CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ENDOCRINOLOGIC and METABOLIC DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 11/19/97

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SLIDES

PRANDIN™ (Repaglinide) TABLETS
NDA 20-741

Introduction

Barry Reit, Ph.D.

Novo Nordisk

Therapeutic Need, 1988

"In general, older patients have more renal failure and cardiovascular and hepatic problems, as well as a tendency to skip meals and snacks. For this reason, it is best to choose an agent with relatively short duration of action, which is less likely to cause profound hypoglycemia."

Ref.: Physician's Guide to Non-Insulin-Dependent (Type II) Diabetes; Diagnosis and Treatment (Second Edition) p.39. ***ADA-CEP*** *1984,1988.*

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Need Continues, 1994

"Severe hypoglycemia is the major complication of sulfonylurea therapy... Elderly patients are more susceptible to hypoglycemia, particularly when they have a tendency to skip meals or when renal function is impaired."

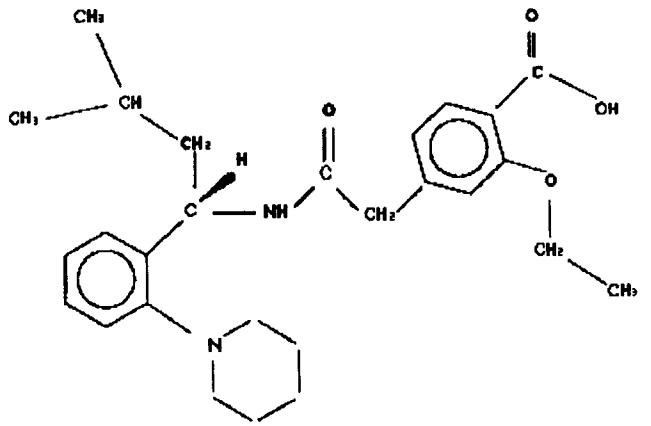
Ref.: Medical Management of Non-Insulin-Dependent (Type II) Diabetes; (Third Edition) p.41. ***ADA-CEP*** *1994.*

Novo Nordisk

Drug Substance

Chemical name: (*S*)-2 ethoxy-4(2[[3-methyl-1-[2-(1-piperidinyl) phenyl]-butyl]-amino]-2 oxoethyl] benzoic acid

INN name: repaglinide



One asymmetric carbon

(*S*)-enantiomer active

Strongly pH-dependent solubility

Highly lipophilic

Discovered by Dr.Karl Thomae GmbH,1986

Drug Product - PRANDIN™

- Formulation: Spray dried granulate with solubilizing agent
- Compressed tablets - 0.5, 1.0, and 2.0 mg
- pH-independent dissolution profile at pH 1-7
- Rapid disintegration and dissolution rate

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Proposed Indication and Usage

Prandin will be indicated...

". . . . as an adjunct to diet and exercise to lower blood glucose in patients with type 2 (non-insulin dependent) diabetes mellitus whose hyperglycemia cannot be controlled satisfactorily by diet and exercise alone."

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NDA Milestones

- U.S. IND filed - March 2, 1992
- End of phase II meeting - December 20, 1994
- Pre-NDA meeting - January 23, 1997
- NDA submitted - June 27, 1997
- Priority review - August 15, 1997
- Safety update submitted - October 14, 1997
- Advisory Committee Meeting - November 19, 1997

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Agenda

- Introduction
  - Barry Reit, Ph.D., Regulatory Affairs
- Pharmacology
  - Jannie Fuhlendorff, Ph.D., Diabetes Biology
- Preclinical Safety
  - Frederick Reno, Ph.D., Consultant in Toxicology
- Clinical Pharmacology & Efficacy
  - Poul Strange, M.D., Ph.D., Clinical Development
- Clinical Safety
  - Martin Edwards, M.D., Clinical Development

PRANDIN (Repaglinide) TABLETS
NDA 20-741

Pharmacology

Jannie Fuhlendorff, Ph.D.

