Echocardiography Evaluation

- Conducted as part of the:
  - Multi-dose placebo-controlled monotherapy study (001)
    - 26 weeks duration
    - Echos at baseline, week 14, and end of study (week 26)
    - Echos have been read for more than 60 patients/dose group
  - Open-Ended, still ongoing (011)
    - Echos done every 6 months for first year, annually therafter
    - Echos have been read for at least 431 patients
      - Duration:

6 months	~150
12 months	~250
2 years	~ 20

Echocardiography Evaluation

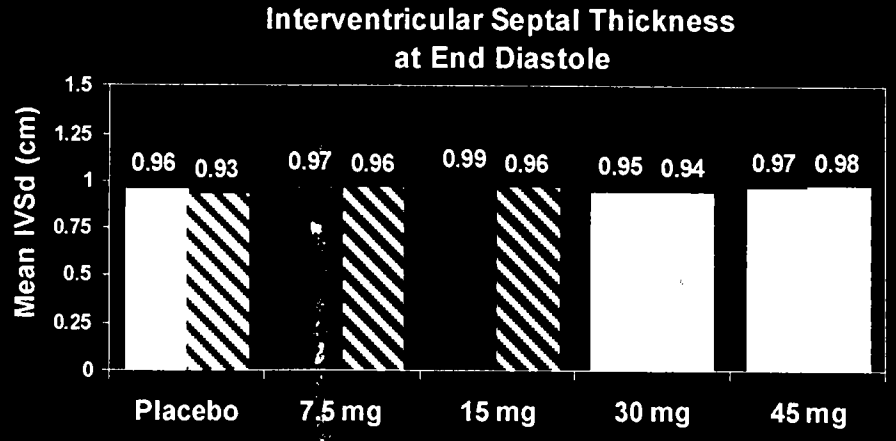
- Echocardiographic parameters include:
  - Left ventricular dimensions
  - Left ventricular mass
  - Fractional shortening
  - Cardiac output
  - Stroke volume
  - Calculated indices
    - Left ventricular mass index
    - Cardiac index

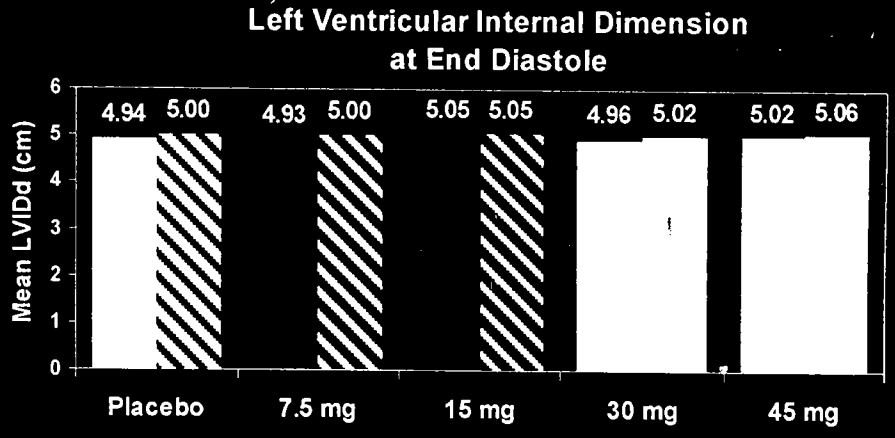
Echocardiography Evaluation for 120-Day Safety Update

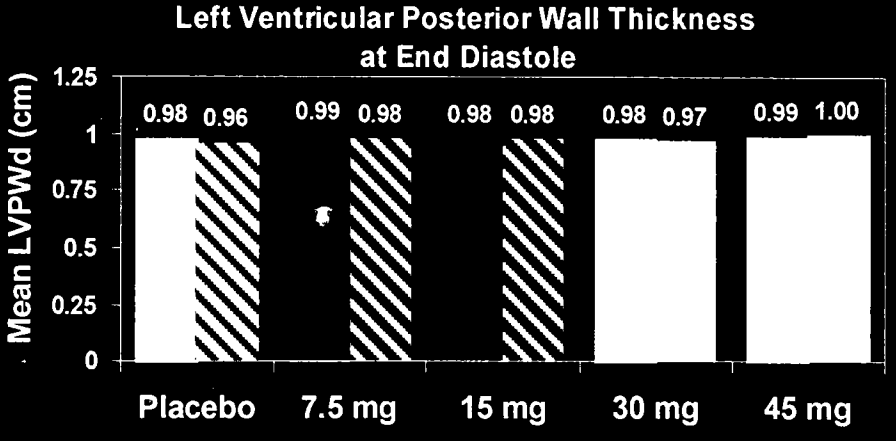
- Additional patients and longer times of exposure in the long-term, open-label study (011)
  - Duration: 1 year ~270
    2 years ~66
  - Duration for 51 rollover ACTOS™ patients: 355-993 days
- Additional analyses of echocardiographic data adjusted for glycemic control (HbA_{1c})

