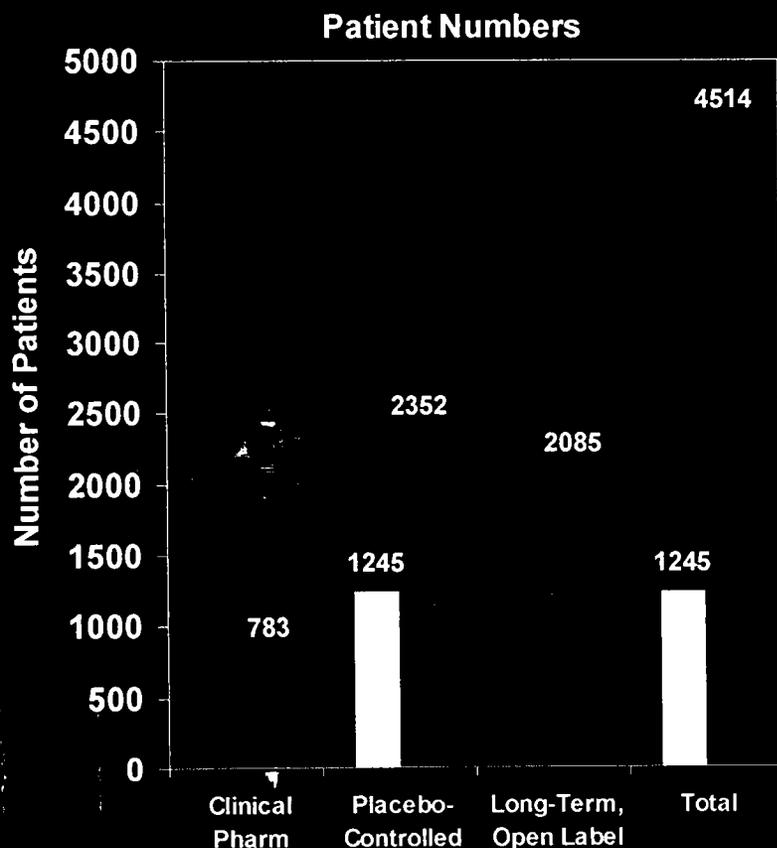
Endocrinologic and Metabolic Drugs Advisory Committee
NDA No. 21-073 ACTOS™ (pioglitazone hydrochloride)

Clinical Safety Assessment

- Exposure information
- U.S. study designs
- U.S. patient demographics
- U.S. patient accountability
- U.S. summary of AEs
- U.S. most frequently reported AEs
- Liver safety
- Other safety considerations

Patient Exposure*

U.S., European, and Japanese Clinical Studies

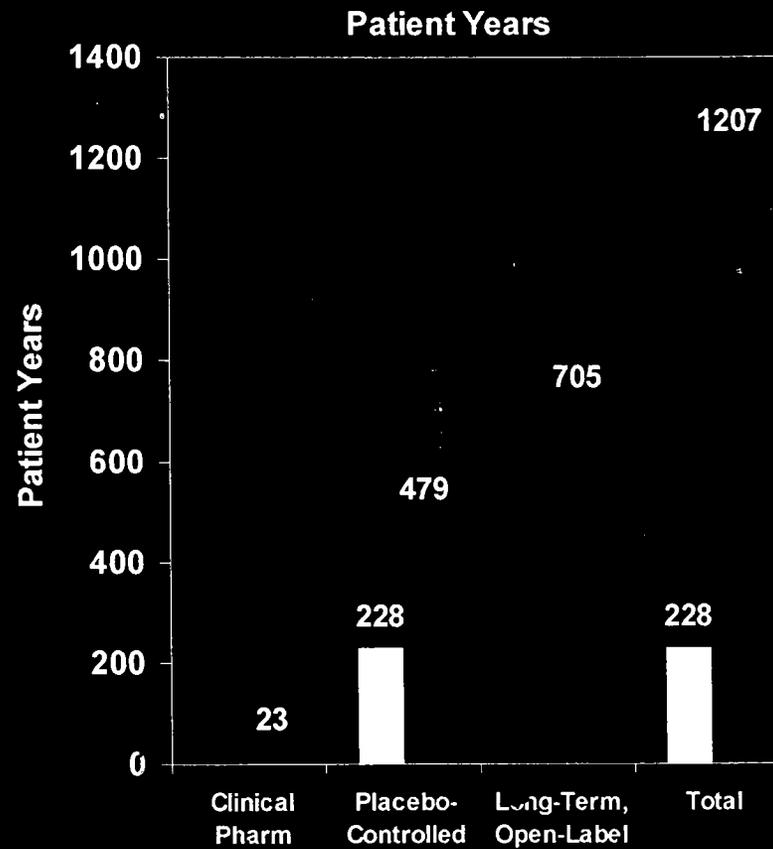
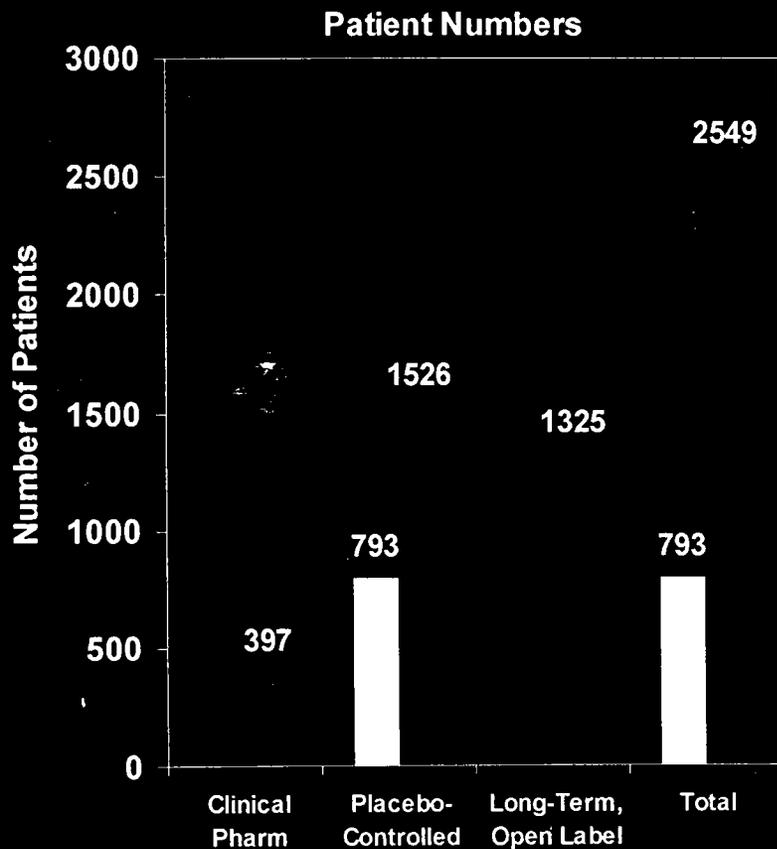


