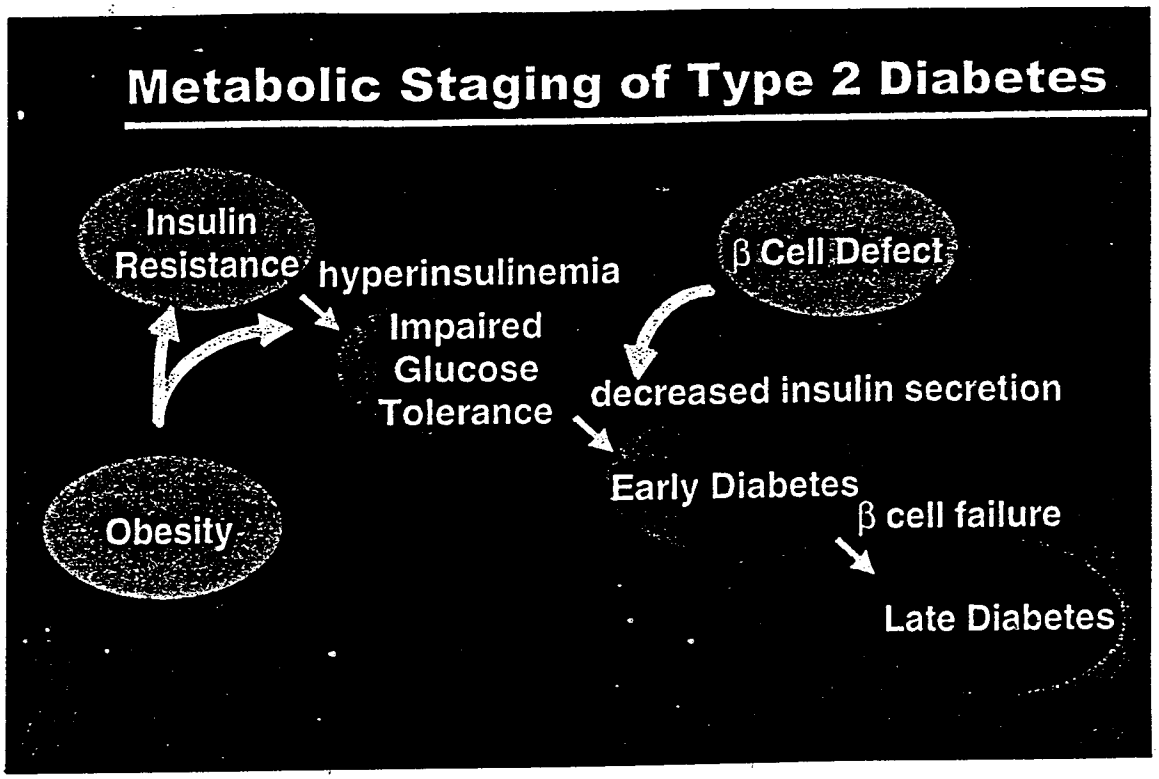
Benefits of Rezulin Therapy

Randall Whitcomb, MD

Vice President, Clinical Research
Parke-Davis


Metabolic Staging of Type 2 Diabetes
Insulin Resistance
hyperinsulinemia
Impaired Glucose Tolerance
β Cell Defect
decreased insulin secretion
Early Diabetes
β cell failure
Late Diabetes
Obesity

Troglitazone Efficacy

- Insulin – Combination
- Proposed - Triple Therapy Trog/SU/Met
- Sulfonylurea – Combination
- Monotherapy
- Impact on beta cell function and atherosclerotic risk factors
- Projected risk reduction for microvascular endpoints

TROGLITAZONE COMBINATION WITH INSULIN

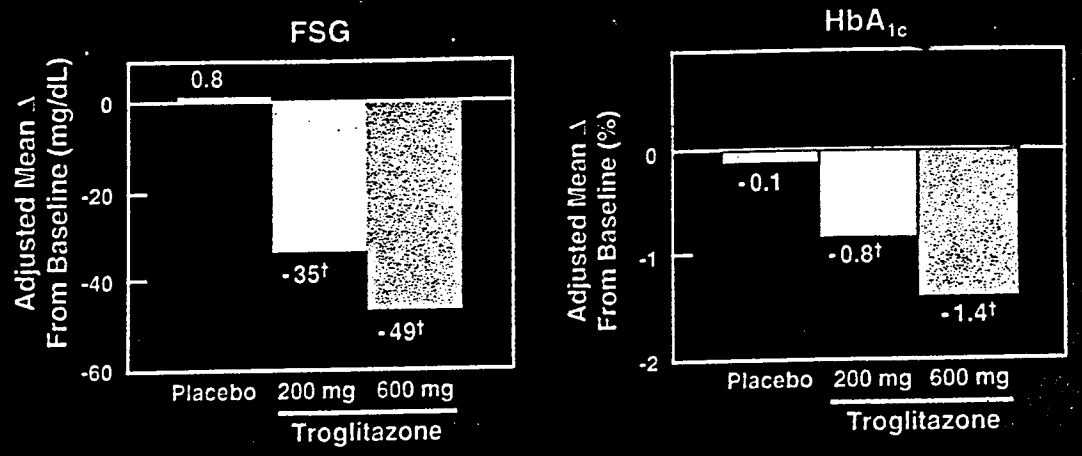
Patient Profile at Baseline

	Mean
Age	56 yr
BMI	35 kg/m^2
Years Diagnosed With Type 2 Diabetes	10.0 yr
Years on Insulin	5.0 yr
Insulin Dose	73 U/day
FSG	216 mg/dL
HbA_{1c}	9.4%

Schwartz S, et al. *NEJM.* 1998:338;861–866.

TROGLITAZONE COMBINATION WITH INSULIN

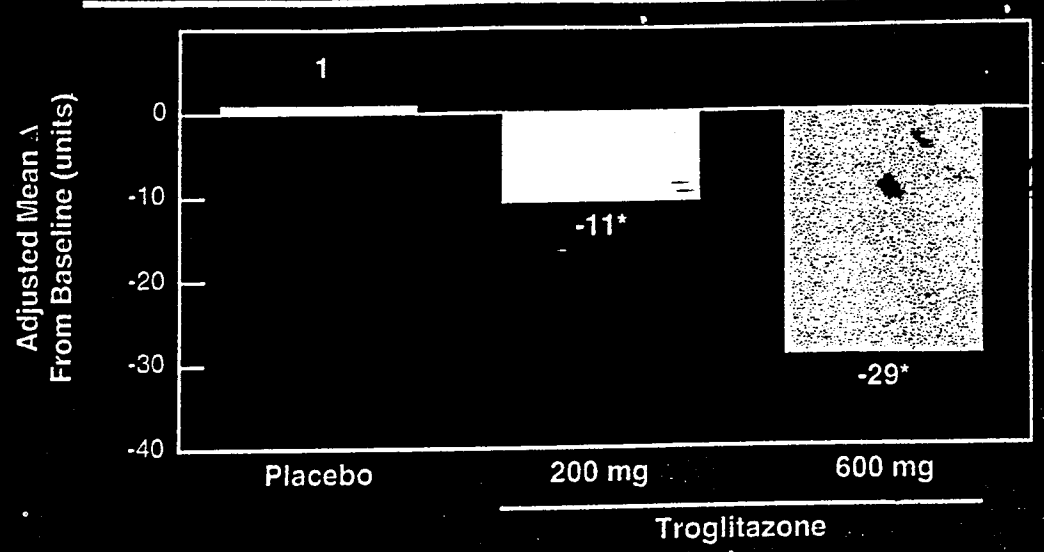
Adjusted Mean Change From Baseline Fasting Serum Glucose (FSG) and HbA_{1c} at Month 6



†$P < 0.0001$ vs placebo (insulin-only group).
Schwartz S, et al. *NEJM.* 1998:338;861–866.

TROGLITAZONE COMBINATION WITH INSULIN

Insulin Dose at Month 6



*$P < 0.0001$ vs placebo (insulin-only group).
Schwartz S, et al. *NEJM.* 1998:338;861–866.

Significant Benefits

- Improvement in glucose control and lowered insulin requirements in patients uncontrolled on insulin