Echocardiography

U.S. Placebo-Controlled Monotherapy Study (001)





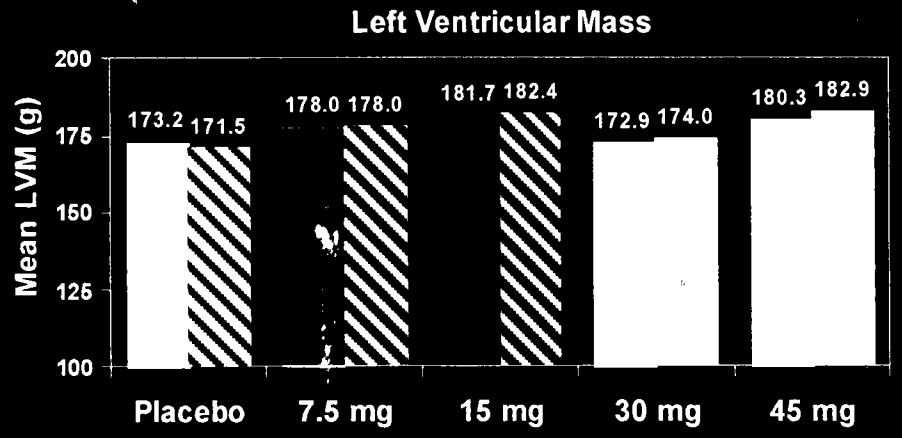


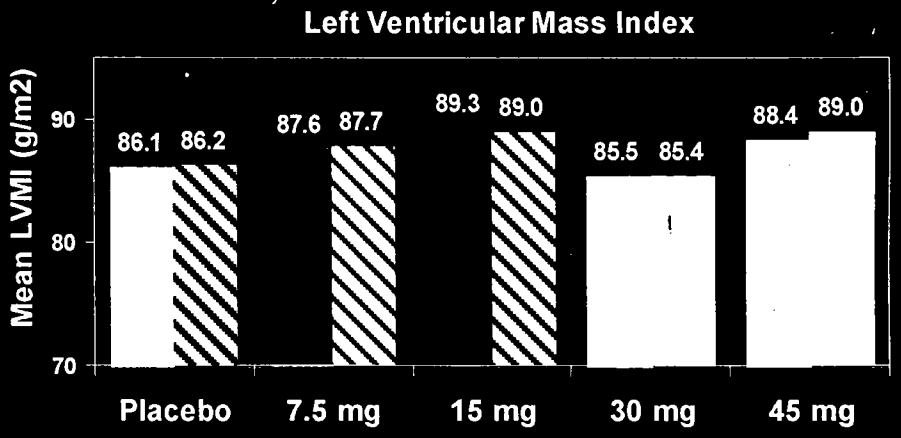
Baseline

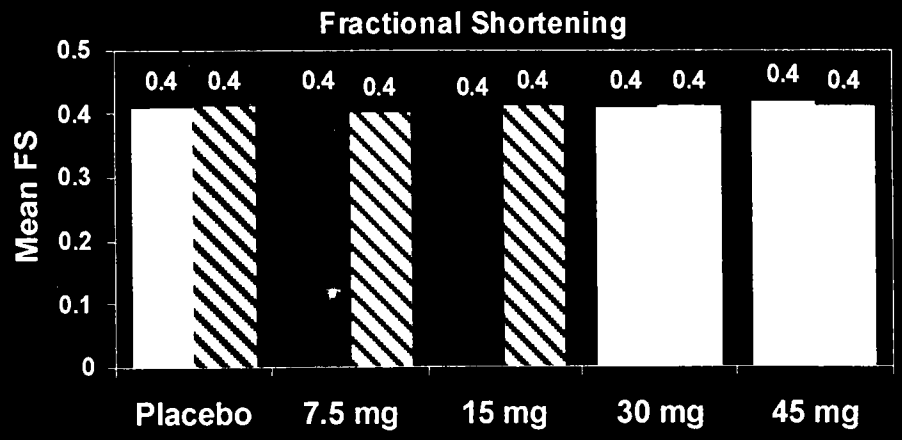
Endpoint

Echocardiography

U.S. Placebo-Controlled Monotherapy Study (001)