■ Placebo

■ ACTOS™

* Included in NDA

Patient Exposure* U.S. Clinical Studies



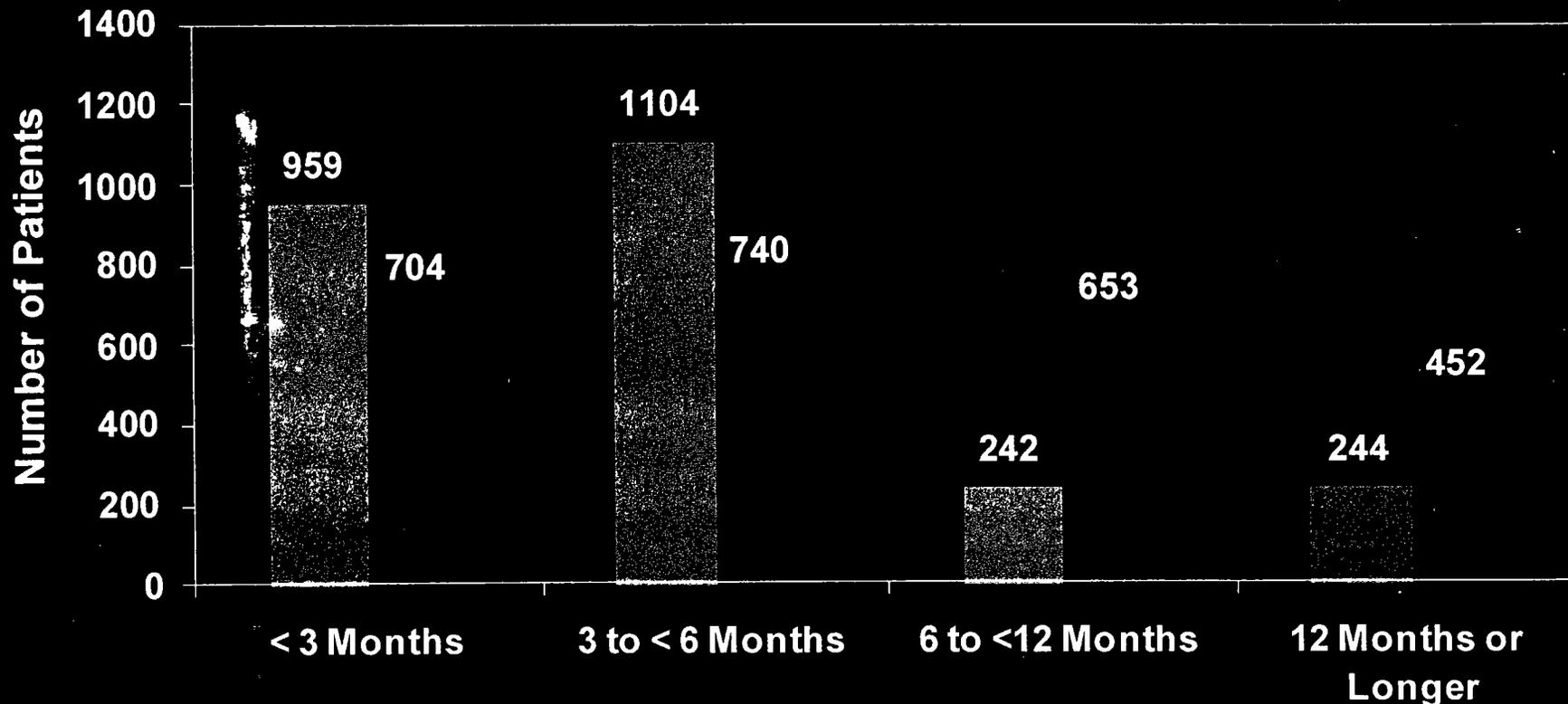
■ Placebo

■ ACTOS™

* Included in NDA

Patient Exposure

U.S. Clinical Studies



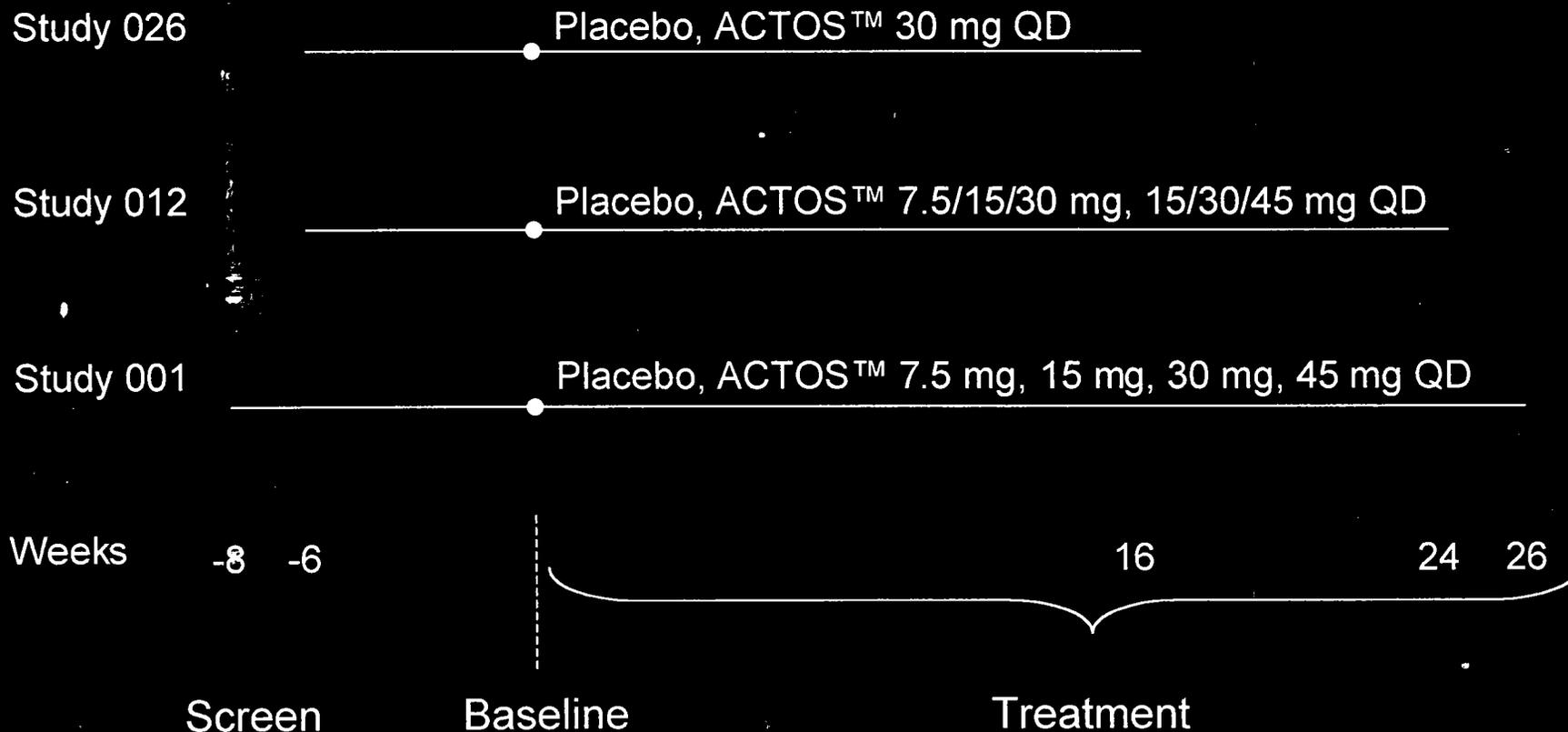
■ In NDA (Patient Years = 1207)

In NDA and 120-Day Safety Update Combined (Patient Years = 1447)

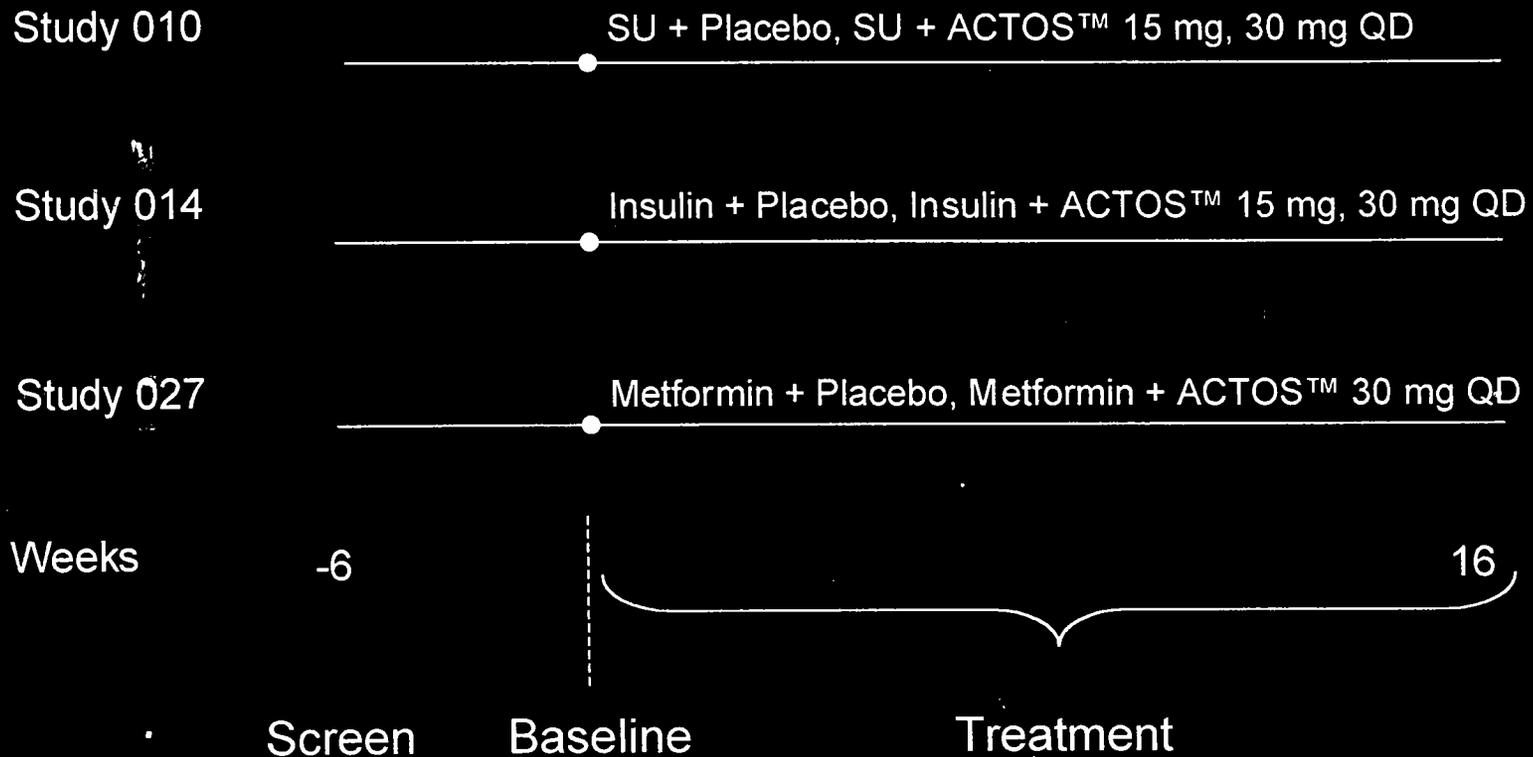
ACTOS™ Was Studied in 6 Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Studies in the U.S.