Triple Therapy Study: Combination Troglitazone / Metformin / Sulfonylurea

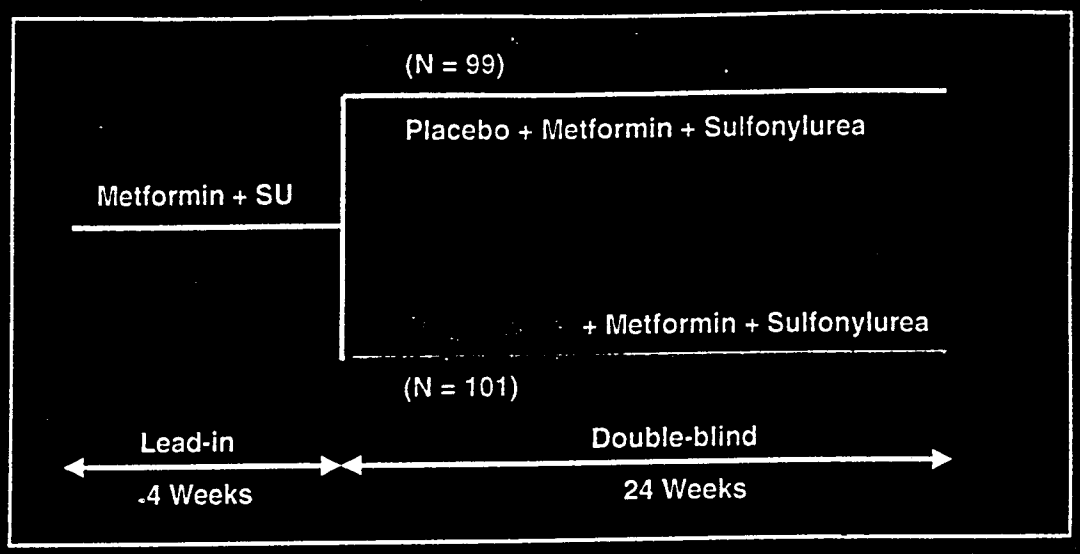
COMBINATION TROGLITAZONE / METFORMIN / SULFONYLUREA

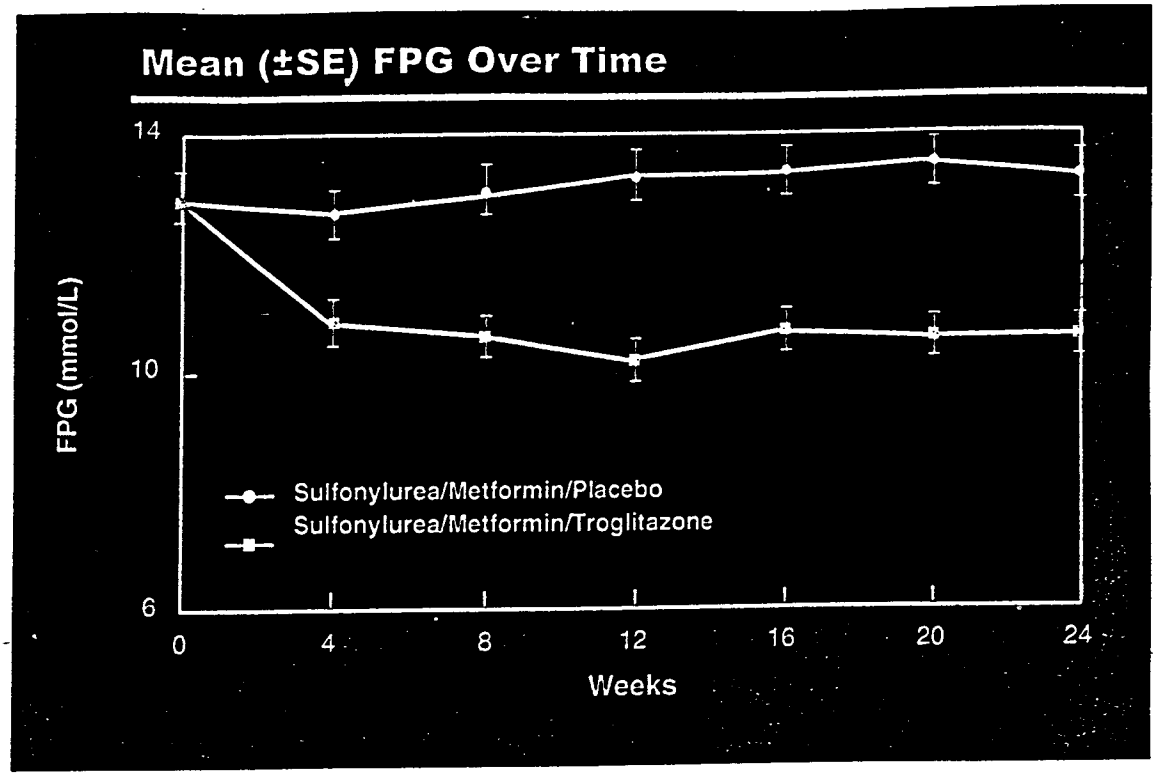
Base-Line Patients Characteristics

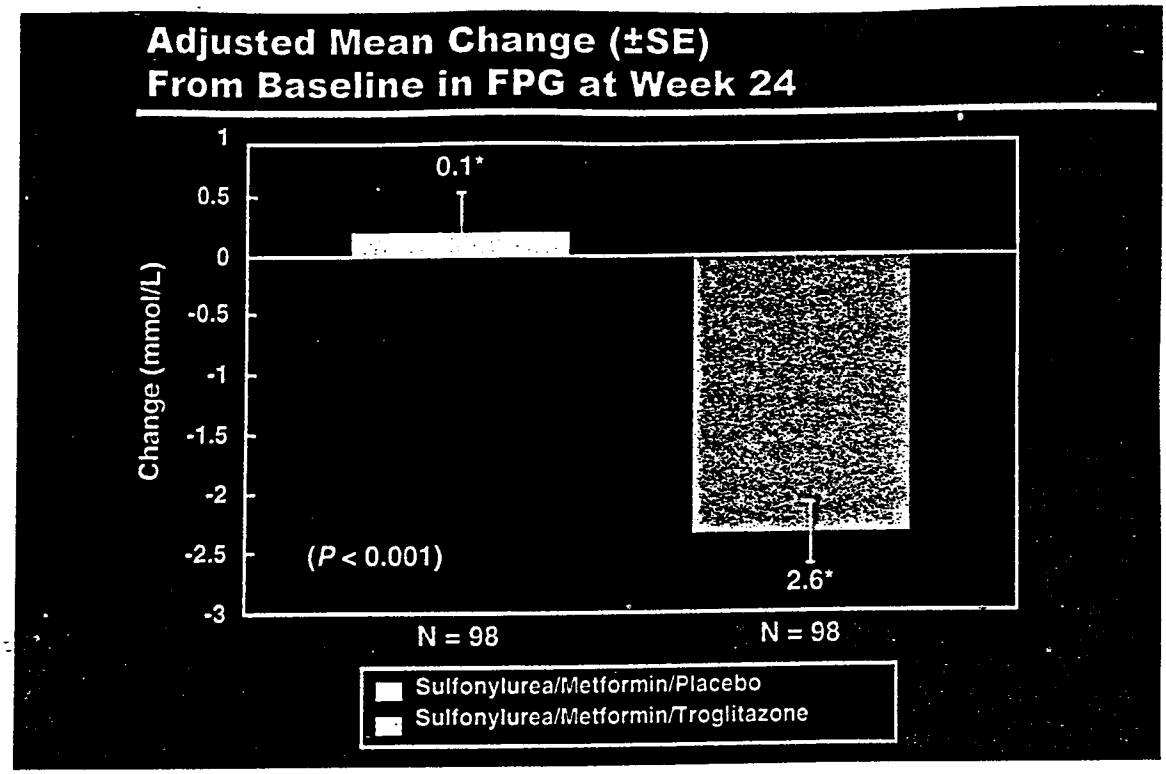
N	200
Age (yr ± SD)	59 ± 9
Duration of Diabetes (yr ± SD)	11.3 ± 7.1
Body-mass Index (± SD)	30.1 ± 4.5
Fasting Plasma Glucose (mg/dL ± SD)	234 ± 56
HbA_{1c} (% ± SD)	9.7 ± 1.2
Fasting Plasma Insulin (μU/mL ± SD)	24 ± 13
Fasting Plasma C-peptide (ng/mL ± SD)	3.4 ± 1.5

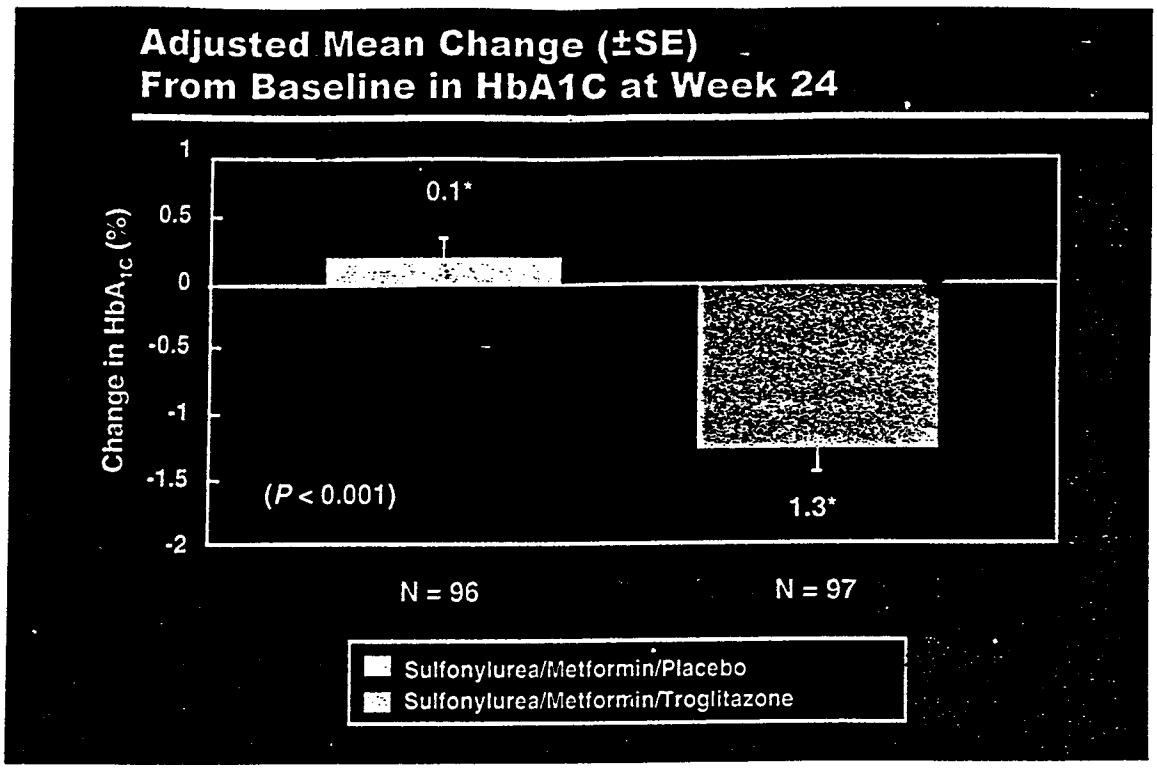
COMBINATION TROGLITAZONE / METFORMIN / SULFONYLUREA

Triple Therapy (Study Design)




Mean (±SE) FPG Over Time
14
10
6
FPG (mmol/L)
Sulfonylurea/Metformin/Placebo
Sulfonylurea/Metformin/Troglitazone
0
4
8
12
16
20
24
Weeks


Adjusted Mean Change (±SE)
From Baseline in FPG at Week 24
Change (mmol/L)
1
0.5
0
-0.5
-1
-1.5
-2
-2.5
-3
0.1*
2.6*
(P < 0.001)
N = 98
N = 98
Sulfonylurea/Metformin/Placebo
Sulfonylurea/Metformin/Troglitazone


Adjusted Mean Change (±SE)
From Baseline in HbA1C at Week 24
Change in HbA1C (%)
1
0.5
0
-0.5
-1
-1.5
-2
0.1*
1.3*
(P < 0.001)
N = 96
N = 97
Sulfonylurea/Metformin/Placebo
Sulfonylurea/Metformin/Troglitazone

Frequency Distribution of Patients With Target HbA_{1c} Levels ≤8% or ≤7%

	Sulfonylurea/Metformin		
	Placebo (n = 96)	Troglitazone (n = 97)	*P*-Value
	%	%	
HbA_{1c} Levels ≤8%	6	43	<0.001
HbA_{1c} Levels ≤7%	1	14	<0.001

Significant Benefits

- Improvement in glucose control and lowered insulin requirements in patients uncontrolled on insulin
- Significant glucose lowering in patients who fail sulfonylurea/metformin combination

Troglitazone + Micronized Glyburide (12 Mg) in Type 2 Diabetes Patients

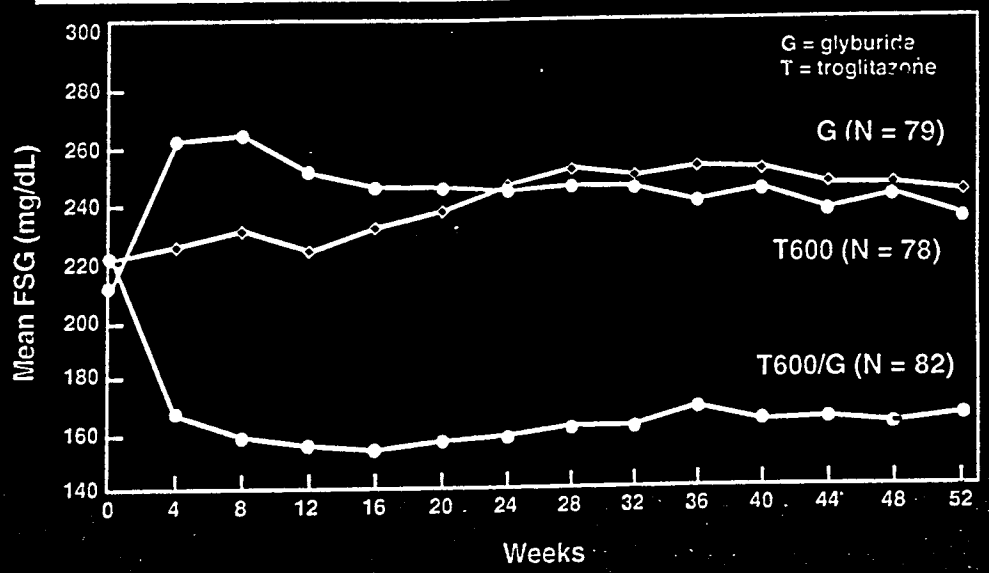
- 1-year, double-blind, active-control trial
- N = 552
- Sulfonylurea failures (FSG >140 mg/dL on maximum dose of glyburide)
- 200, 400, 600 mg troglitazone alone or with 12 mg micronized glyburide vs glyburide alone

Horton ES et al. *Diabetes Care.* 1998;21:1462–1469.