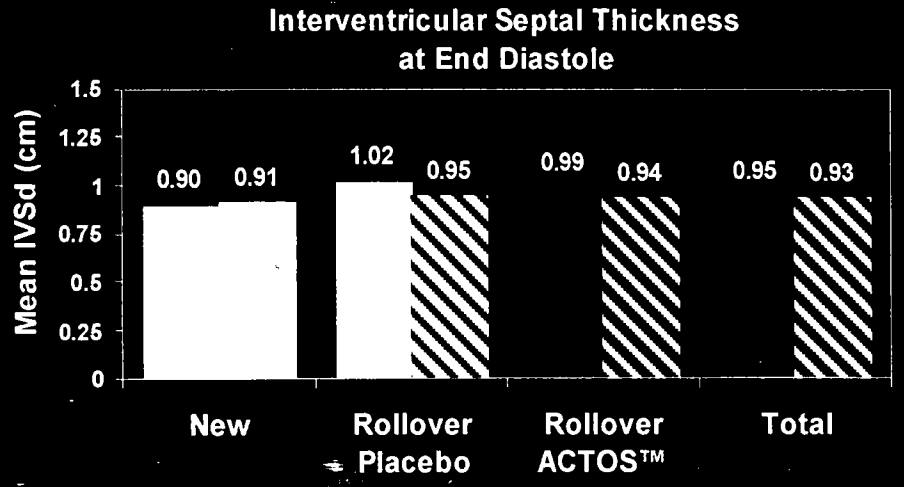


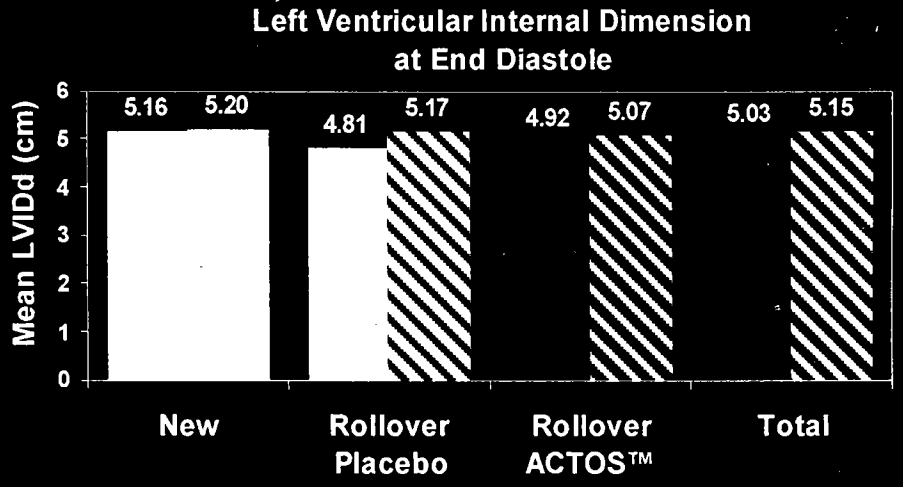


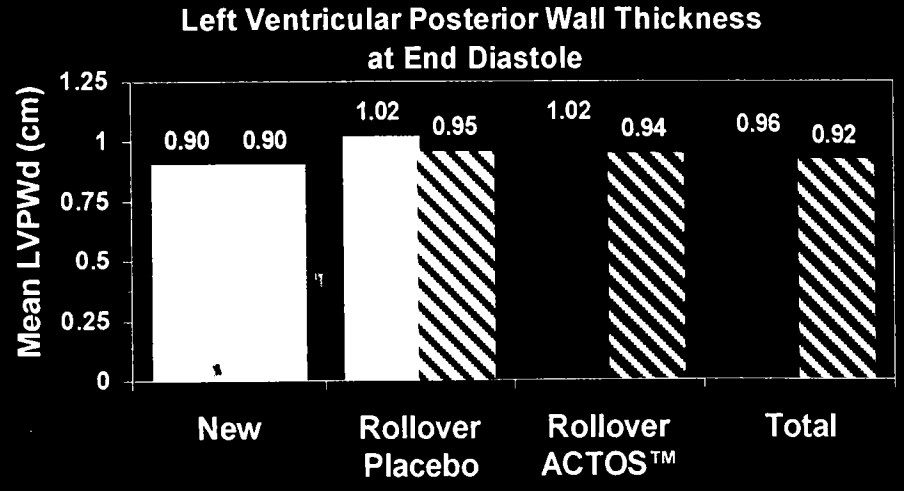


Echocardiography

U.S. Open-Label, Long-Term Study (011)