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Preclinical Pharmacology

- Potent insulin secretagogue
- Mechanism is via the ATP-sensitive potassium channel; does not cause direct exocytosis
- Distinct binding sites
- Glucose dependent insulin secretion (no secretion at 0 mM glucose)
- No inhibition of proinsulin biosynthesis

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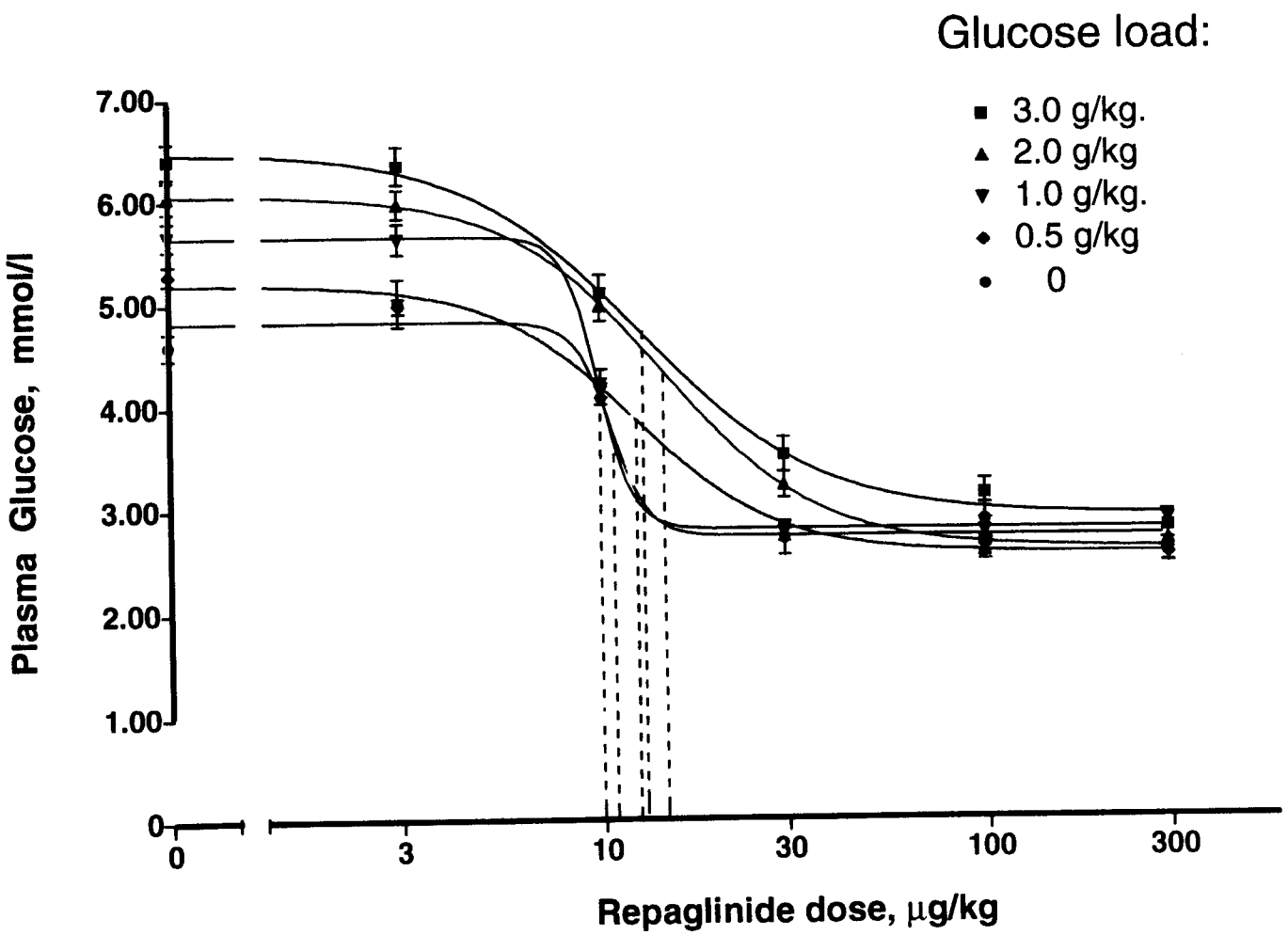
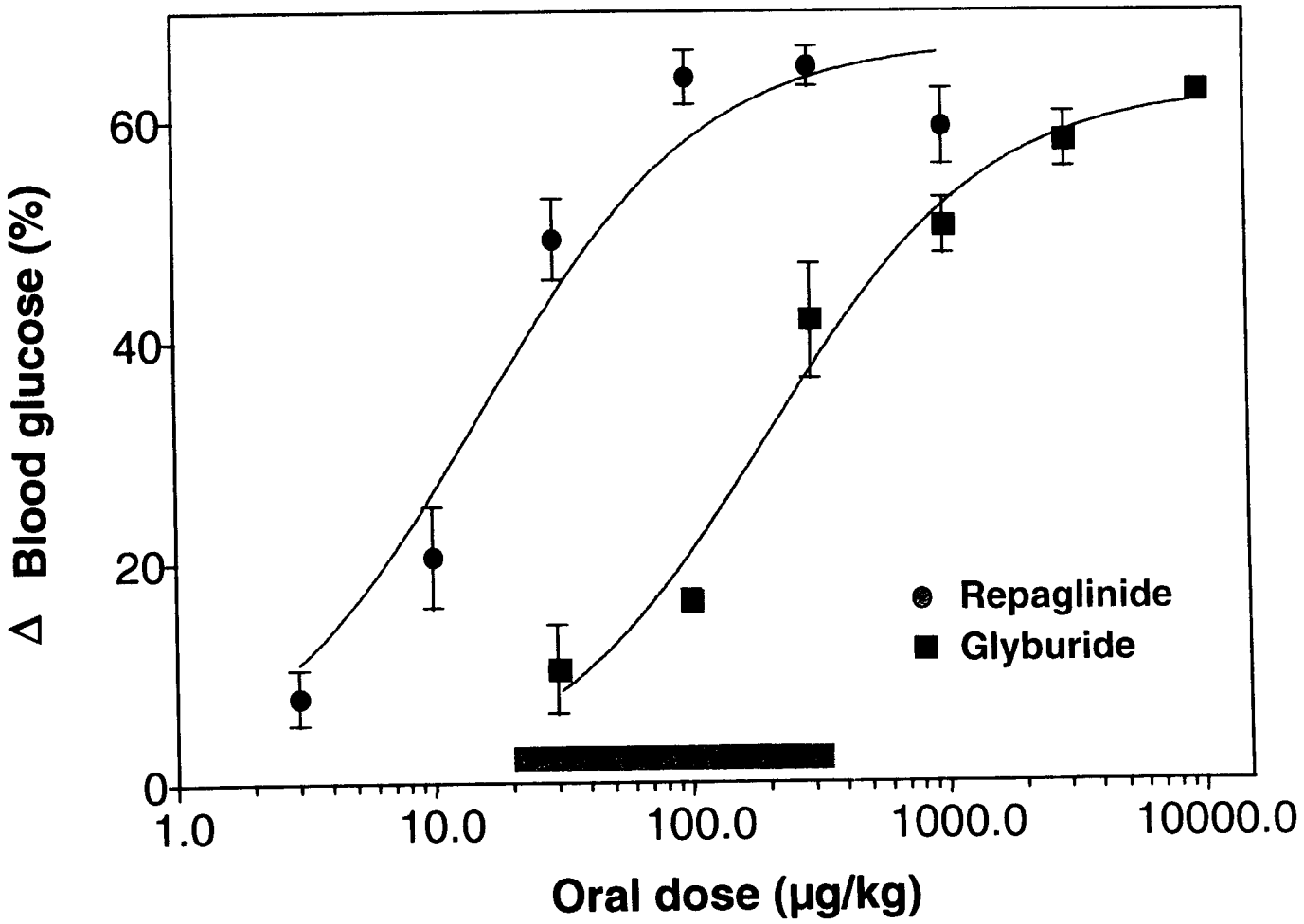
Fasted Glucose Loaded Rats