TROGLITAZONE + MICRONIZED GLYBURIDE (12 MG)

Fasting Serum Glucose

Mean Levels Over Time (ITT)

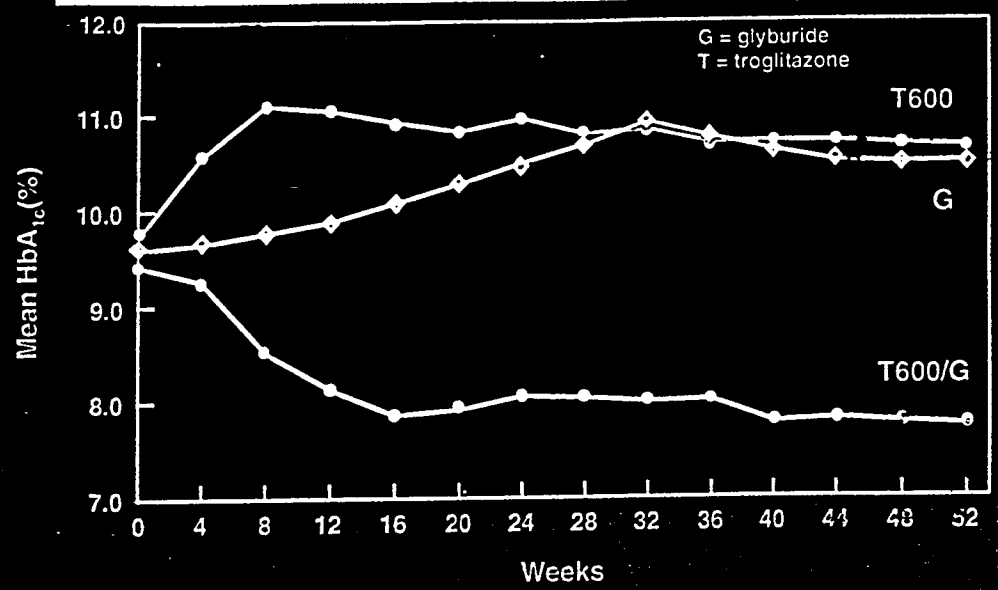


Horton ES et al. *Diabetes Care.* 1998;21:1462–1469.

TROGLITAZONE + MICRONIZED GLYBURIDE (12 MG)

HbA_{1c}

Mean Levels Over Time (ITT)

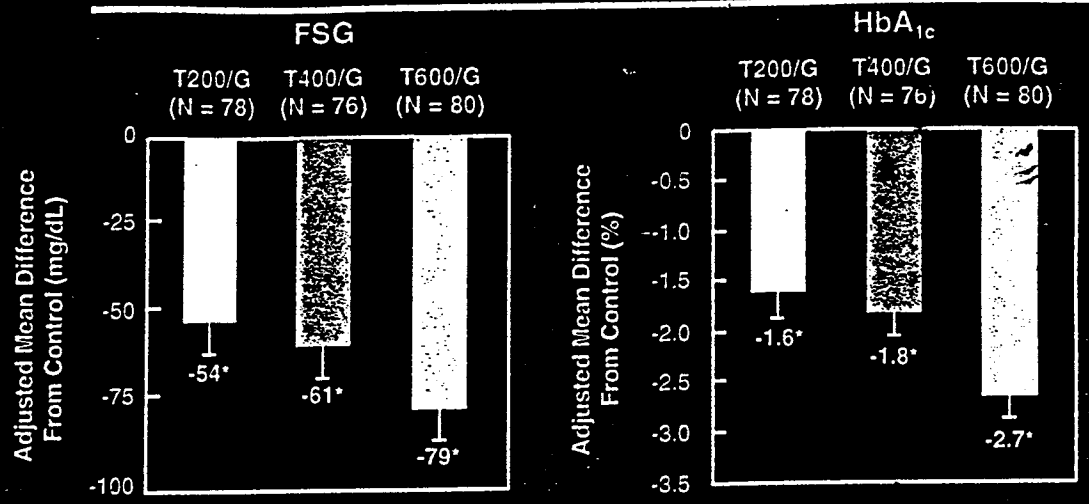


Horton ES et al. *Diabetes Care.* 1998;21:1462–1469.

TROGLITAZONE + MICRONIZED GLYBURIDE (12 MG)

FSG and HbA_{1c}

Mean Difference vs Control at 12 Months (ITT)



*$P < 0.0001$.

Horton ES et al. *Diabetes Care.* 1998;21:1462–1469.

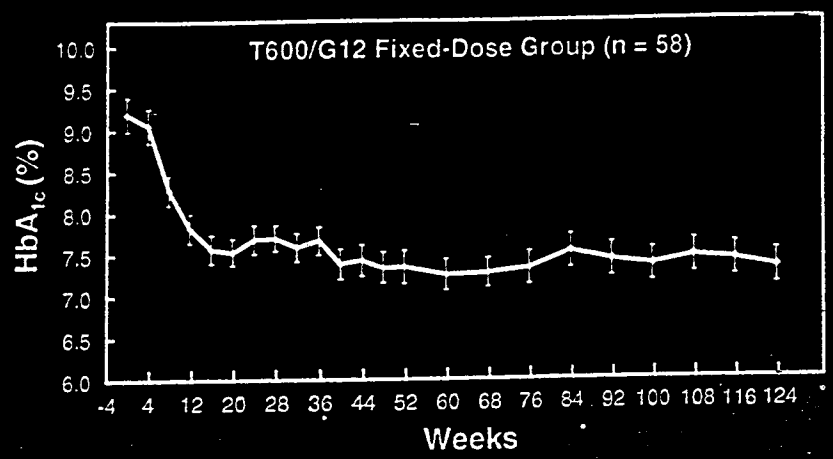
Frequency Distribution of Patients With Target HbA_{1c} Levels ≤8% or ≤7%

	Glyburide	Troglitazone/Glyburide 200 mg/ 12 mg	400 mg/ 12 mg	600 mg/ 12 mg
	%	%	%	%
HbA_{1c} Levels ≤8%	10	33	33	60
HbA_{1c} Levels ≤7%	1	22	21	41

Horton ES et al. *Diabetes Care.* 1998;21:1462–1469.

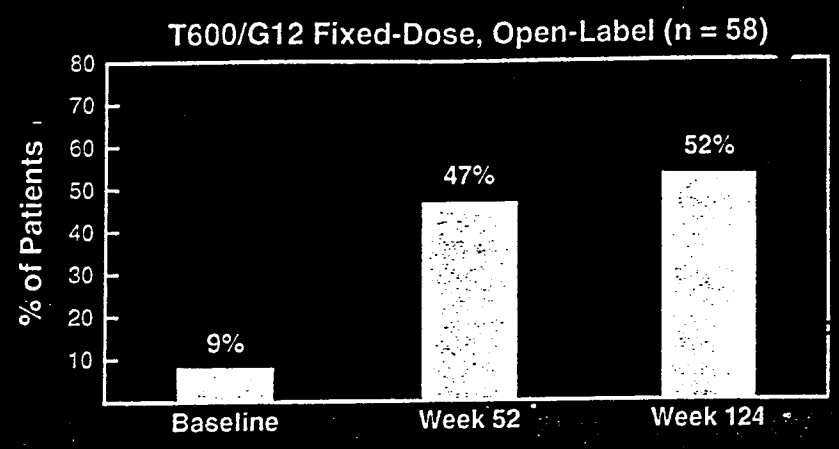
COMBINATION TROGLITAZONE/SULFONYLUREA OPEN-LABEL EXTENSION STUDY

Mean HbA_{1c} Levels Over Time



Draznin B, et al. *Diabetes.* 1998:47;(suppl 1) AO330.

Percentage of Patients at HbA_{1c} Level ≤7%



Draznin B, et al. *Diabetes*. 1998:47;(suppl 1) AO330.

Significant Clinical Benefits

- Improvement in glucose control and lowered insulin requirements in patients uncontrolled on insulin
- Significant glucose lowering in patients who fail sulfonylurea/metformin combination
- Significant and sustained glucose lowering in combination with sulfonylurea

6-Month Monotherapy Study

- 6-month, double-blind, placebo-controlled study
- N = 402 (86 diet-only therapy)
- Mean HbA_{1C} 8.5 ± 1.7%
- 100 mg, 200 mg, 400 mg, 600 mg troglitazone

Fonseca VA. *J Clin Endocrinol Metab.* 1998:83;3169–3176.

TROGLITAZONE MONOTHERAPY

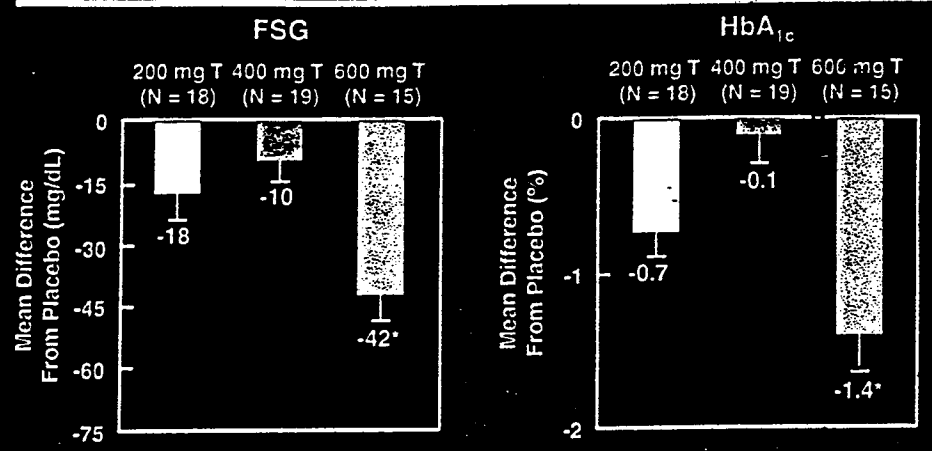
Fasting Serum Glucose

Mean Levels Over Time (ITT)

Fonseca VA. *J Clin Endocrinol Metab.* 1998:83;3169–3176.

TROGLITAZONE MONOTHERAPY

Mean Difference in FSG and HbA_{1c} vs Placebo at Month 6 (ITT)

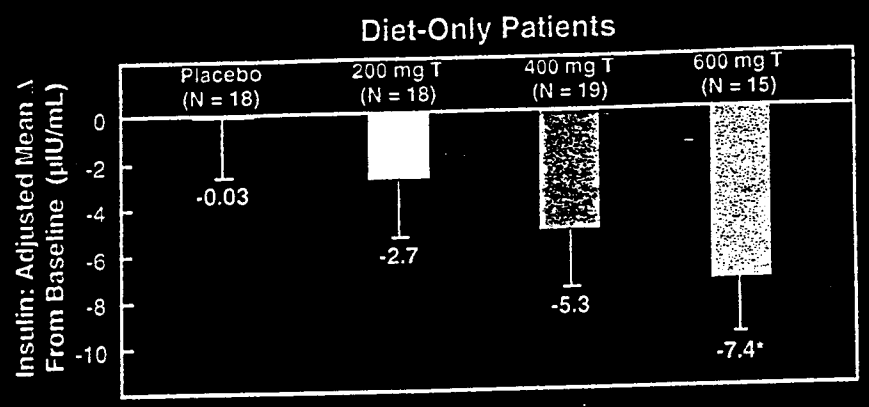


*$P < 0.05$.

Fonseca VA. *J Clin Endocrinol Metab*.1998:83;3169–3176.

TROGLITAZONE MONOTHERAPY

Serum Insulin: Adjusted Mean Change From Baseline at Month 6 (ITT)

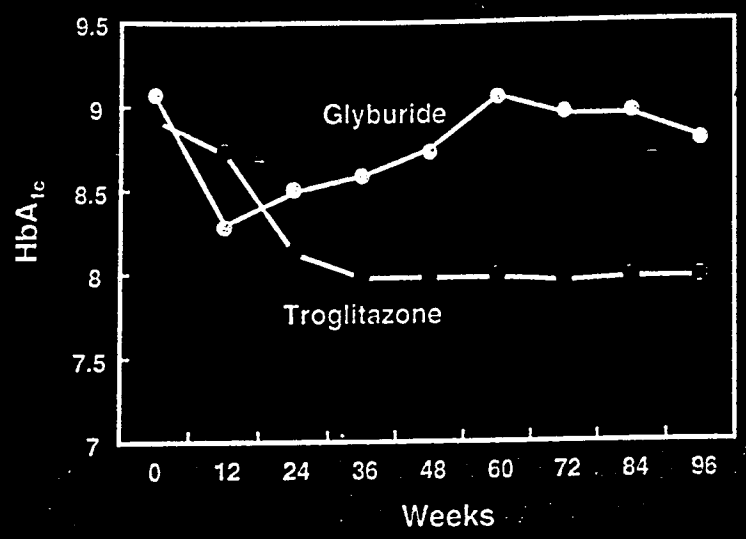


*$P \leq 0.01$ vs placebo.