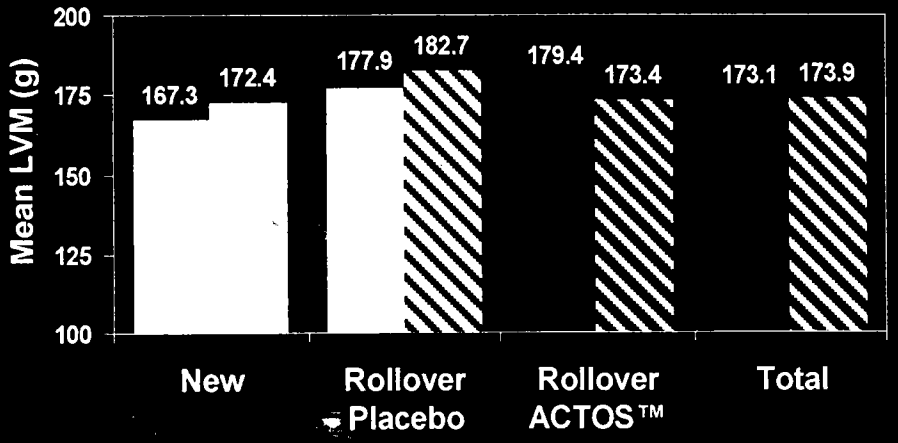
Baseline

Last Available

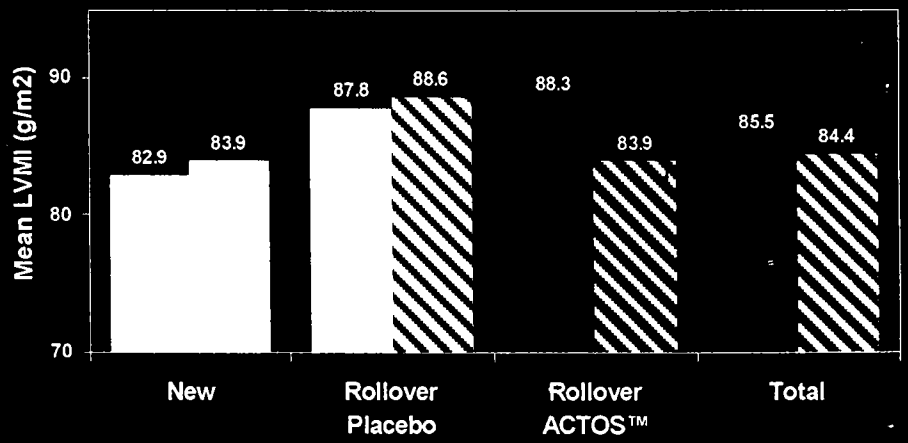
Echocardiography

U.S. Open-Label, Long-Term Study (011)

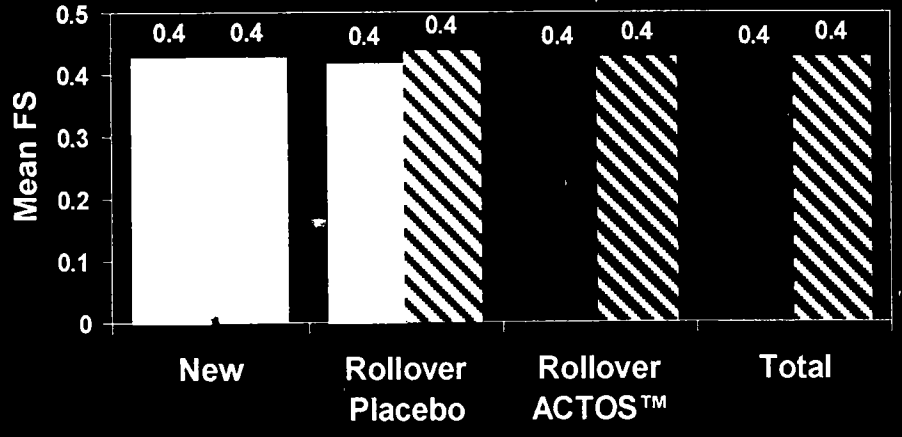
Left Ventricular Mass

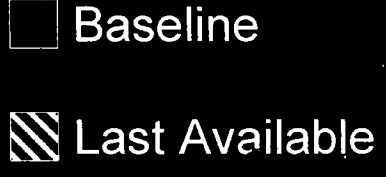


Left Ventricular Mass Index



Fractional Shortening





Echocardiography Conclusions

- No evidence from Study 001 or Study 011 (clinical cut off for NDA) of echocardiographic differences between placebo or ACTOS™ dose groups
- No evidence of echocardiographic changes in patients receiving ACTOS™ for extended periods of time (up to 2 years) (120-Day Safety Update data)
- Preliminary evaluation of echocardiographic data for patients who received placebo or ACTOS™ with similar HbA_{1c} values indicate no impact of ACTOS™ on echocardographic variables (120-Day Safety Update data)

Other Safety Considerations

- CPK

Summary of CPK Elevations ≥10 ULN U.S. Clinical Studies

7 cases out of 1881 (0.37%)

↓

All on ACTOS™

↓

7 cases represented are isolated values during study

↓

3 cases associated with exercise

1 case associated with atorvastatin

None of these cases discontinued due to an elevated CPK. There were no symptoms or adverse events associated with these elevations.