- In 3 monotherapy studies
- In 3 combination therapy studies [one each with sulfonylurea (SU), metformin, or insulin]
 - No required change in regimen of companion medication
- ACTOS™ given once daily (for all doses)
 - 7.5 mg to 45 mg as monotherapy
 - 15 mg and 30 mg in combination with SU and insulin
 - 30 mg in combination with metformin
- Duration: 16 to 26 weeks

Monotherapy Study Design



Combination Therapy Study Design



Long-Term, Open-Label Study Design

Study 011

Rollover Monotherapy

ACTOS™ 7.5 mg, 15 mg, 30 mg, 45 mg, or 60 mg QD

New Monotherapy

ACTOS™ 7.5 mg, 15 mg, 30 mg, 45 mg, or 60 mg QD

Study 031

Rollover Monotherapy

ACTOS™ 15mg, 30 mg, or 45 mg QD

Rollover Combination

ACTOS™ 15 mg, 30 mg or 45 mg QD with SU, Metformin, or Insulin

Weeks

-8

open-ended, ongoing

Screen

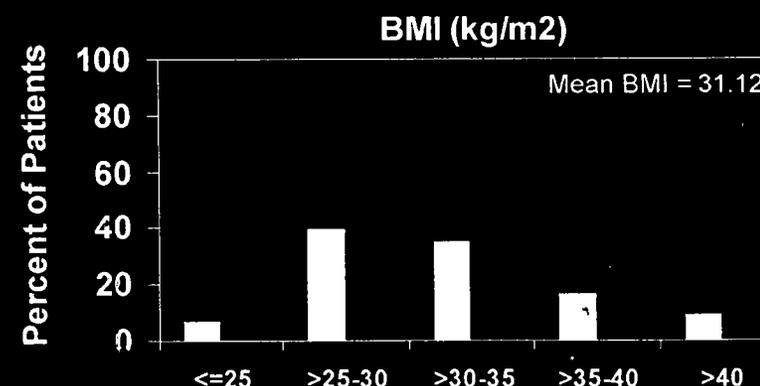
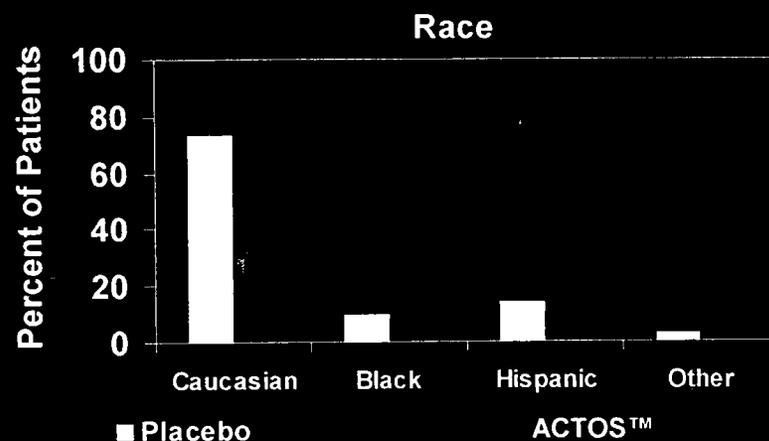
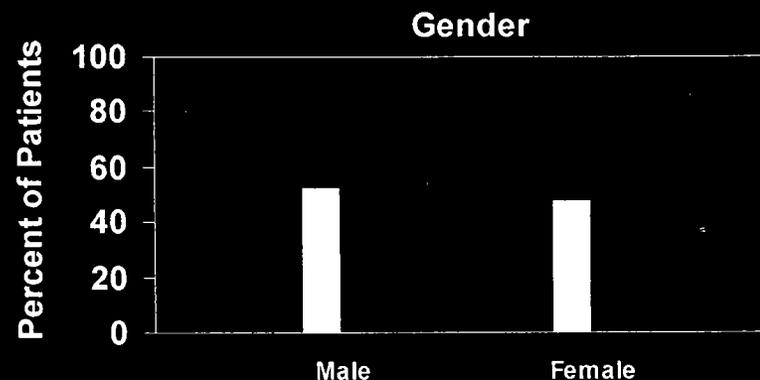
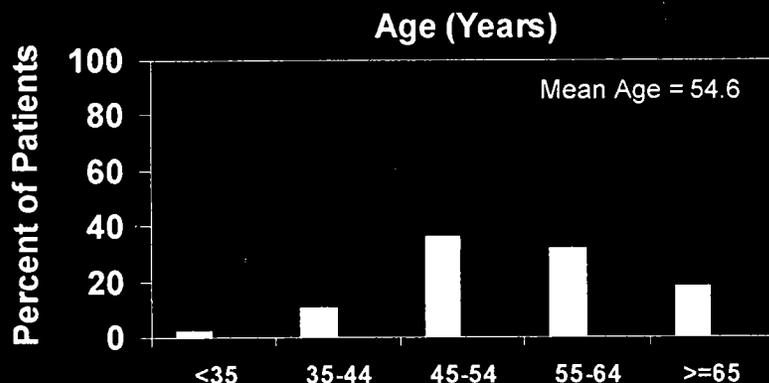
Baseline

Treatment

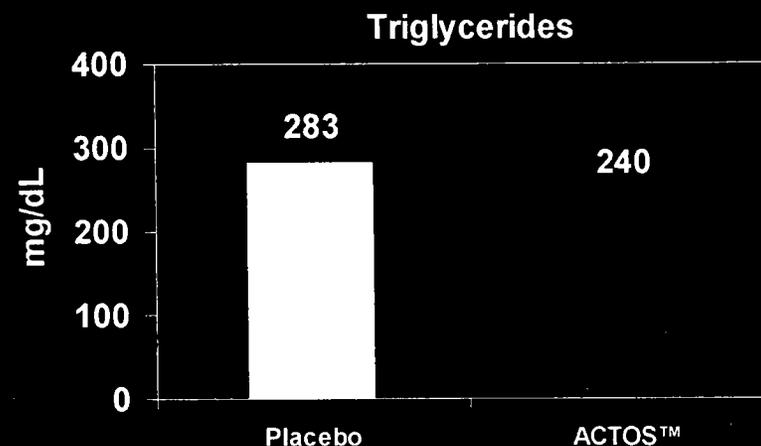
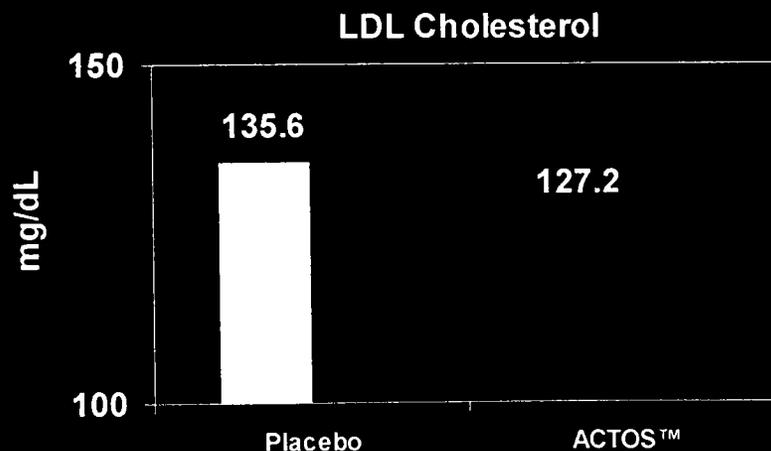
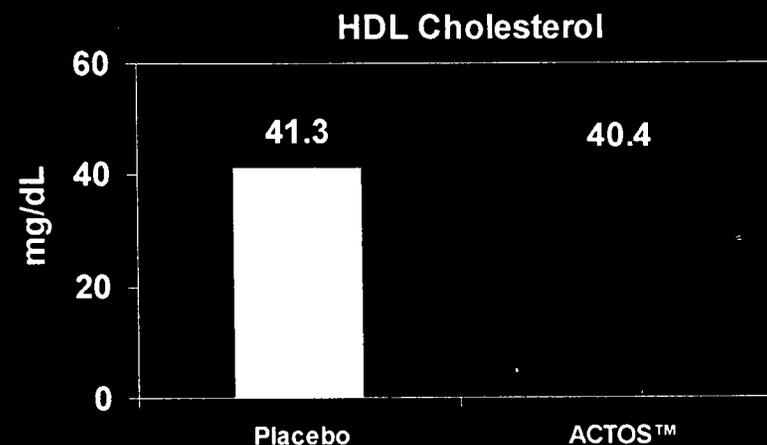
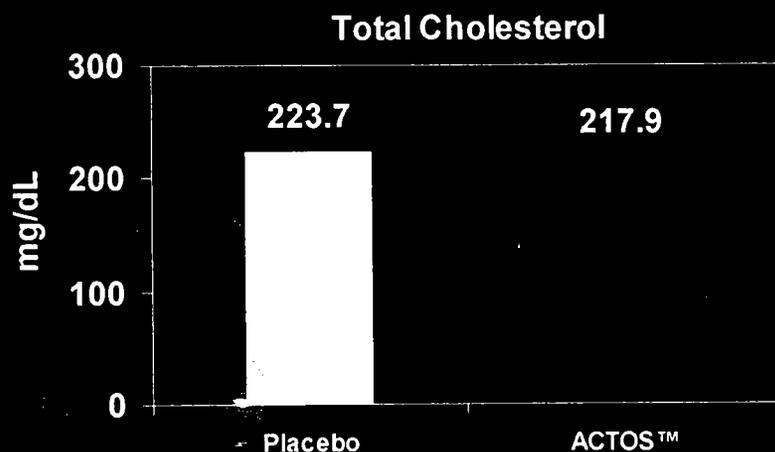
U.S. Clinical Studies Were Designed to Include a Spectrum of Patients with Type 2 Diabetes in a Wide Range of Clinical Situations