Fonseca VA. *J Clin Endocrinol Metab.* 1998:83;3169–3176.

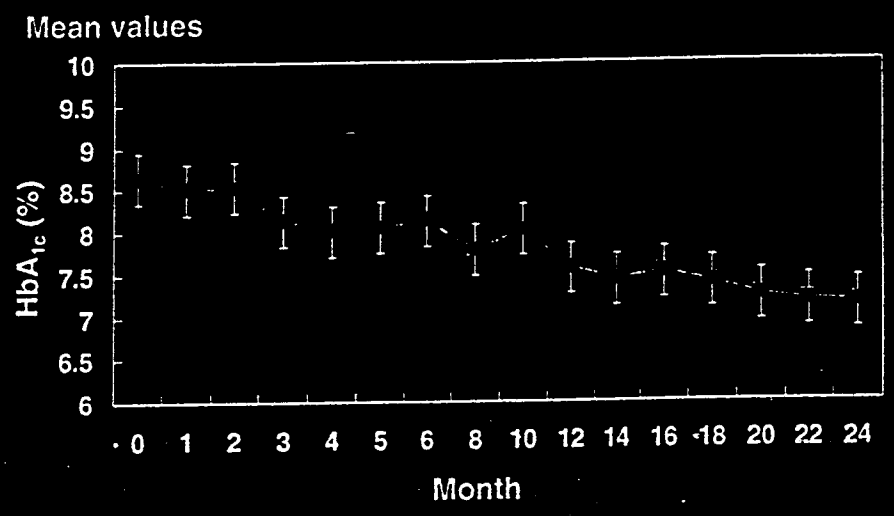
991-042

Mean Levels of HbA_{1c}



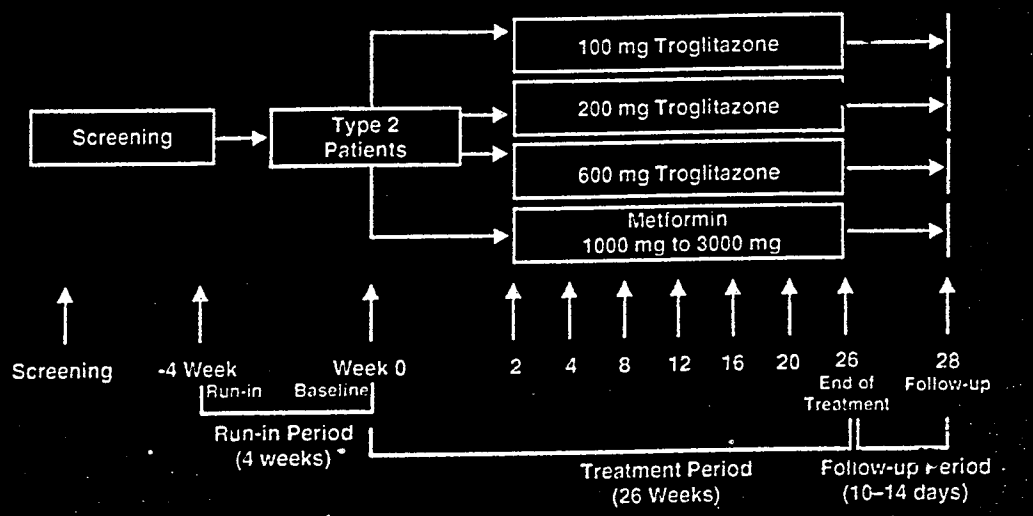
Troglitazone Monotherapy

OL Extension 400 and 600 mg Patients (n=36)



TROGLITAZONE VS METFORMIN

Study Design



TROGLITAZONE VS METFORMIN

Glycemic Parameters at Week 26

	Troglitazone 200 mg	Troglitazone 600 mg	Metformin 1000–3000 mg
HbA_{1c}			
n‡	91	96	92
Week 26 value	7.9	7.3	7.3
% Change from Metformin	8	1	–
P-value	0.002	0.737	–
Fasting Serum Glucose (mmol/L)			
n	91	98	95
Week 26 value	10.0	9.2	9.0
% Change from Metformin	11	2	–
P-value	0.002	0.489	–

TROGLITAZONE COMPARATOR VS METFORMIN

Proportion of Patients with $HbA_{1C} \geq 1\%$ Decrease from Baseline (Responder) at Week 26 (ITT)

	Troglitazone 200 mg	Troglitazone 600 mg	Metformin 1000–3000 mg
Number of Patients	95	103	97
HbA_{1C} Responder	23 (25%)	37 (39%)	32 (35%)
HbA_{1C} Non-Responder	68 (75%)	59 (61%)	60 (65%)

TROGLITAZONE VS METFORMIN

Insulin Parameters at Week 26

	Troglitazone 200 mg	Troglitazone 600 mg	Metformin 1000–3000 mg
Insulin (μU/mL)			
n	91	96	92
Week 26 value	6.9	6.5	8.5
% Change from Metformin	-20	-23	–
P-value	<0.001	<0.001	–

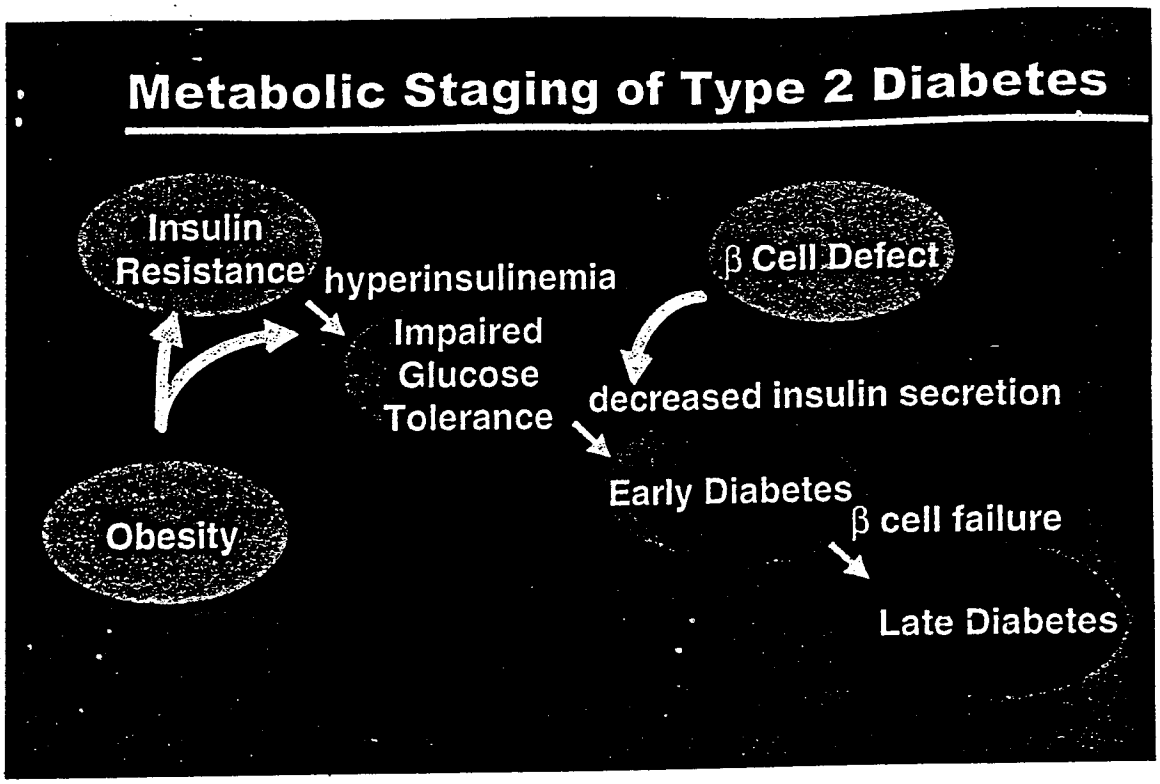
TROGLITAZONE COMPARATOR VS METFORMIN

Change in Body Weight (kg) at Week 26 (ITT)

	Troglitazone 200 mg	Troglitazone 600 mg	Metformin 1000–3000 mg
Number of Patients	90	94	95
Mean Baseline	80.8	76.7	82.7
Mean Week 26	80.4	76.9	81.1
Mean Difference	-0.4	0.2	-1.6

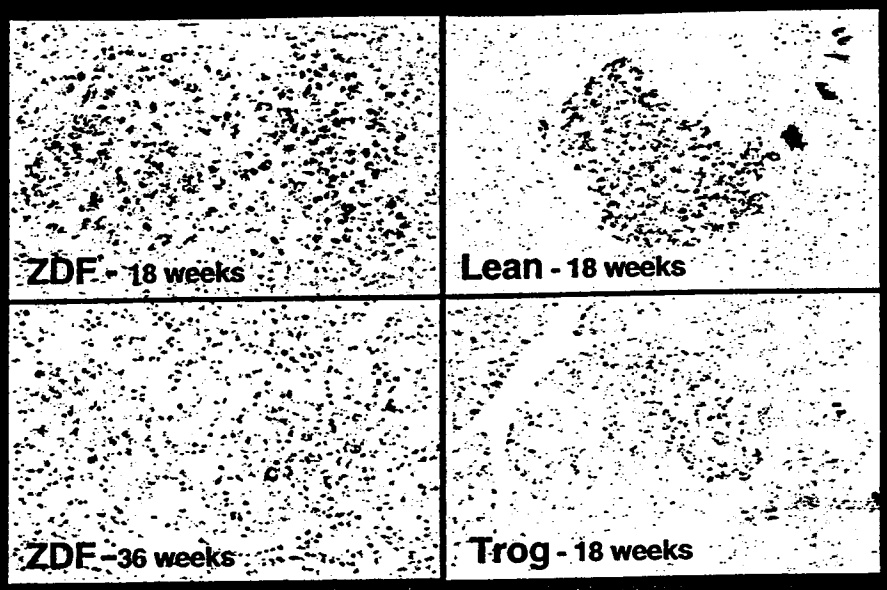
Significant Benefits

- Improvement in glucose control and lowered insulin requirements in patients uncontrolled on insulin
- Significant glucose lowering in patients who fail sulfonylurea/metformin combination
- Significant and sustained glucose lowering in combination with sulfonylurea
- Effective as monotherapy both short- and long-term


Metabolic Staging of Type 2 Diabetes
Insulin Resistance
hyperinsulinemia
Impaired Glucose Tolerance
β Cell Defect
decreased insulin secretion
Early Diabetes
β cell failure
Late Diabetes
Obesity