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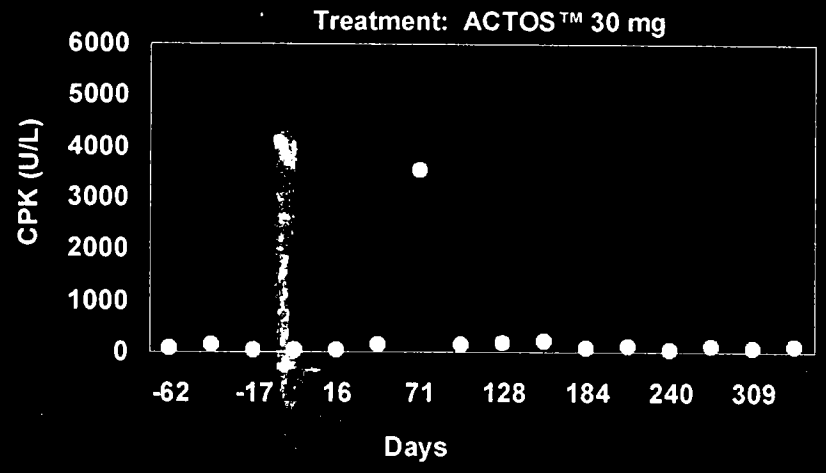
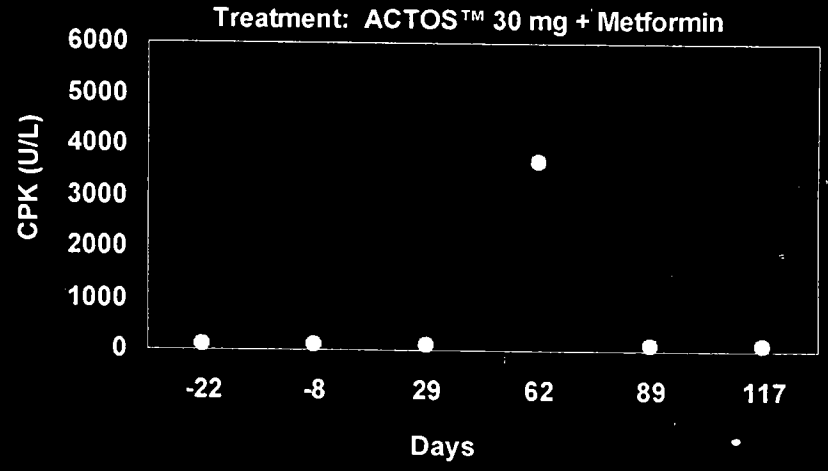
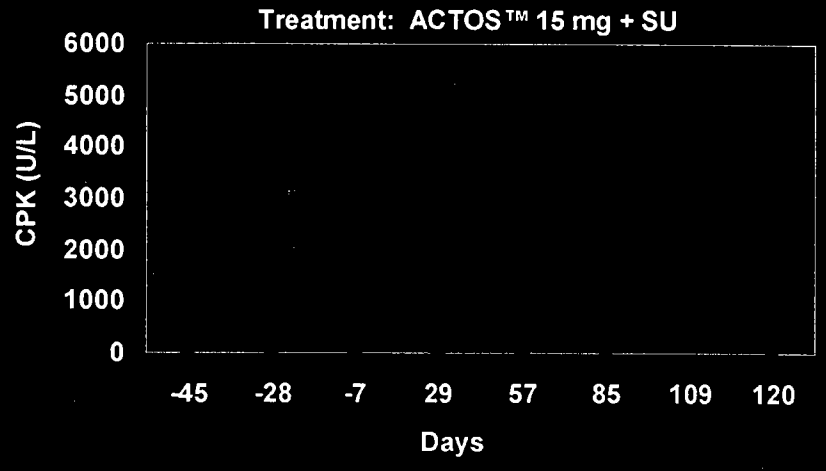
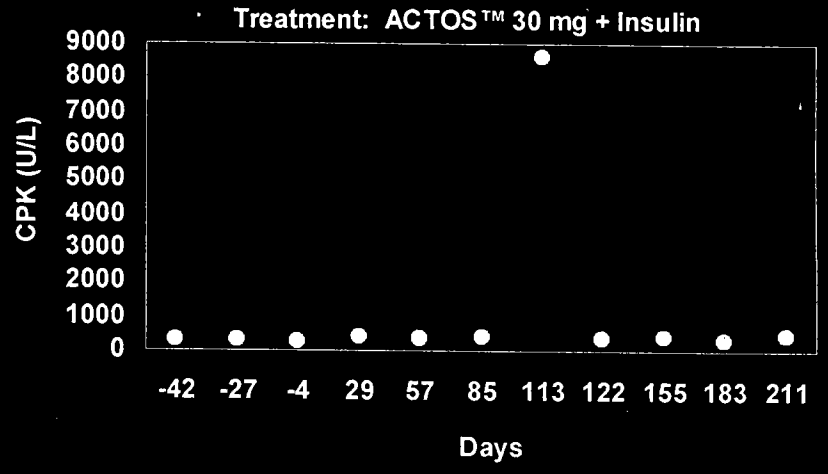
CPK Elevations (≥ 10 x ULN)