- Selected inclusion criteria at screening
 - Diagnosis of type 2 diabetes mellitus using the criteria of the National Diabetes Data Group
- Selected inclusion criteria at baseline
 - Age: 30 to 75 years
 - Body mass index (BMI): 25 to 45 kg/m²
 - HbA_{1c}: ≥ 8.0% (≥ 7.0% in one monotherapy study)
 - C-peptide: > 1.0 ng/mL (> 0.7 ng/mL in insulin combination study)

U.S. Placebo-Controlled Monotherapy Studies Demographic and Baseline Characteristics

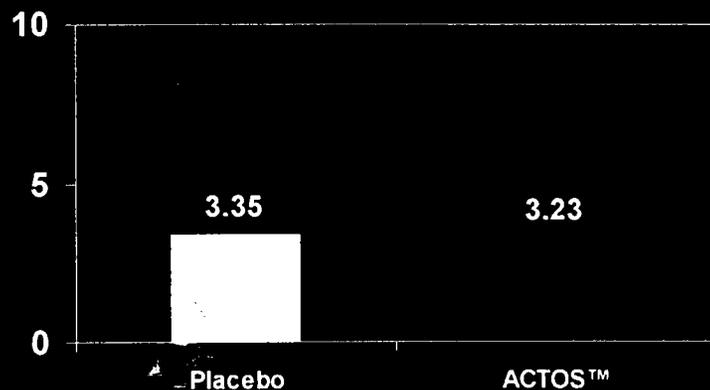


U.S. Placebo-Controlled Monotherapy Studies Demographic and Baseline Characteristics

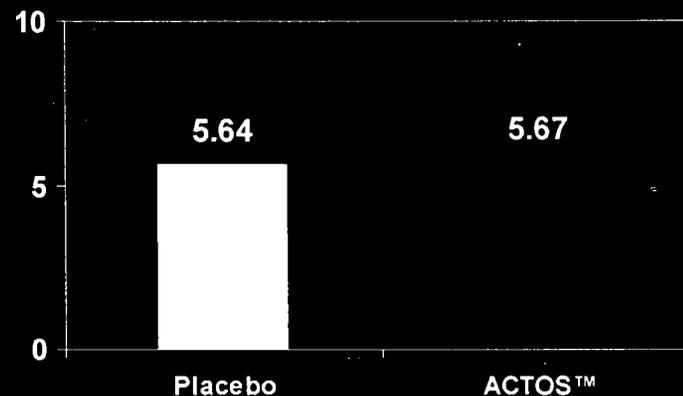


U.S. Placebo-Controlled Monotherapy Studies Demographic and Baseline Characteristics