Insulin

Rat Pancreas



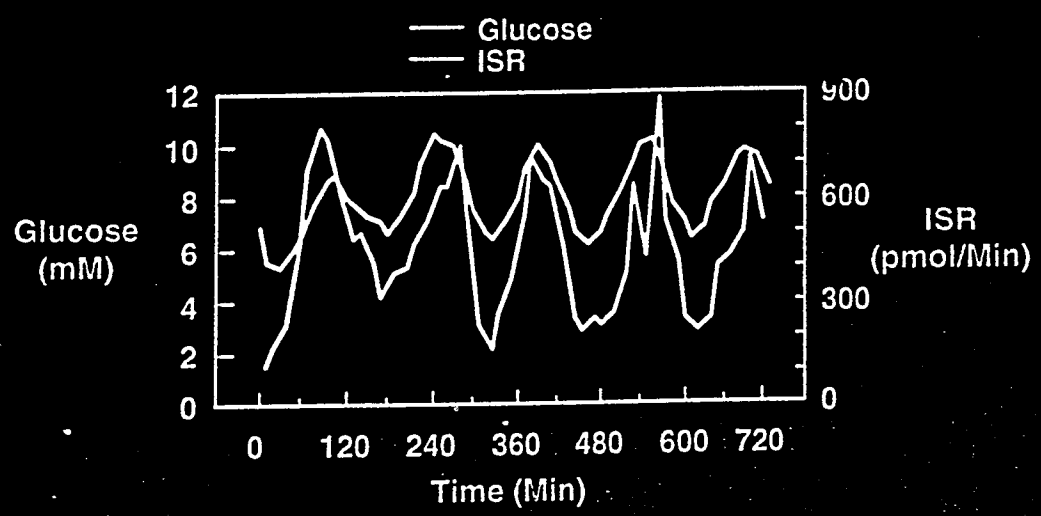
1

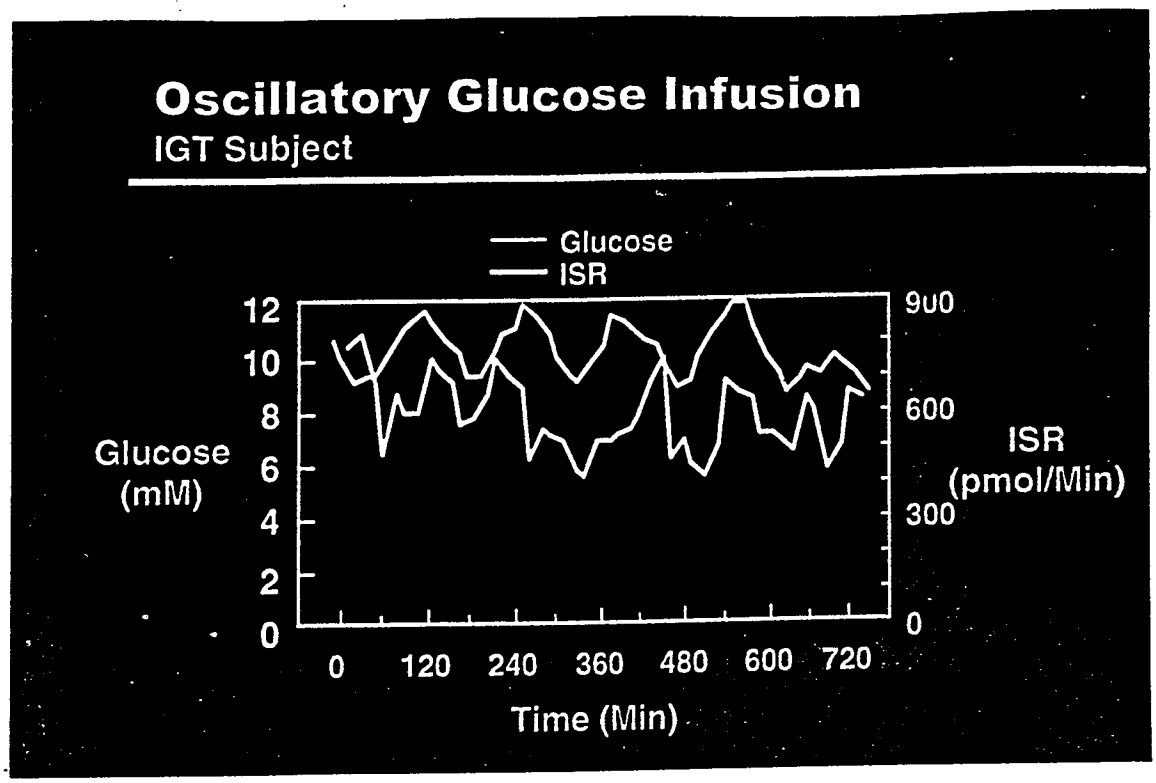
Aims of Study

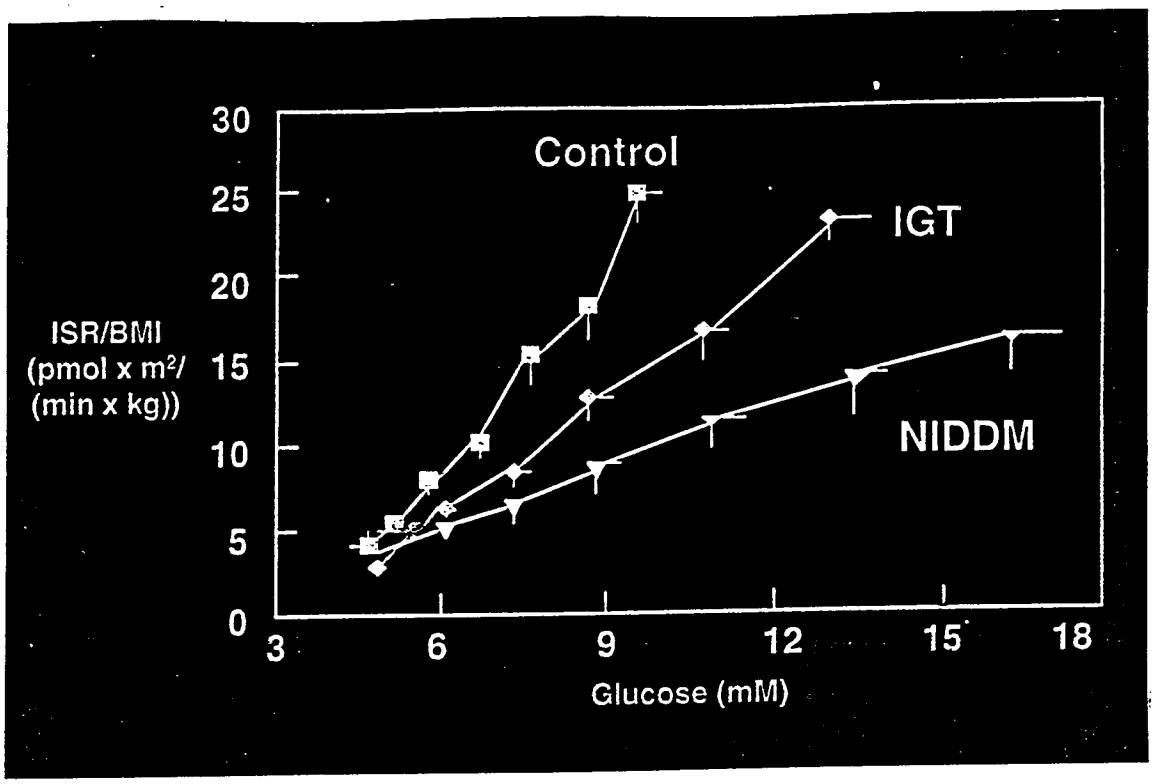
To determine whether the alterations in insulin secretion and β-cell glucose signaling seen in subjects with impaired glucose tolerance are reversible by treatment with troglitazone

Oscillatory Glucose Infusion

Control Subject




Oscillatory Glucose Infusion
IGT Subject
Glucose
ISR
Glucose (mM)
12
10
8
6
4
2
0
900
600
300
0
ISR (pmol/Min)
0
120
240
360
480
600
720
Time (Min)


Control
IGT
NIDDM
ISR/BMI
(pmol x m²/
(min x kg))
30
25
20
15
10
5
0
3
6
9
12
15
18
Glucose (mM)

Study Design

- Randomized double blind placebo controlled trial
- Subjects with IGT (n = 24) were randomly allocated to treatment with placebo or troglitazone (400 mg q d)

Cavaghan MK, et al. *JCI* 110;1997

Clinical Protocols

At baseline and after treatment the following tests were performed

- Frequently sampled IVGTT with tolbutamide
- Entrainment to glucose oscillations
- Insulin secretory response to a graded IV glucose infusion

Cavaghan MK, et al. *JCI* 110;1997

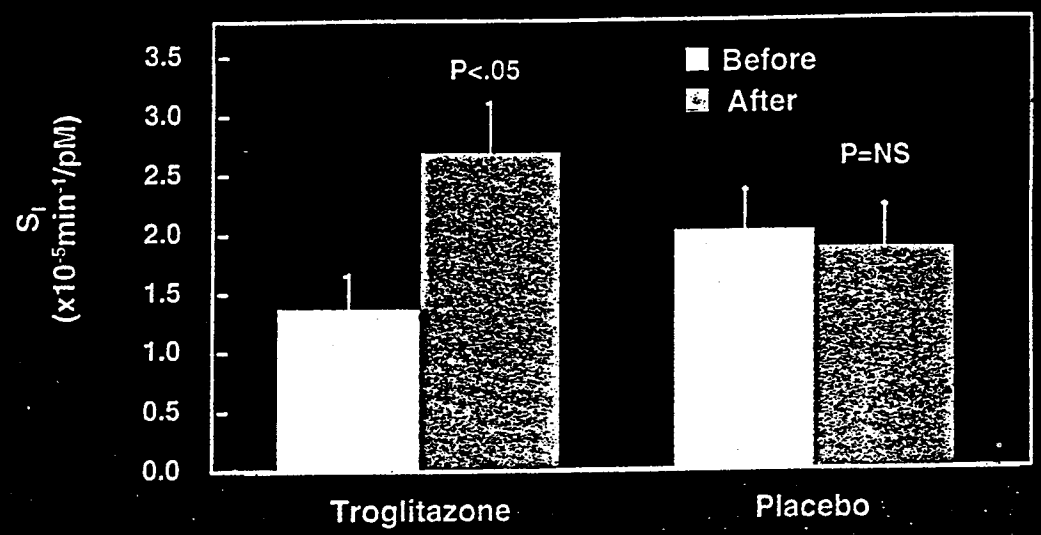
Subject Characteristics

- n = 24 (17 female, 7 male)

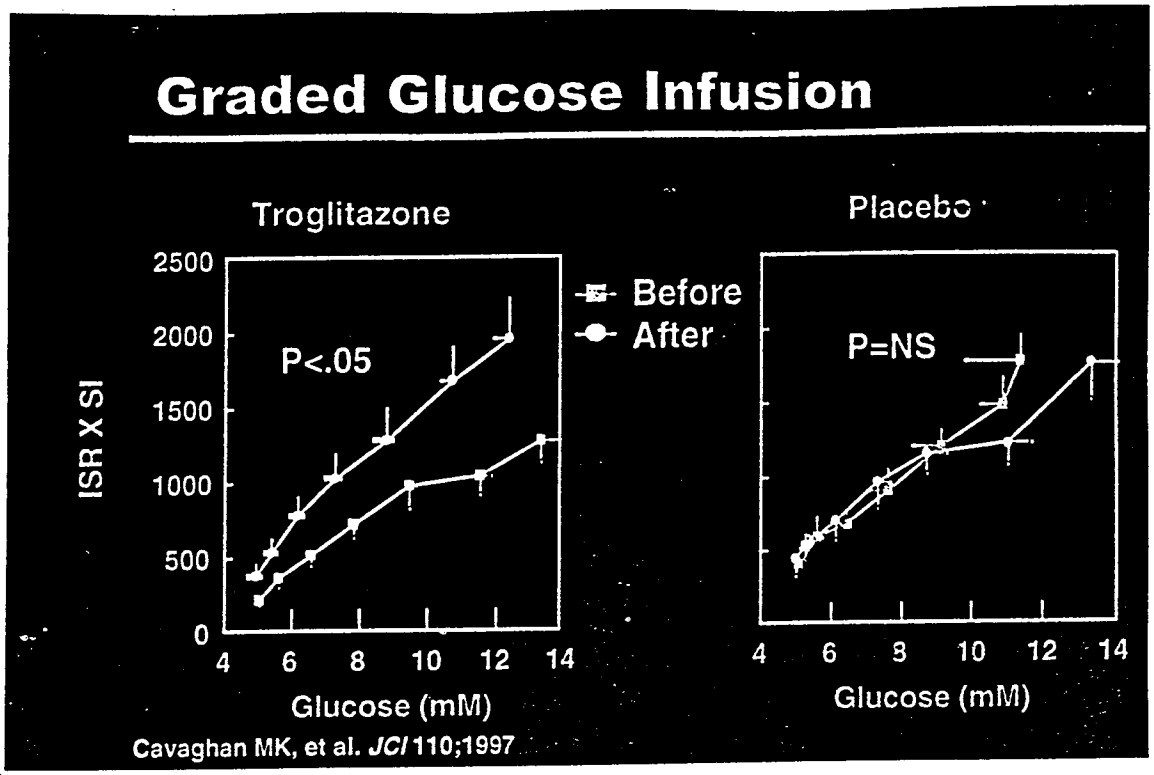
• Age (Yr)	43 ± 3.3
• Weight (kg)	102 ± 3.4
• BMI (kg/m^2)	37 ± 1.32
• HbA1c (%)	6.27 ± 0.18
• Fasting BS (mg/dL)	101 ± 2.7
• 2-h glucose (mg/dL)	186 ± 8.2