U.S. Clinical Studies



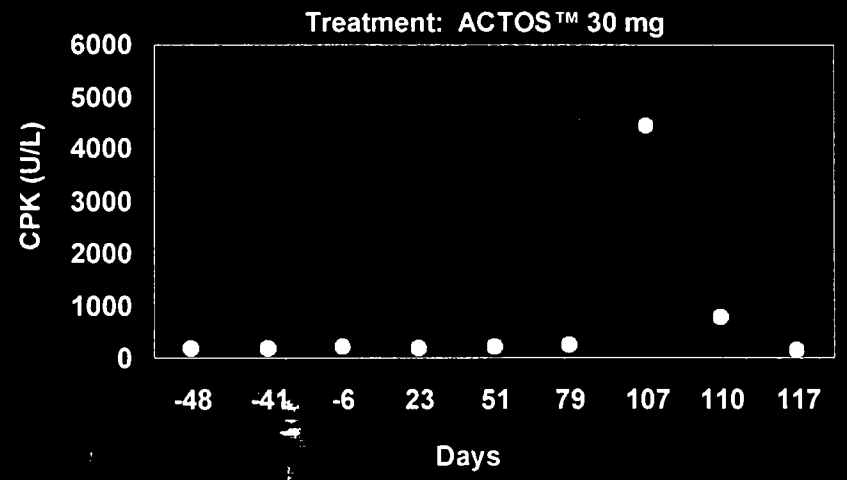


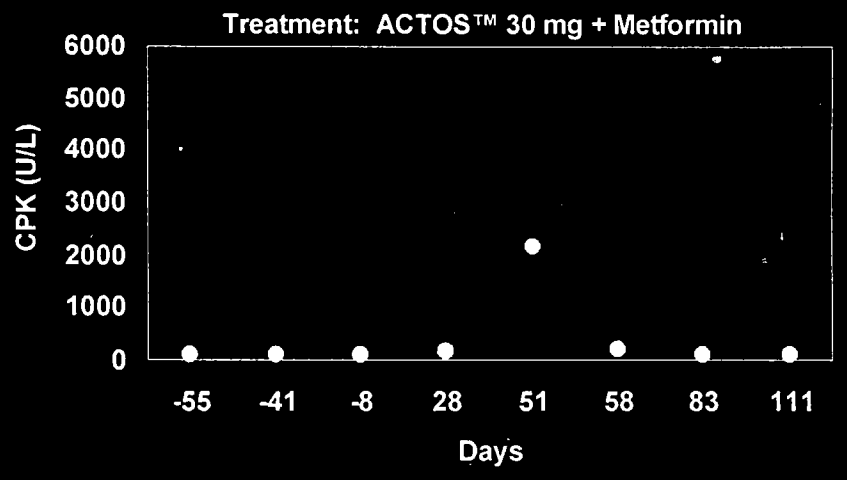


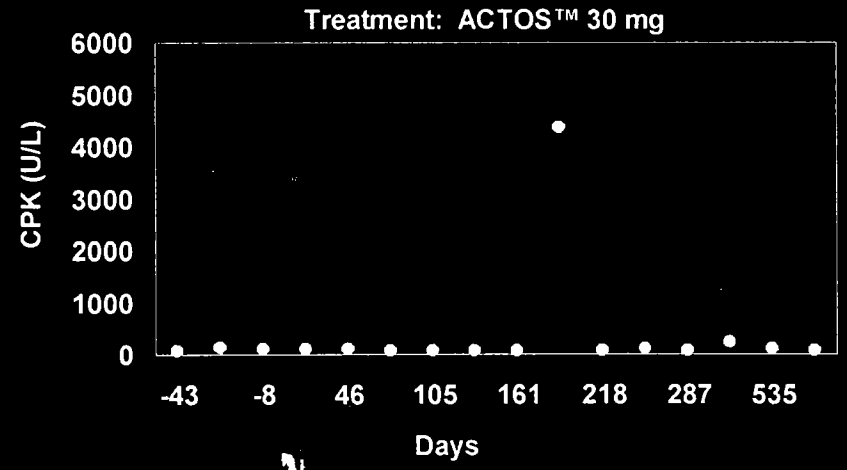


CPK Elevations (≥ 10 x ULN)