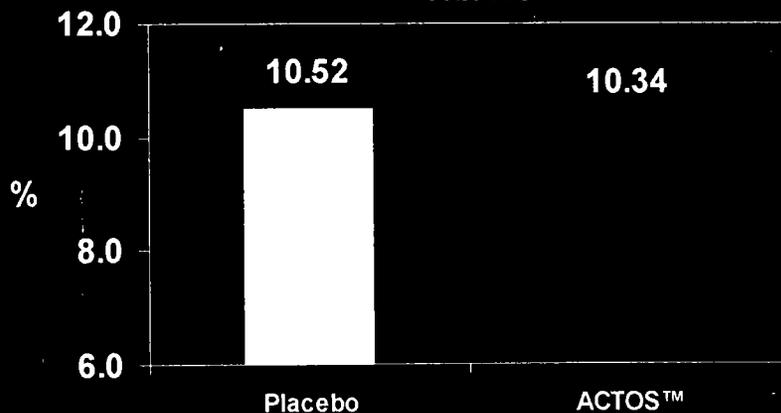
Ratio of LDL/HDL



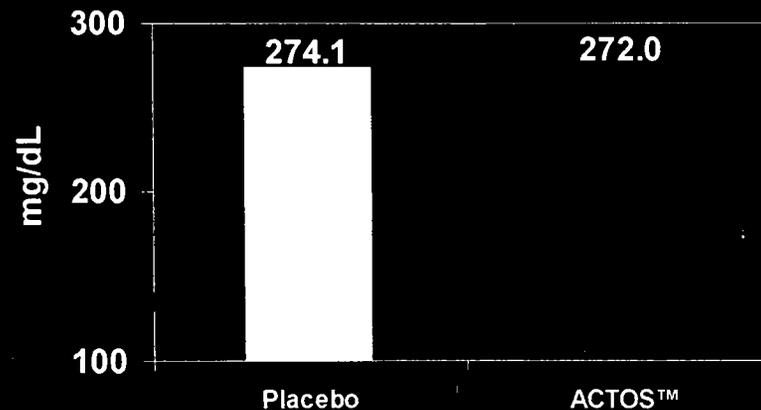
Ratio of Total Cholesterol/HDL



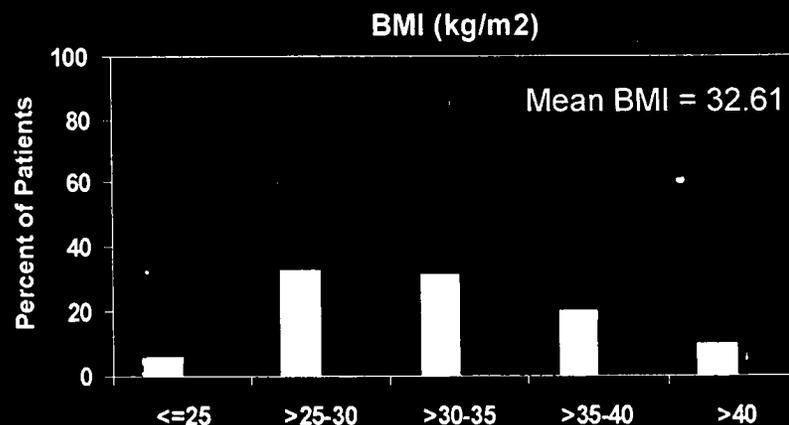
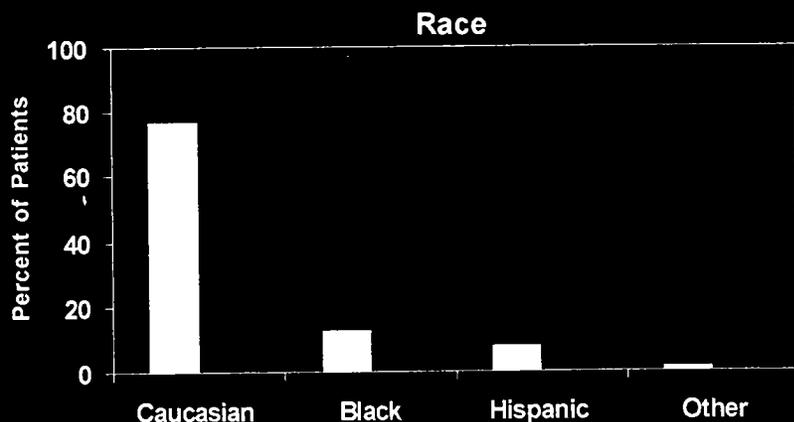
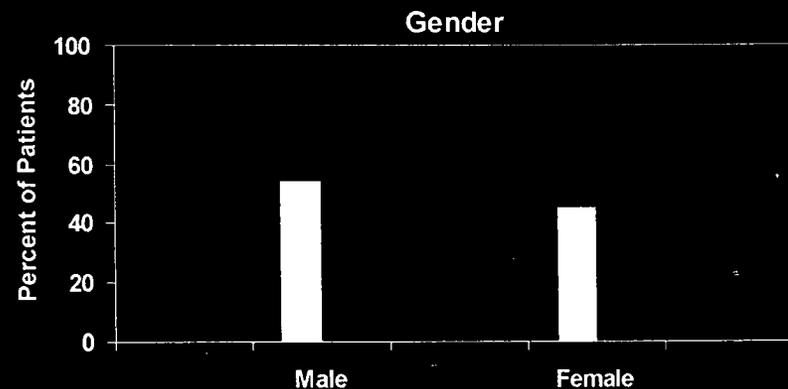
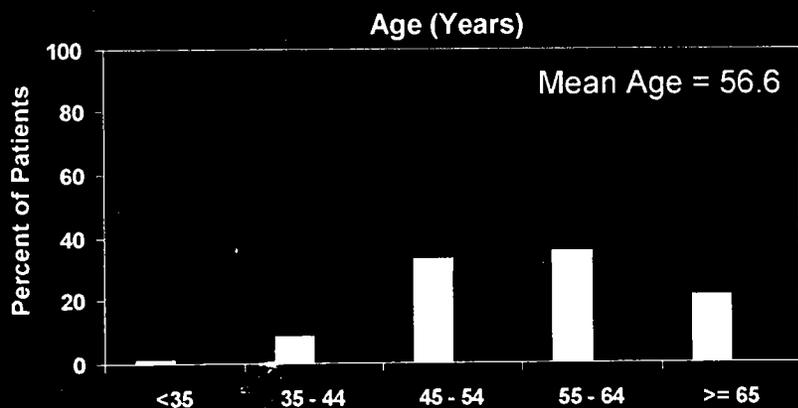
HbA1c



FBG



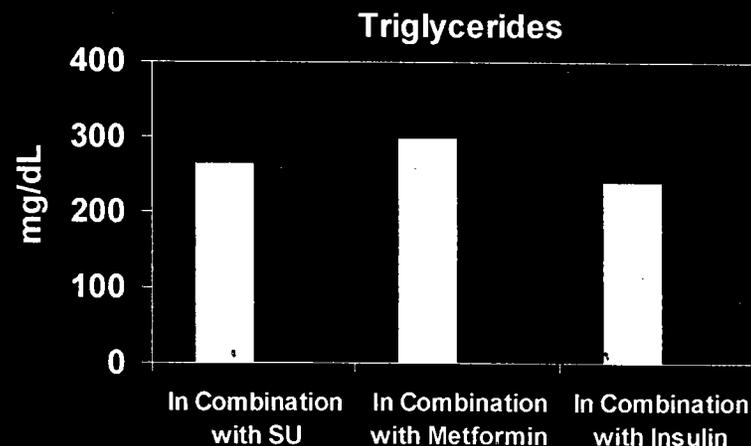
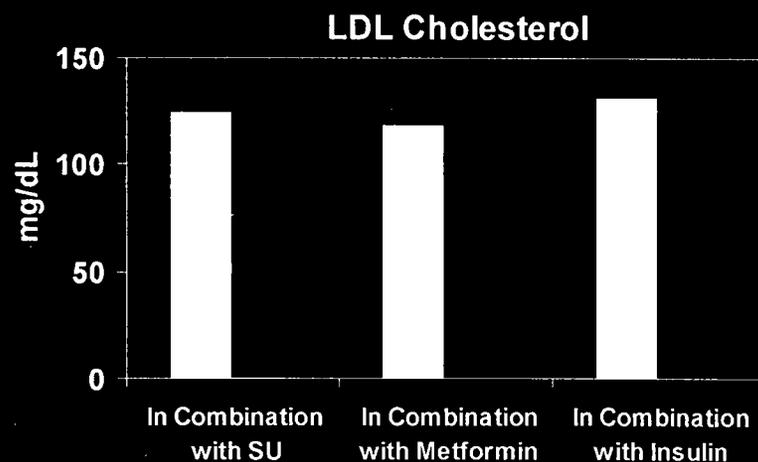
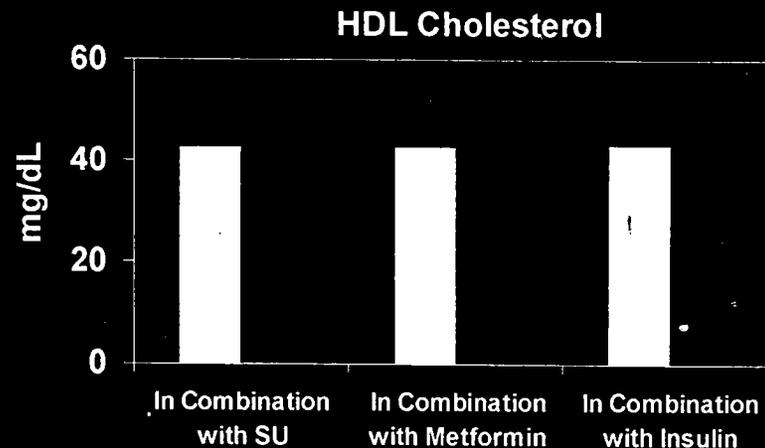
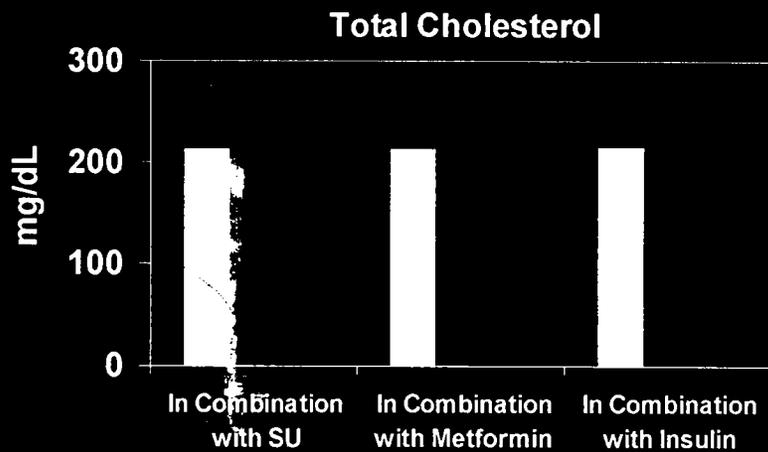
U.S. Placebo-Controlled Combination Therapy Studies Demographic and Baseline Characteristics



Companion + Placebo

Companion + ACTOS™

U.S. Placebo-Controlled Combination Therapy Studies Demographic and Baseline Characteristics

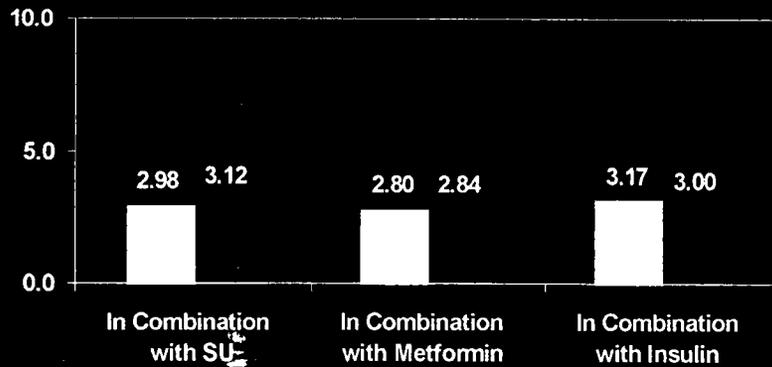


Companion + Placebo

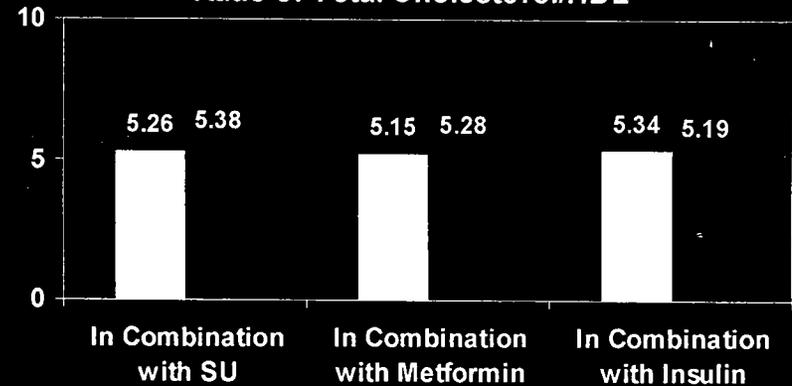
Companion + ACTOS™ 15 mg

U.S. Placebo-Controlled Combination Therapy Studies Demographic and Baseline Characteristics