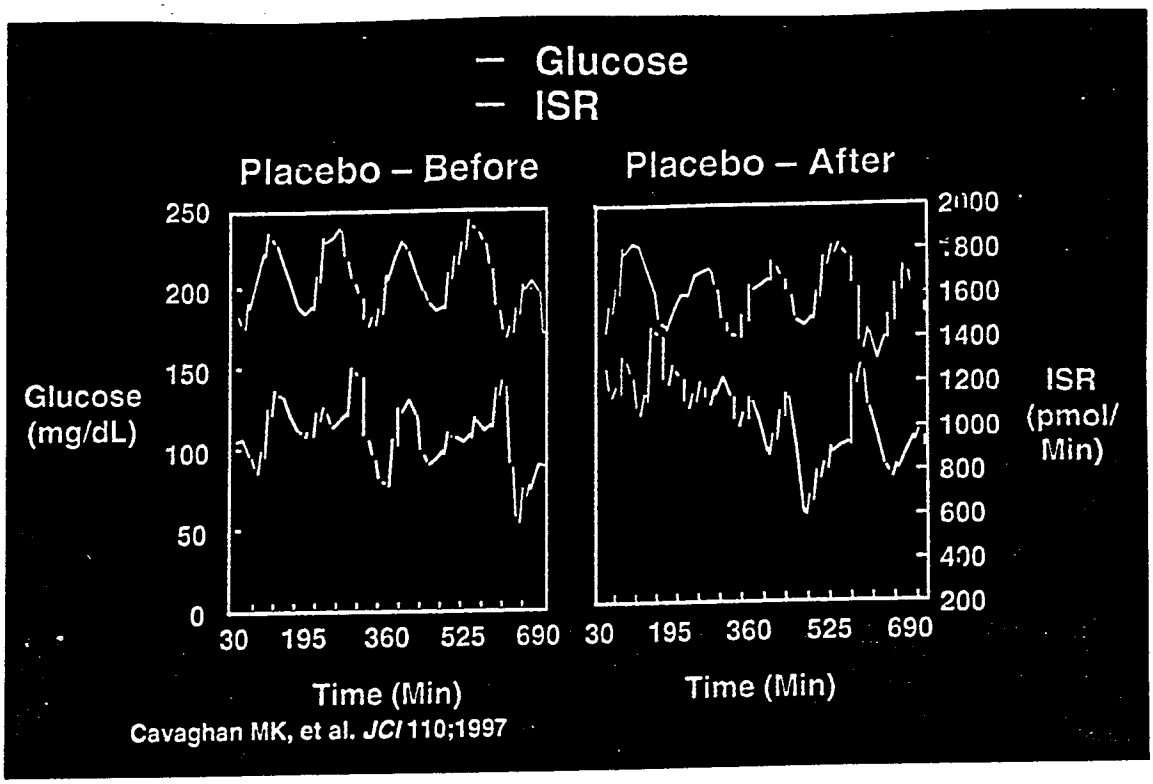
Cavaghan MK, et al. *JCI* 110;1997

Insulin Sensitivity (S_I)

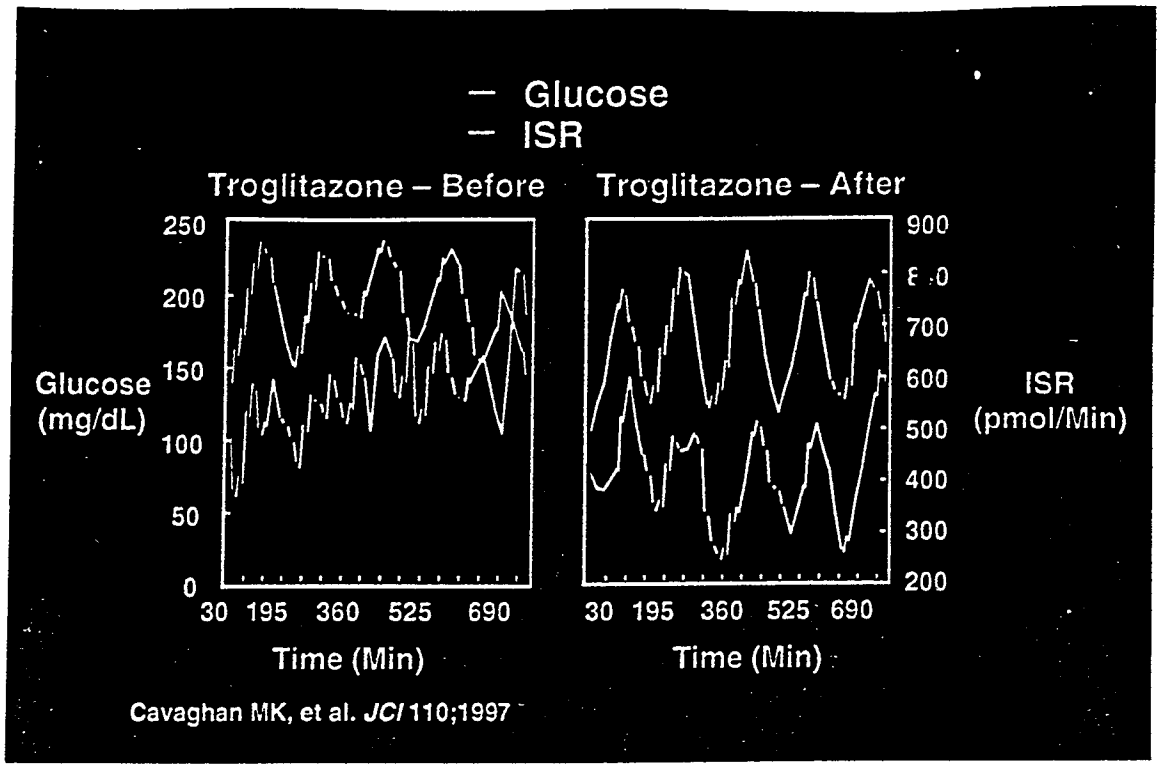


Cavaghan MK, et al. *JCI* 110;1997


Graded Glucose Infusion
Troglitazone
Placebo
ISR X SI
2500
2000
1500
1000
500
0
P<.05
P=NS
Before
After
4
6
8
10
12
14
Glucose (mM)
Cavaghan MK, et al. JCI 110;1997



Cavaghan MK, et al. *JCI* 110;1997


— Glucose
— ISR
Troglitazone – Before
Troglitazone – After
Glucose (mg/dL)
250
200
150
100
50
0
30 195 360 525 690
Time (Min)
30 195 360 525 690
Time (Min)
900
700
600
500
400
300
200
ISR (pmol/Min)
Cavaghan MK, et al. JCI 110;1997

Significant Benefits

- Improvement in glucose control and lowered insulin requirements in patients uncontrolled on insulin
- Significant glucose lowering in patients who fail sulfonylurea/metformin combination
- Significant and sustained glucose lowering in combination with sulfonylurea
- Effective as monotherapy both short- and long-term
- Positive effects on beta cell function

Troglitazone Has Salutary Effects on Atherosclerotic Risk Factors: Lipids

- Decreases free fatty acids
- Decreases triglycerides
- Increases HDL
- Increases LDL particle size
- Decreases LDL oxidation
- Decreases ApoB levels

Troglitazone Has Salutary Effects on Atherosclerotic Risk Factors: Vascular Function

- Decreases PAI-1 activity
- Decreases platelet activation
- Decreases intimal-medial thickening
- Decreases E-selectin levels
- Decreases vascular reactivity
- Increases flow mediated coronary dilation

Beneficial Effects of Troglitazone in Vasospastic Angina Pectoris With Diabetes Mellitus

- Diabetic patients with angiographically documented coronary vasospasm and residual angina pectoris
- Treatment with troglitazone for 4 mos; n = 8
- Anginal episodes assessed at baseline and 4 mos.
- Flow-mediated vasodilation assessed at baseline and 4 mos.

Murakami et al. ACC 1998 (abstract);1162–131.

Beneficial Effects of Troglitazone in Vasospastic Angina Pectoris With Diabetes Mellitus

	Premedication (%)	Postmedication (%)	*P*-Value
AP; Minutes Per Month	72 ± 68	14 ± 17	0.04
Flow-mediated Dilation	4.3 ± 1.4	6.6 ± 1.6	0.03
GTN (Endothelium-independent vasodilation)	11.5 ± 4.3	13.3 ± 2.9	NS

Murakami et al. *ACC.* 1998 (abstract):1162–131.

Significant Benefits

- Improvement in glucose control and lowered insulin requirements in patients uncontrolled on insulin
- Significant glucose lowering in patients who fail sulfonylurea/metformin combination
- Significant and sustained glucose lowering in combination with sulfonylurea
- Effective as monotherapy both short- and long-term
- Positive effects on beta cell function and atherosclerotic risk factors

Comparison of Reduction in Risk

	Type 2 UKPDS	Type 1 DCCT	Rezulin Model
Microvascular Disease	21%	76%	51%

Significant Benefits

- Improvement in glucose control and lowered insulin requirements in patients uncontrolled on insulin
- Significant glucose lowering in patients who fail sulfonylurea/metformin combination
- Significant and sustained glucose lowering in combination with sulfonylurea
- Effective as monotherapy both short- and long-term
- Positive effects on beta cell function and atherosclerotic risk factors
- Projected risk reduction for microvascular endpoints

Summary of Risk - Benefit Assessment

Robert Zerbe, MD
Sr. Vice-President, Clinical Research
and Development
Parke-Davis

Questions for Consideration

1. Does Rezulin play a causative role in cases of severe hepatotoxicity?
2. What is the risk of such events?
3. How does this risk compare to that of other therapies?
4. What are the benefits of Rezulin?
5. Is the risk:benefit ratio for Rezulin favorable?
6. What additional steps can be taken to further improve both safety and efficacy of Rezulin?

1. Does Rezulin Play a Causative Role in Cases of Severe Hepatotoxicity?

- The data indicate that Rezulin is associated with rare cases of idiosyncratic liver failure

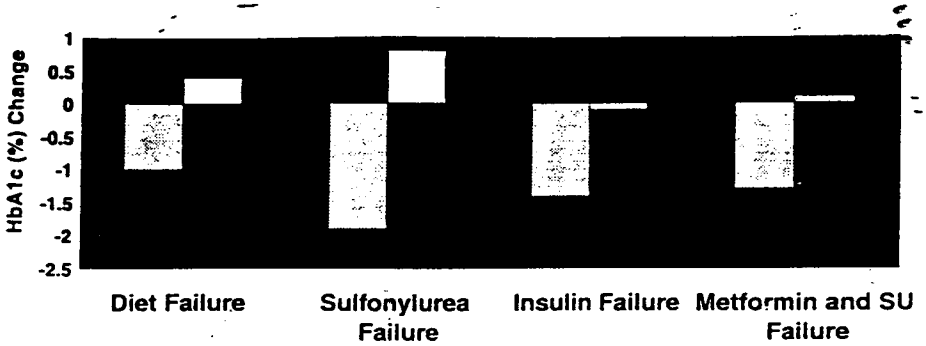
2. What Is the Risk of Such Events?