U.S. Clinical Studies







Other Safety Considerations

- Urinary cytology

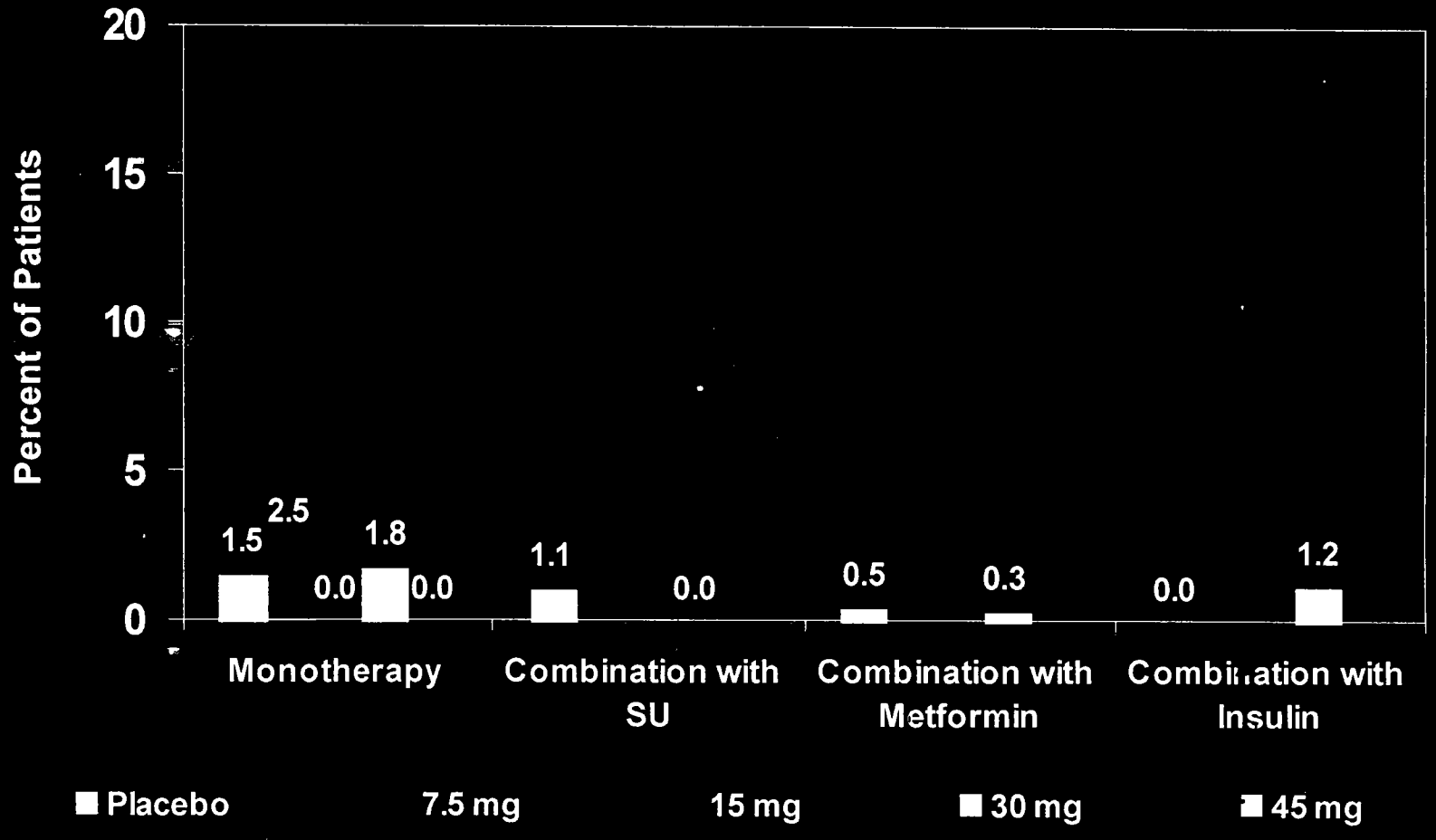
Urinary Cytology

- Evaluated because of preclinical finding
- Evaluation included prospective evaluation of urinary cytology
- All patients were evaluated prior to receiving double-blind study medication and during study
- Some patients withdrew due to urinary cytology findings -- benign results
- First systematic urinary cytology study in patients with type 2 diabetes mellitus