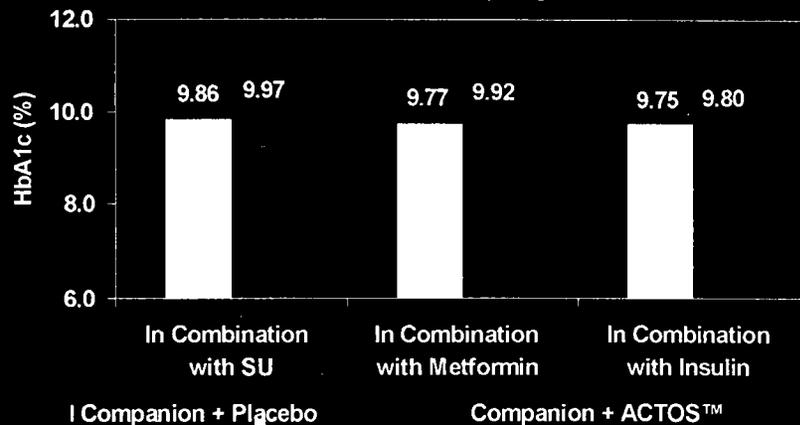
Ratio of LDL/HDL



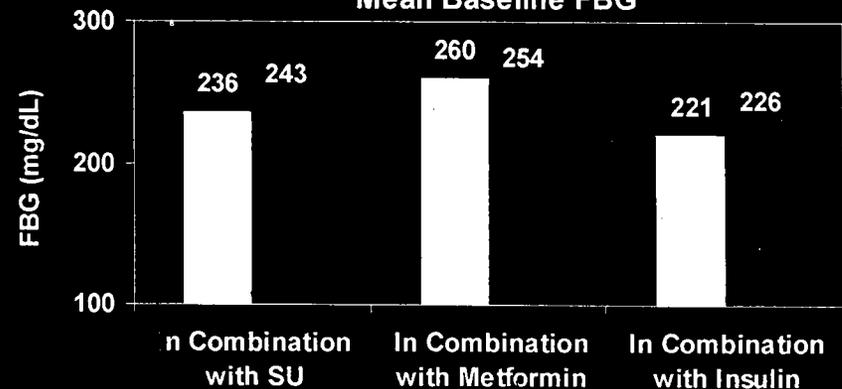
Ratio of Total Cholesterol/HDL



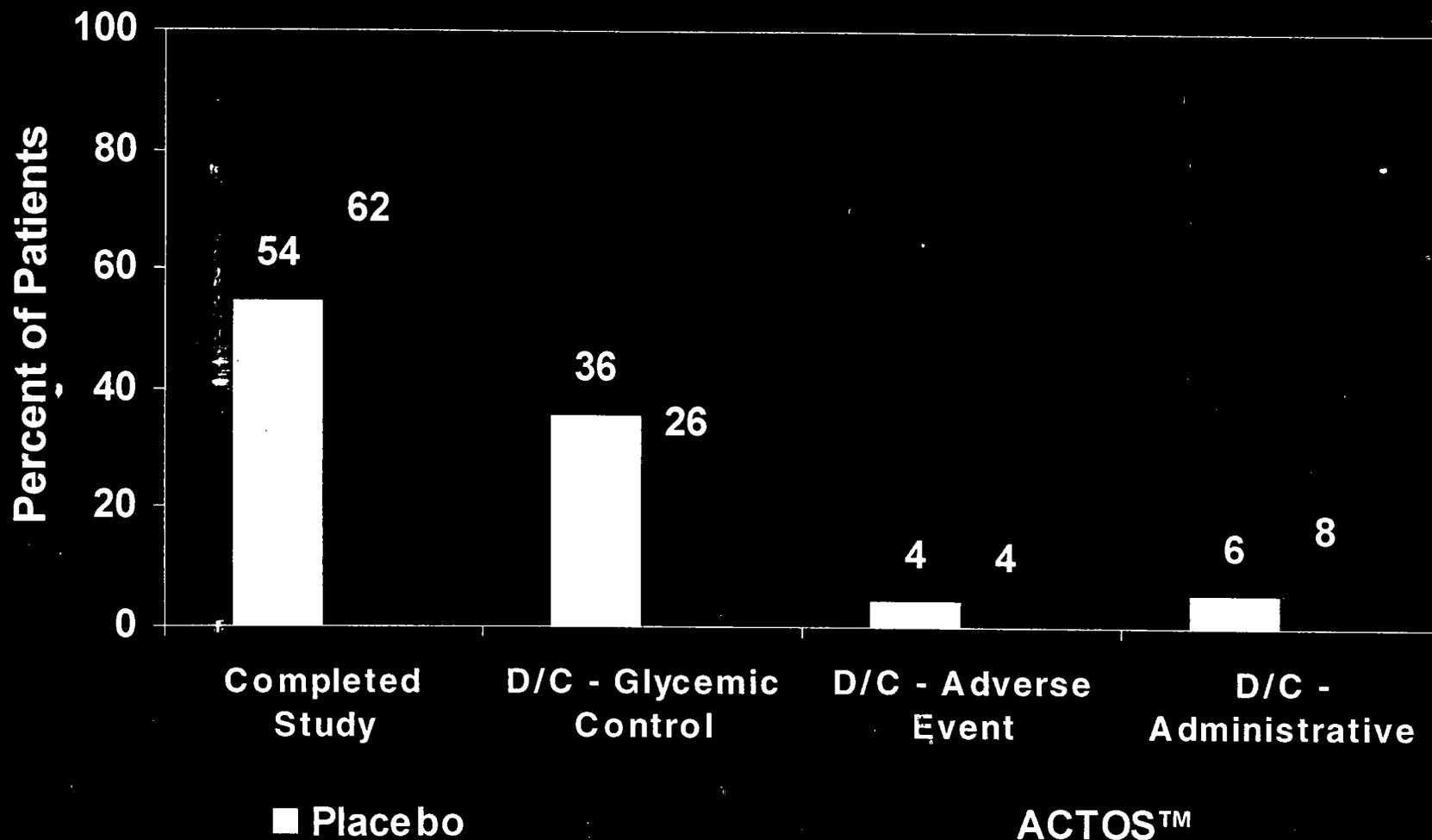
Mean Baseline HbA1c



Mean Baseline FBG

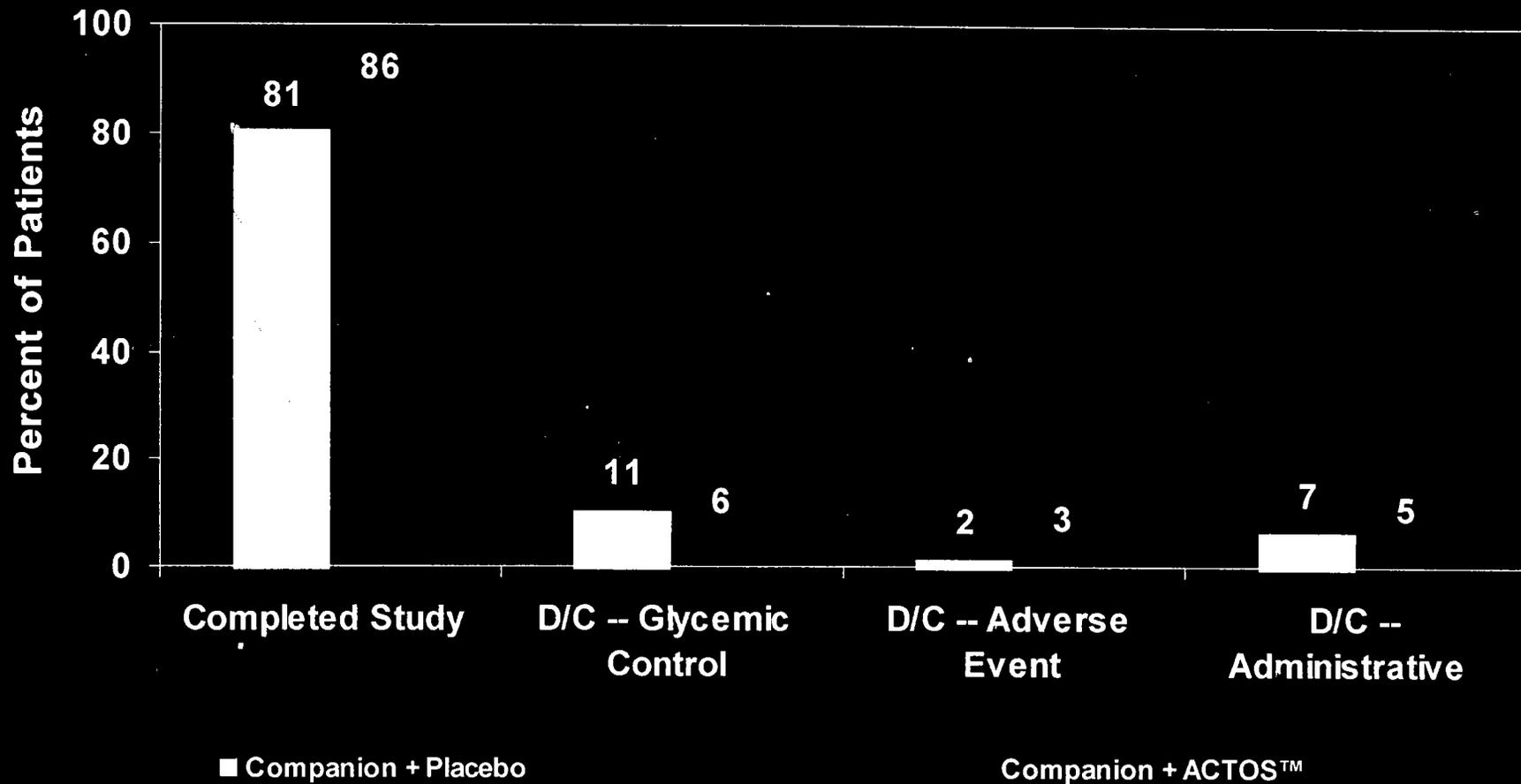