- The risk is low, and has decreased since monitoring was implemented

3. How Does the Risk Compare to That of Other Therapies?

- Though the pathologies differ from drug to drug, all of the available treatments for type 2 diabetes, including Rezulin, carry a similar, albeit small, risk of death

Efficacy of Rezulin



* $P < 0.05$

4. What Are the Benefits of Rezulin?

- Efficacy has been demonstrated in a spectrum of combinations as well as monotherapy. It's unique mechanism of action is complementary and appears to be preserving endogenous pancreatic function, which translates into better and longer lasting control.

5. Is the Risk:Benefit Ratio for Rezulin Favorable?

- Risk is low and comparable to alternative therapies
- Benefit is complementary and unique, adding significantly to the therapeutic armamentaium in a life threatening disease
- Risk:benefit is surely acceptable given this uniqueness of benefit

6. What Additional Steps can be Taken to Further Improve Both Safety and Efficacy of Rezulin?

- Warn against the use in patients with pre-existing liver disease
- Refine trial period and patient definition for monotherapy
- Patient package insert
- Expand education program
- Clinical Studies to identify greatest benefit

Hepatic Events in oral antidiabetic – exposed patients in a Midwestern employer claims database (preliminary data)

Judith K. Jones, MD, PhD
The Degge Group, Ltd.
March 26, 1999

PRELIMINARY DATA: NOT FOR QUOTATION

Midwestern Employer Database Study

- Population of 1.6 million persons in midwestern employer insurance database (1994-1998)
- 14,379 persons exposed to oral antidiabetics
- 10,713 persons with exposed from 1/1/95 through 9/30/98 with at least 6 months eligibility prior to first Rx and eligible for all benefits during period:
  - **New Diabetics (ND): no prior oral antidiabetics**
  - **Established Diabetics(ED): prior oral antidiabetic therapy**

PRELIMINARY DATA: NOT FOR QUOTATION

Midwest Employer Database
Methods

- All patients were followed from first Rx for each antidiabetic to end of eligibility period
- Counted if prior Rx in last 60 days
- Cohorts examined by drug exposure, thus not mutually exclusive
- Thus New Diabetic for Drug 1 would be Established
- Diabetic for next antidiabetic Rx
- All health care utilization, hepatic events and liver function monitoring identified for each patient by both calender and therapy month

PRELIMINARY DATA: NOT FOR QUOTATION

Midwest Employer Database

Study Population

[Each cohort not mutually exclusive]

10,713 Diabetics on Oral Therapy 1995-98

Glyburide	Glipizide	Metformin	Troglitazone	Acarbose
522 EDs 2130 NDs	1136 EDs 2153 NDs	4393 EDs 1363 NDs	2471 EDs 217 NDs	612 EDs 109 NDs

Overall demographics:

~ 42 % Female; 58% Males for each

Age < 20: < 1%

20-39 2.4-3.7%

40-59 68-74%

60-64 21-29%

[Age > 65 not reliably covered for Rx]

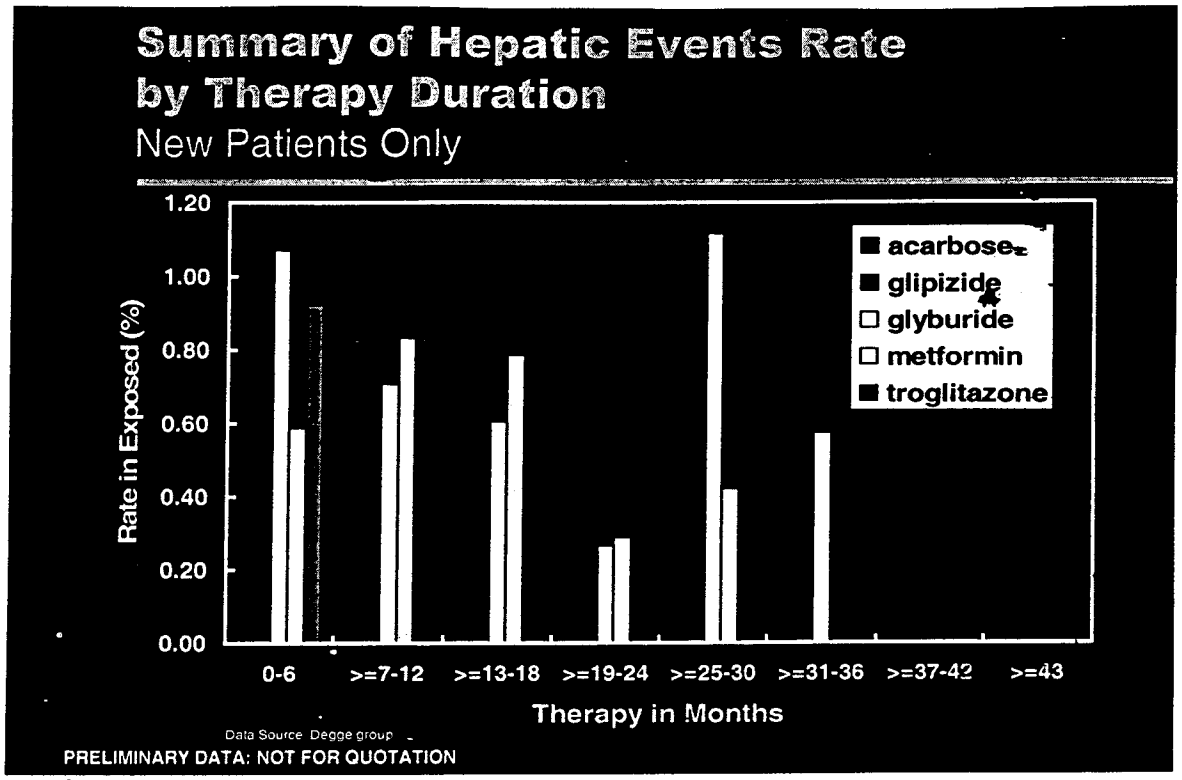
PRELIMINARY DATA: NOT FOR QUOTATION

ICD-9CM CODES

- 570 -Acute and subacute Necrosis of Liver
- 572.2- Hepatic Coma
- 573.3- Hepatitis, Unspecified
- 573.9- Liver Disorder, Unspecified
- 782.4- Jaundice
- E932.3- Adverse Effects In Diabetic Due to Diabetic Medication

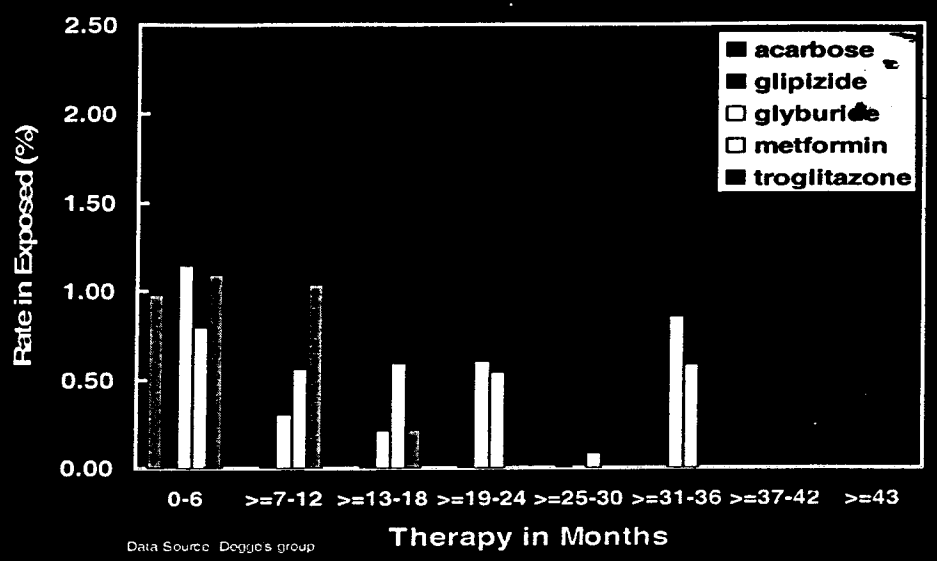
Source: International Classification of Diseases(ICD-9-CM) 1998 Edition

PRELIMINARY DATA: NOT FOR QUOTATION


Summary of Hepatic Events Rate
by Therapy Duration
New Patients Only
1.20
1.00
0.80
0.60
0.40
0.20
0.00
Rate in Exposed (%)
acarbose
glipizide
glyburide
metformin
troglitazone
0-6
>=7-12
>=13-18
>=19-24
>=25-30
>=31-36
>=37-42
>=43
Therapy in Months
Data Source Degge group
PRELIMINARY DATA: NOT FOR QUOTATION

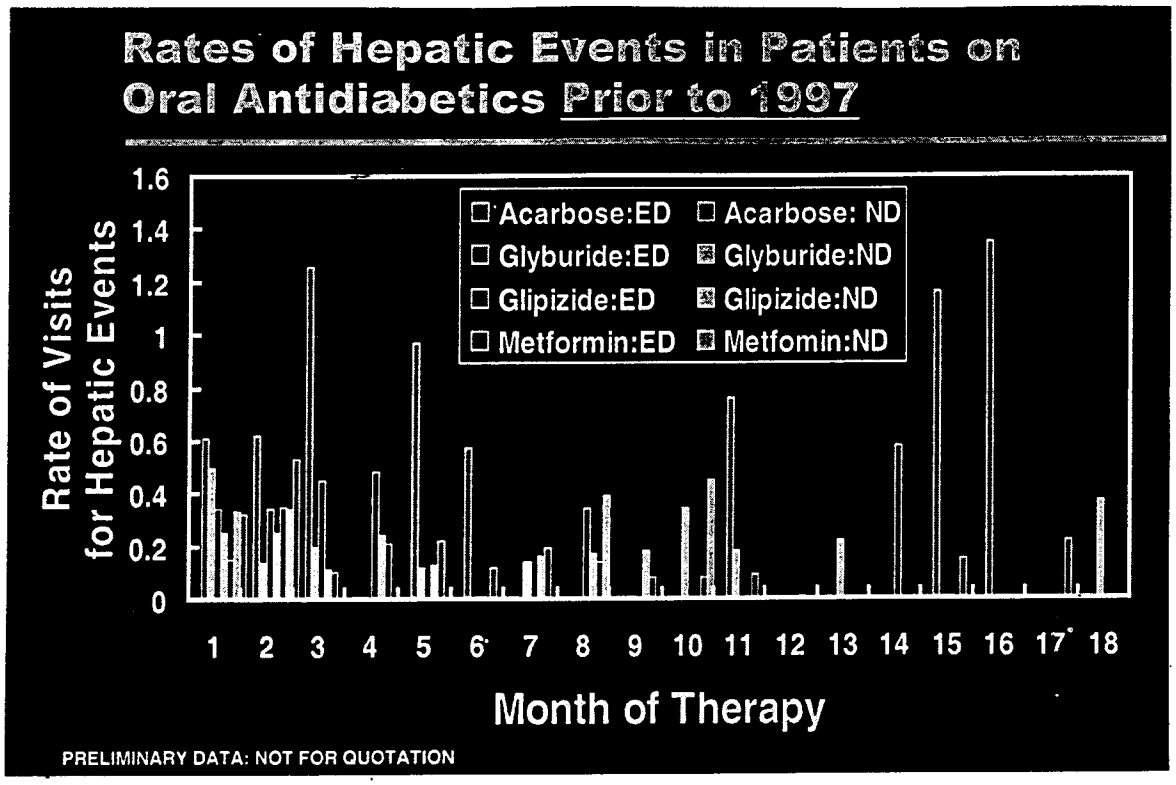
Summary of Hepatic Events Rate by Therapy Duration

Established Patients Only



Data Source: Doggies group

PRELIMINARY DATA: NOT FOR QUOTATION


Rates of Hepatic Events in Patients on Oral Antidiabetics Prior to 1997
Rate of Visits for Hepatic Events
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Acarbose:ED
Acarbose: ND
Glyburide:ED
Glyburide:ND
Glipizide:ED
Glipizide:ND
Metformin:ED
Metfomin:ND
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Month of Therapy
PRELIMINARY DATA: NOT FOR QUOTATION

Cases of Hepatic Necrosis, Coma or Jaundice

Oral Antidiabetic-Exposed Patients
Midwestern Database

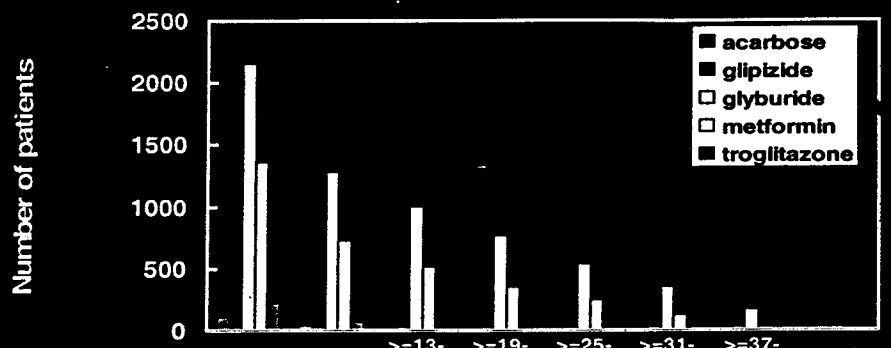
		ICD 9 Code Group			
Exposure Group	N	Transplant	Necrosis	Coma	Jaundice
Glyburide	2652	1	-	-	4
Glipizide	3289	-	3	1	2
Metformin	5756	-	1	1	5
Troglitizone	2688	-	-	-	1*
Acarbose	721	-	-	-	1

*2 Other cases occurred before troglitazone available.