Urinary Cytology Classes

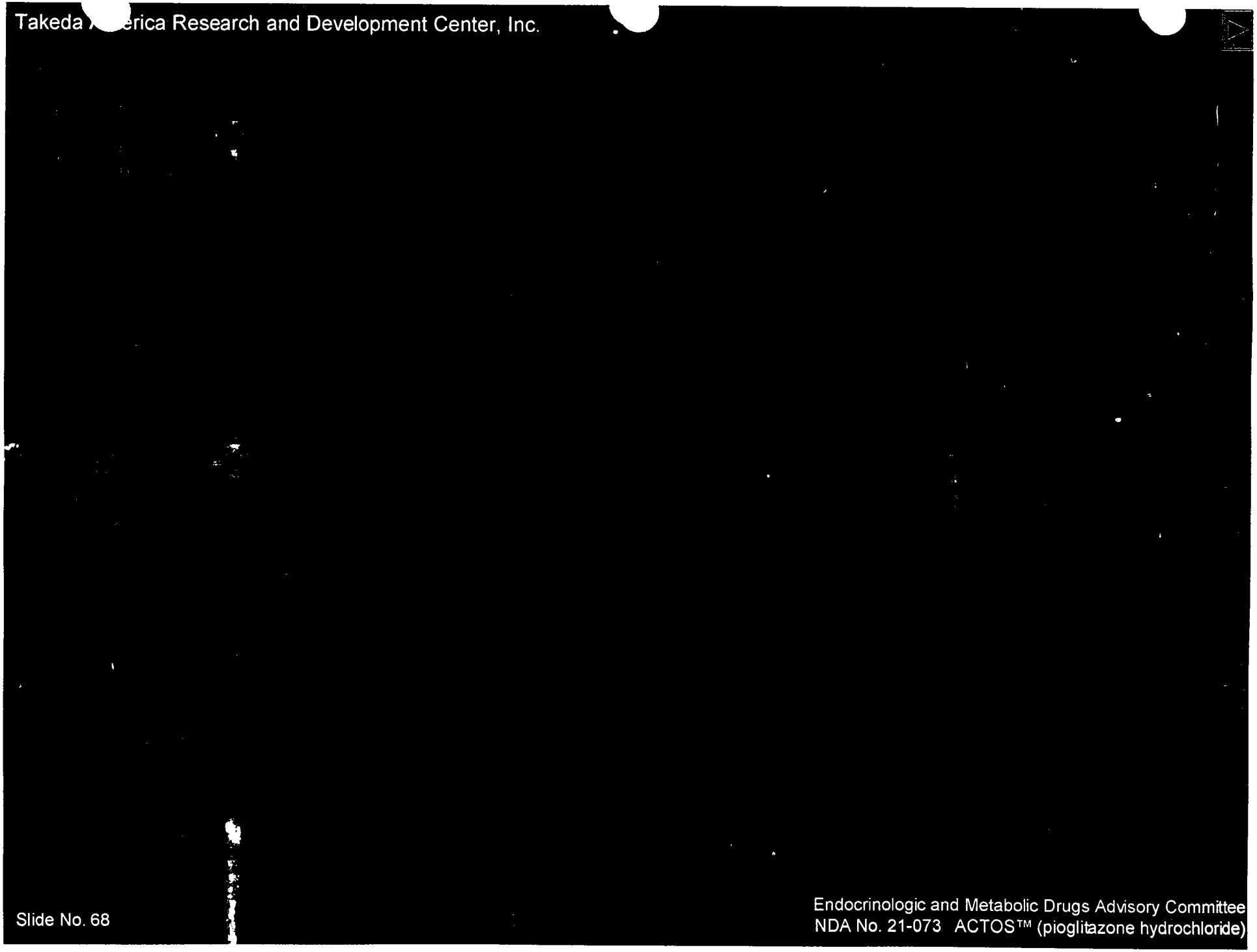
- Diagnostic Cytology Laboratories, Inc. classification:
  1) Renal tubular cells
  2) Reactive urothelial cells and/or inflammatory cells
  3a) Atypical urothelial cells, likely reactive
  3b) Atypical urothelial cells of undetermined significance
  3c) Atypical urothelial cells, likely dysplastic/neoplastic
  4) Abnormal urothelial cells with neoplastic features

Urinary Cytology Class 3c Results



Urine Cytology

No new cases of bladder tumors were identified during prospective evaluation of urinary cytology in patients in the placebo-controlled monotherapy and combination therapy studies conducted in the United States



Clinical Perspective

David E. Kelley, M.D.
Associate Professor of Endocrinology and Metabolism
University of Pittsburgh School of Medicine

Clinical Perspective

- Undiagnosed and under-treated diabetes continue to be important medical problems in the United States
- Not enough people are being treated, treatment is often delayed, and treatment often does not meet the goal of optimal control

Benefits of Agents of the Thiazolidinedione Class

- Targets **insulin resistance**, a key underlying physiologic defect of Type 2 diabetes:
  - Enhances cellular responses to insulin
  - Increases insulin-dependent glucose disposal
  - The net result is to **improve insulin sensitivity** in insulin-resistant patients

Benefits of Agents of the Thiazolidinedione Class

- Thiazolidinediones achieve statistically and clinically significant improvement in HbA_{1c} and FBG
- Durability of glycemic response is an attribute of TZDs, and distinct from the response pattern observed with other classes of oral agents

Benefits of Agents of the Thiazolidinedione Class

- The mechanism of action of TZDs is distinct from other classes of oral agents
- TZDs are useful not only as monotherapy, but in combination
- Permits the flexibility necessary for most diabetes management regimens

Clinical Trials - ACTOS™ Safety Profile

- ACTOS™ studied in monotherapy and combination therapy
- Among the most commonly reported AEs, rates were similar to placebo
- Generally safe and well tolerated

Clinical Trials - ACTOS™ Safety Profile

- No evidence of hepatotoxicity
- No evidence of increased cardiac risk
- Mild anemia, likely a class effect
  - Only 9/2549 (0.35%) patients were discontinued due to anemia
- Edema, likely a class effect, was generally mild to moderate

Clinical Trials - ACTOS™ Safety Profile

- No adverse effects on serum lipid profiles (notably LDL/HDL; total cholesterol/HDL ratios)
- No significant hypoglycemia with monotherapy
- Occasional mild to moderate hypoglycemia with combination therapy
- No drug interactions identified

Clinical Trials - Safety Profile

- Overall -- safety profile appears equal to or better than other available diabetes drugs

Summary

- *ACTOS™ has important **advantages** for the clinician to improve ease of use and therefore compliance:*
  - *Once daily dosing*
  - *Flexibility for monotherapy or combination therapy*
  - *No hypoglycemia as monotherapy*
  - *Good safety and tolerability*