U.S. Placebo-Controlled Monotherapy Studies Patient Accountability

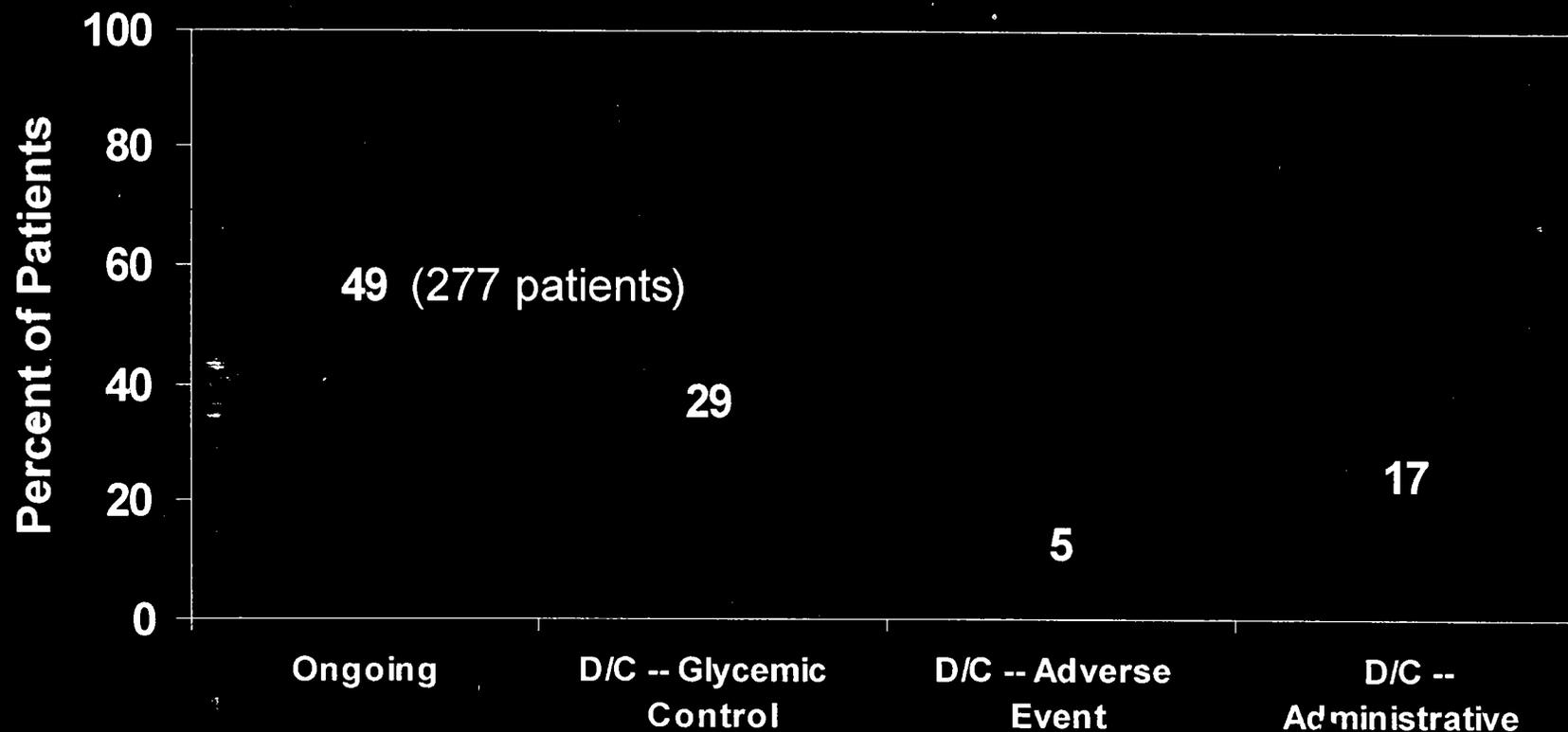


U.S. Placebo-Controlled Combination Therapy Studies

Patient Accountability



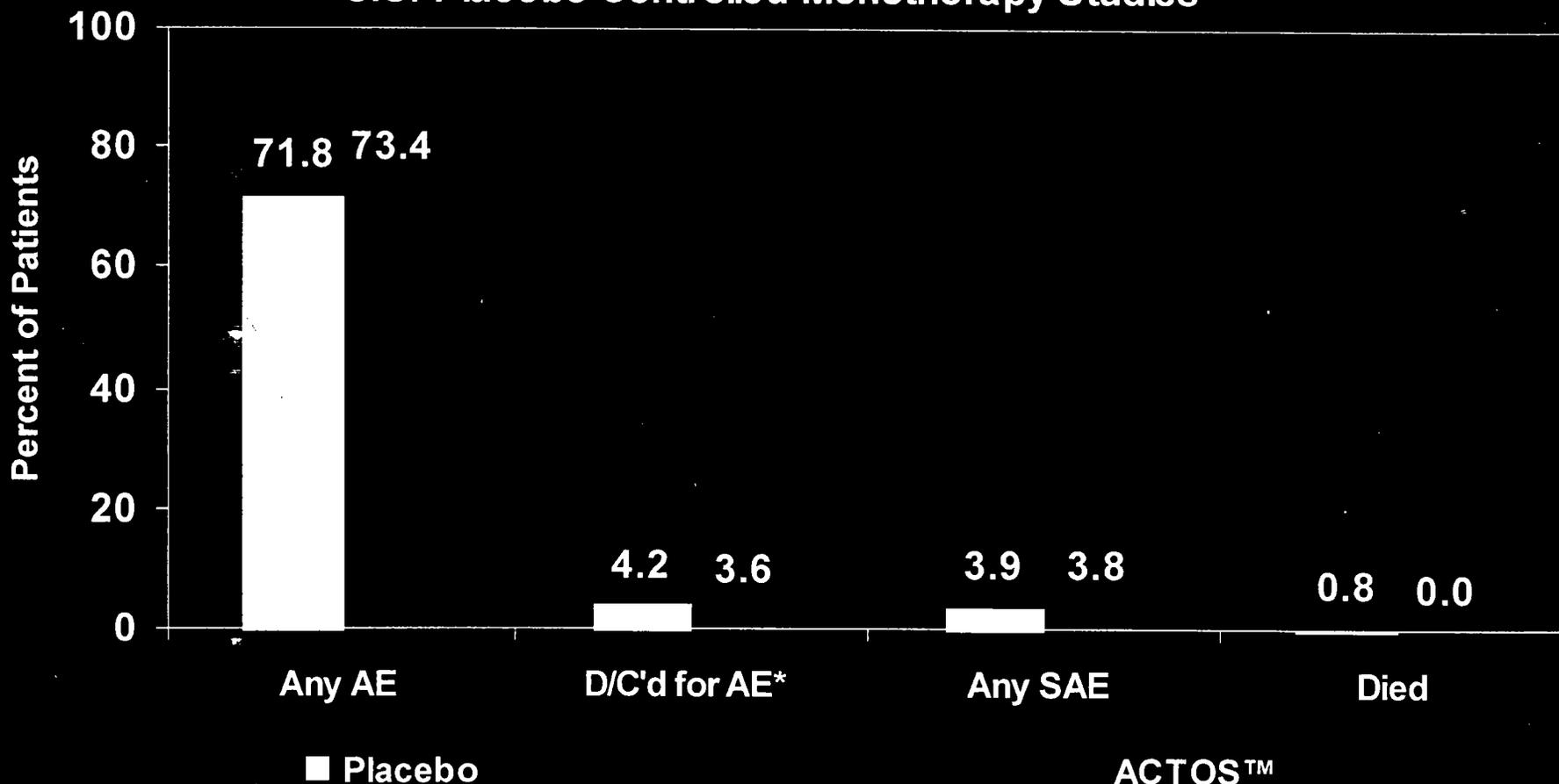
U.S. Long-Term, Open-Label Monotherapy Study Patient Accountability