PRELIMINARY DATA: NOT FOR QUOTATION

Summary of Number of Patients Exposed by Therapy Duration

New Patients Only



	0-6	>=7-12	>=13-18	>=19-24	>=25-30	>=31-36	>=37-42	>=43
acarbose	109	38	18	10	5			
glipizide	2130	1218	992	773	591	385	214	33
glyburide	2153	1274	994	760	538	350	167	21
metformin	1363	723	510	350	238	122	25	
troglitazone	217	70	13					

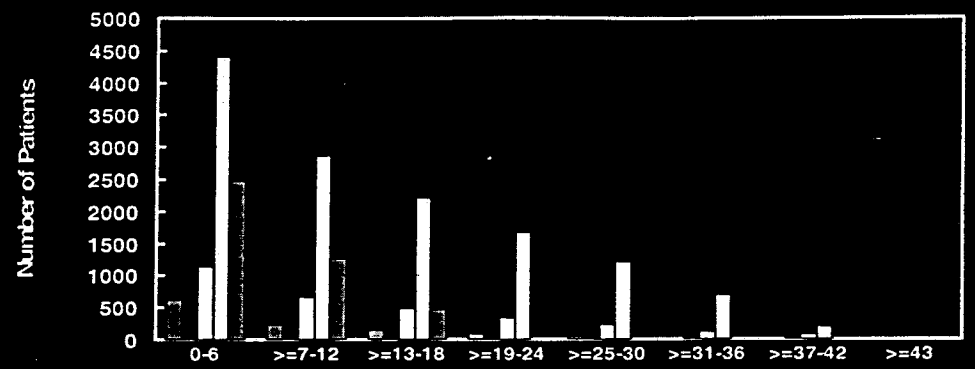
Data Source: Degge group

Therapy Duration in Months

PRELIMINARY DATA: NOT FOR QUOTATION

Summary of Number of Patients Exposed by Therapy Duration

Established Patients Only



	0-6	>=7-12	>=13-18	>=19-24	>=25-30	>=31-36	>=37-42	>=43
acarbose	612	220	139	78	45			
glipizide	522	287	225	154	114	78	44	4
glyburide	1136	662	473	333	223	117	64	3
metformin	4393	2867	2210	1665	1205	691	194	
troglitazone	2471	1256	465					

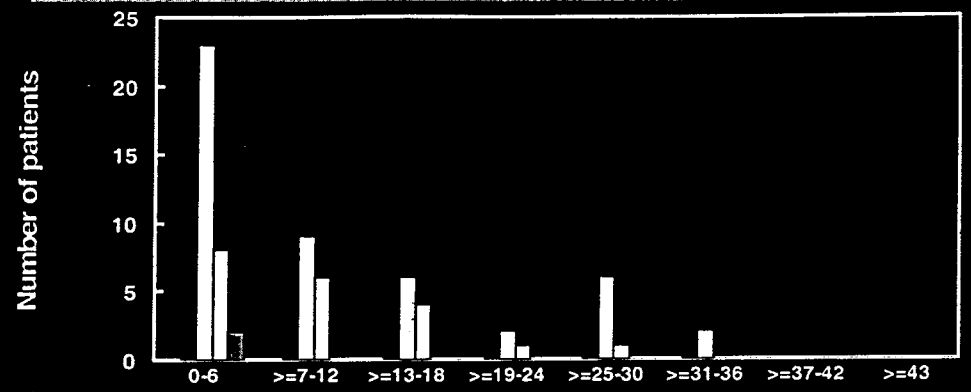
Data Source Degge group

Therapy Duration in Months

PRELIMINARY DATA: NOT FOR QUOTATION

Summary of Hepatic Events by Therapy Duration

New Patients Only



	0-6	>=7-12	>=13-18	>=19-24	>=25-30	>=31-36	>=37-42	>=43
acarbose								
glipizide	17	5	4	5	3	2		
glyburide	23	9	6	2	6	2		
metformin	8	6	4	1	1			
troglitazone	2							

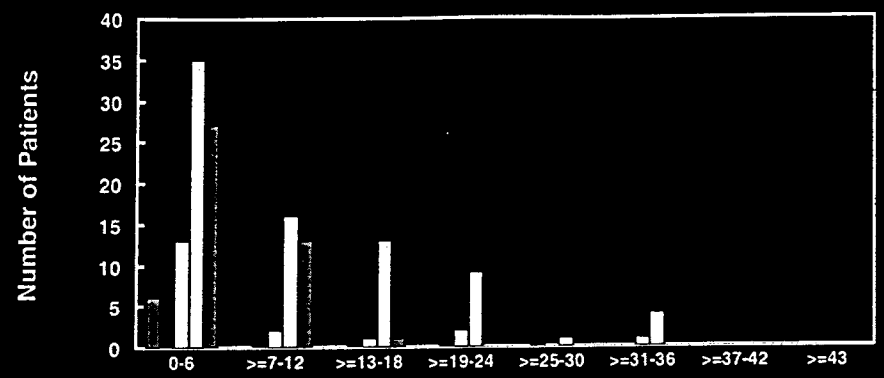
Therapy Duration in Months

Data Source Degge group

PRELIMINARY DATA: NOT FOR QUOTATION

Summary of Hepatic Events by Therapy Duration

Established Patients Only



	0-6	>=7-12	>=13-18	>=19-24	>=25-30	>=31-36	>=37-42	>=43
acarbose	6							
glipizide	7	1	5	1	1			
glyburide	13	2	1	2		1		
metformin	35	16	13	9	1	4		
troglitazone	27	13	1					

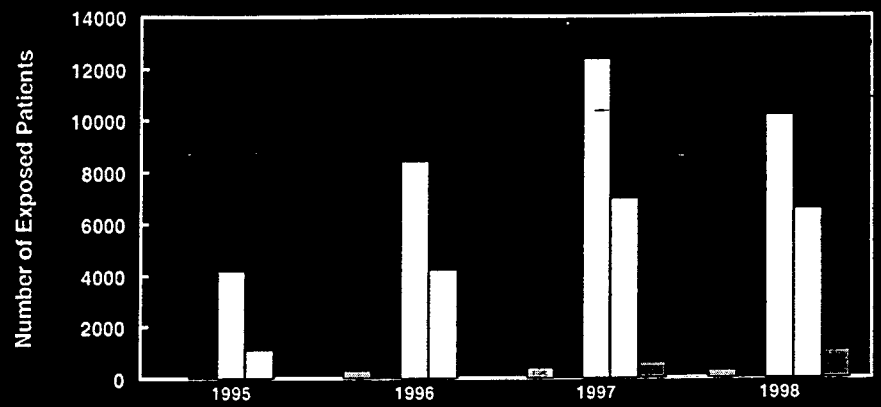
Data Source: Doggies group

Therapy Duration in Months

PRELIMINARY DATA: NOT FOR QUOTATION

Summary of Hepatic Data of Total Patient Exposure by Calendar Year

New Patients Only

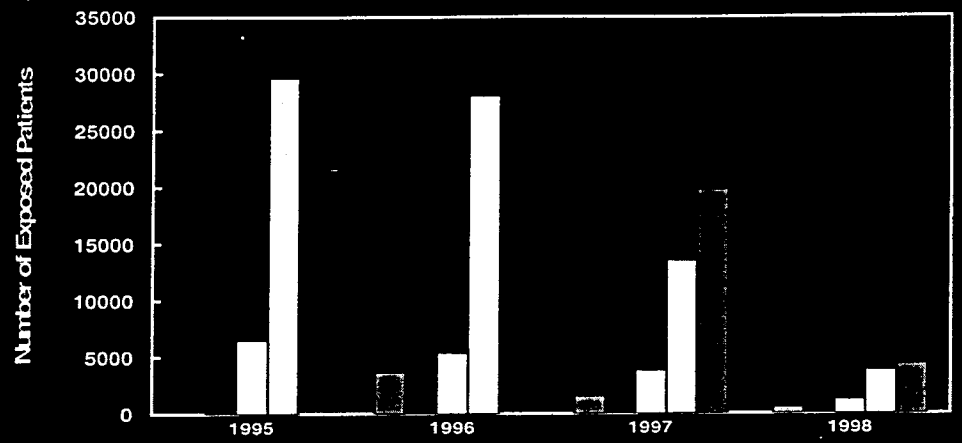


	1995	1996	1997	1998
Acarbose	0	270	372	284
Glipizide	5296	9307	11342	8737
Glyburide	4168	8384	12347	10161
Metformin	1077	4183	6940	6546
Troglitazone	0	0	584	1068

PRELIMINARY DATA: NOT FOR QUOTATION

Summary of Hepatic Data by First Therapy Start Year

Established Patients Only

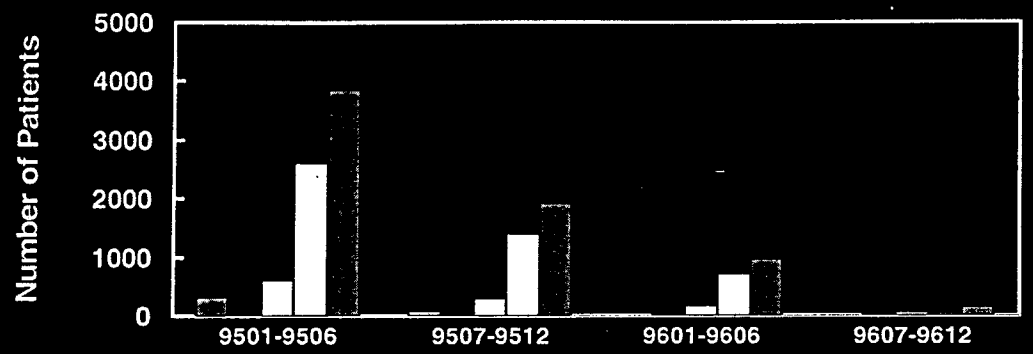


	1995	1996	1997	1998
Acarbose	13	3636	1535	542
Glipizide	3860	2280	1364	389
Glyburide	6466	5349	3779	1205
Metformin	29602	28049	13504	3813
Troglitazpne	0	0	19769	4321

PRELIMINARY DATA: NOT FOR QUOTATION

Summary of Number of Patients Exposed by Therapy Duration

Established Patients Only



	9501-9506	9507-9512	9601-9606	9607-9612
acarbose	315	67		
glipizide	327	158	91	39
glyburide	593	292	163	63
metformin	2605	1392	700	44
Grand Total	3840	1909	954	146

Data Source: Degge group

Therapy Duration in Months

PRELIMINARY DATA: NOT FOR QUOTATION