ACTOS™

Summary of Adverse Events (AEs)

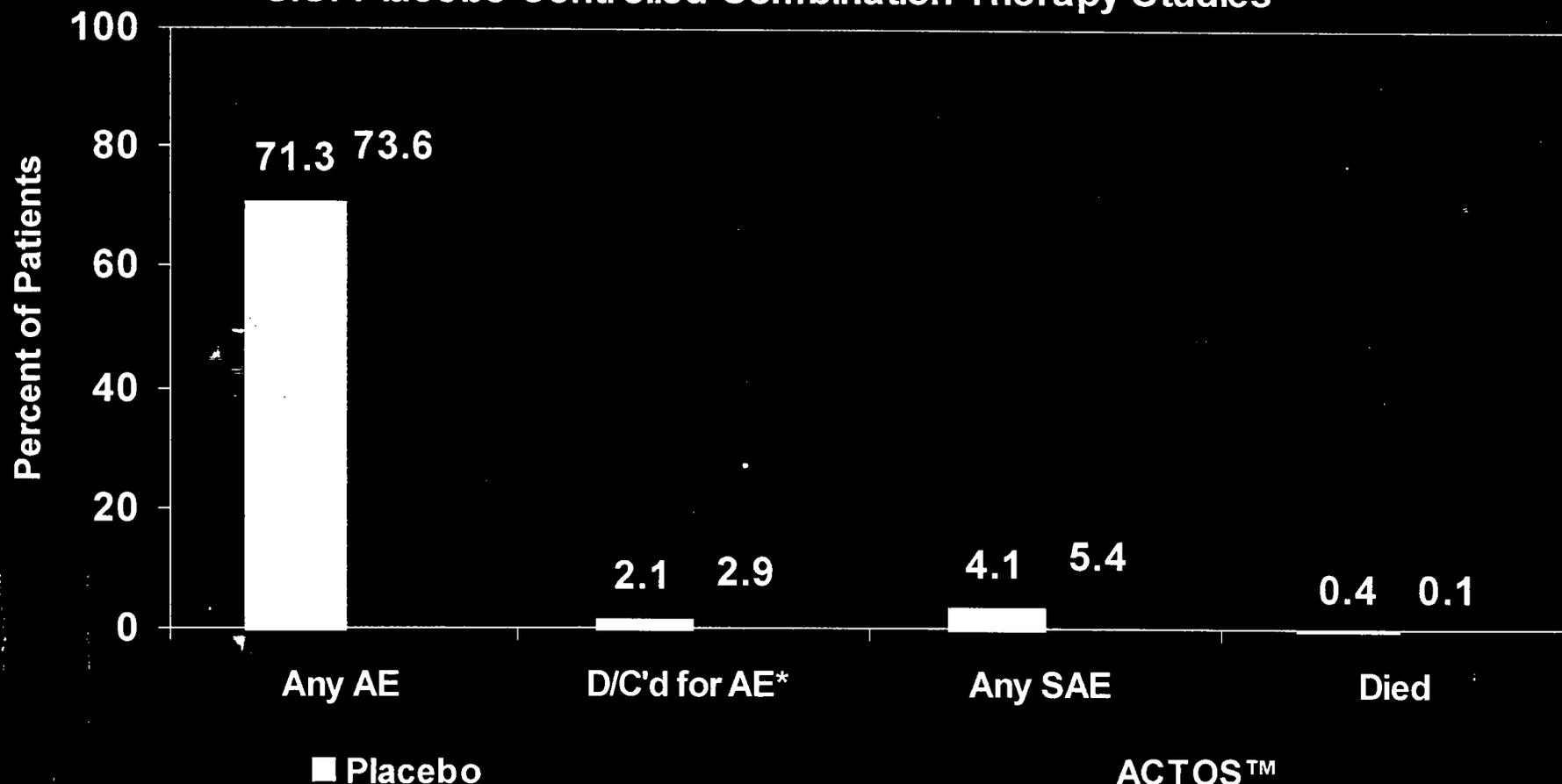
U.S. Placebo-Controlled Monotherapy Studies



* Not glucose related

Summary of Adverse Events (AEs)

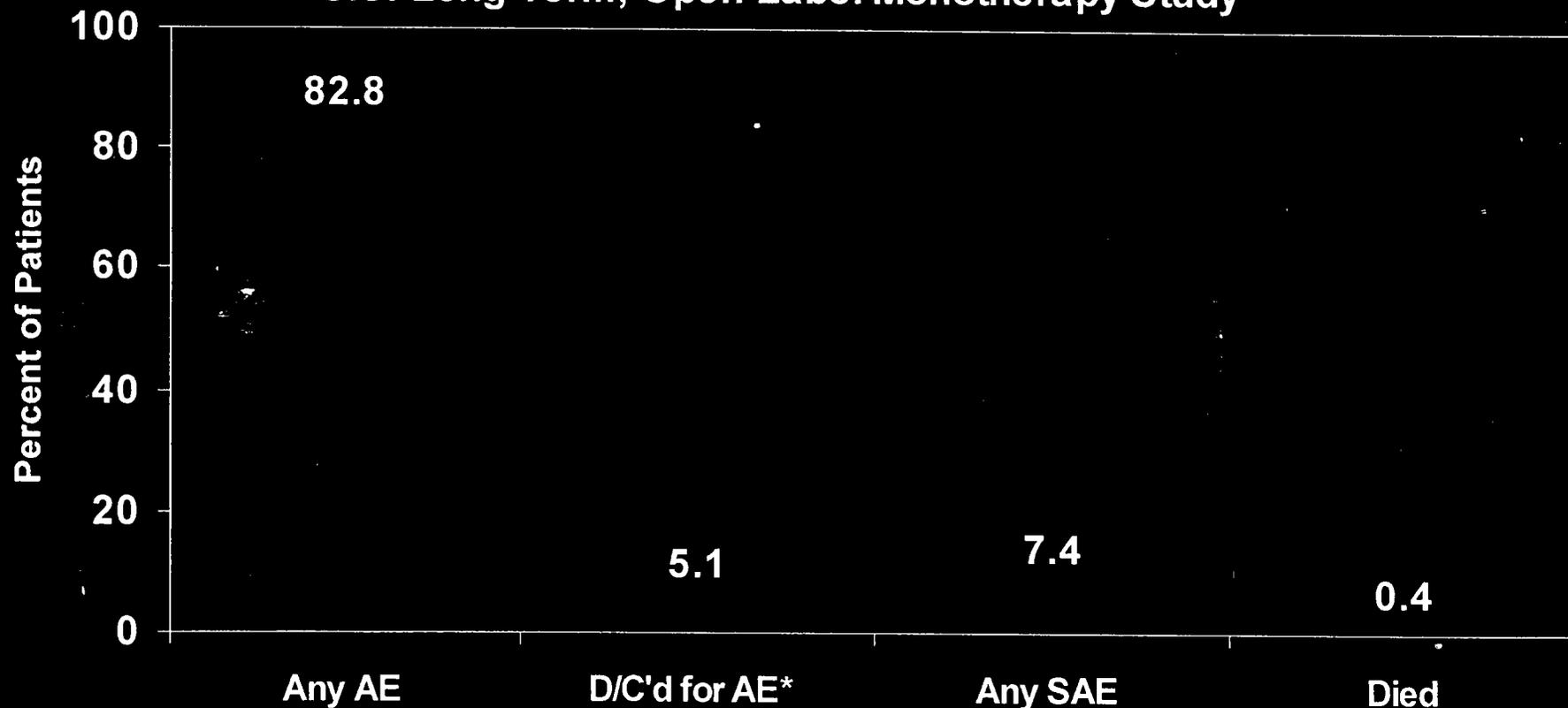
U.S. Placebo-Controlled Combination Therapy Studies



* Not glucose related

Summary of Adverse Events (AEs)

U.S. Long-Term, Open-Label Monotherapy Study



ACTOS™

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