In vivo Potency: Blood Glucose

Normal fed rats after oral dosing



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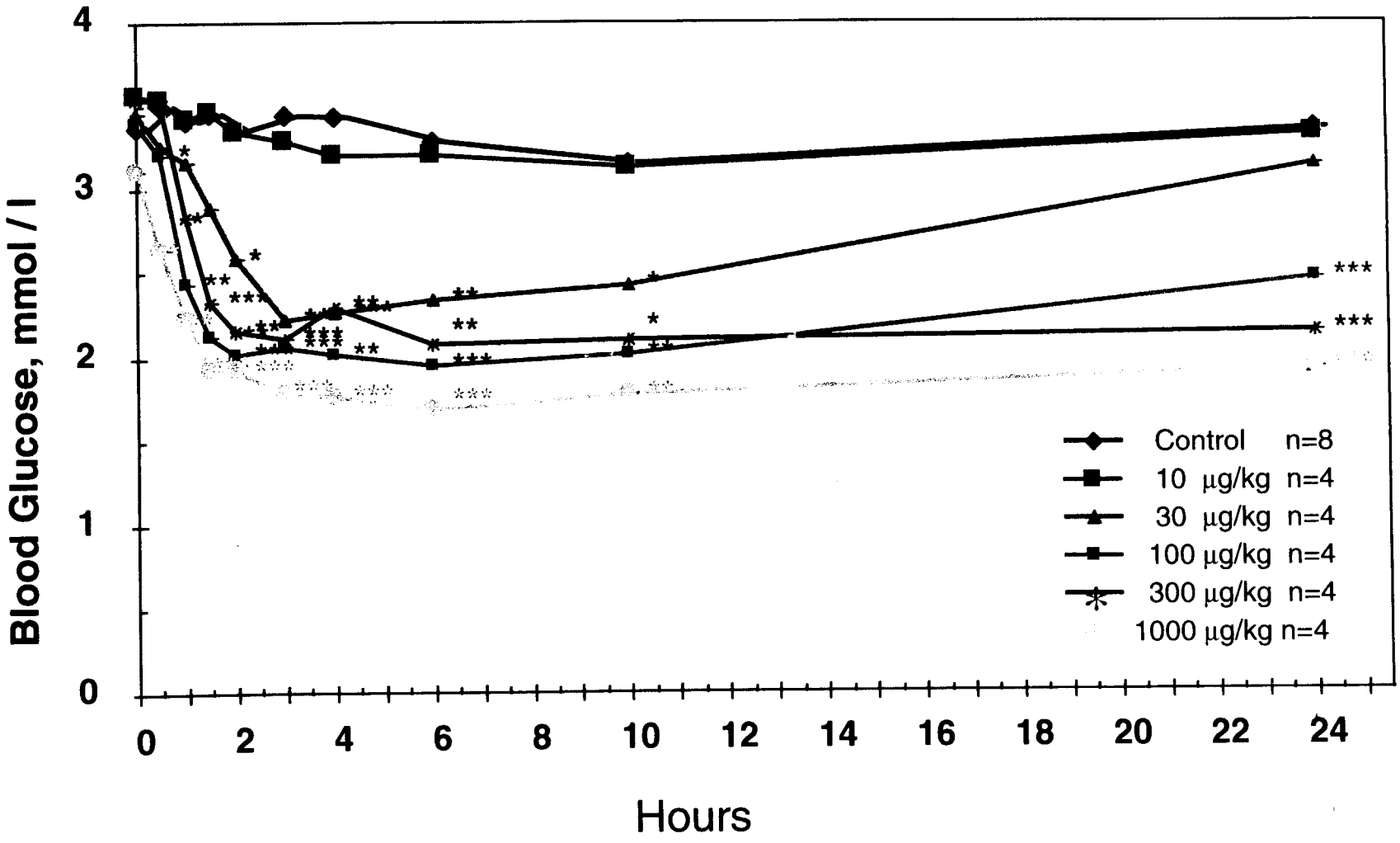
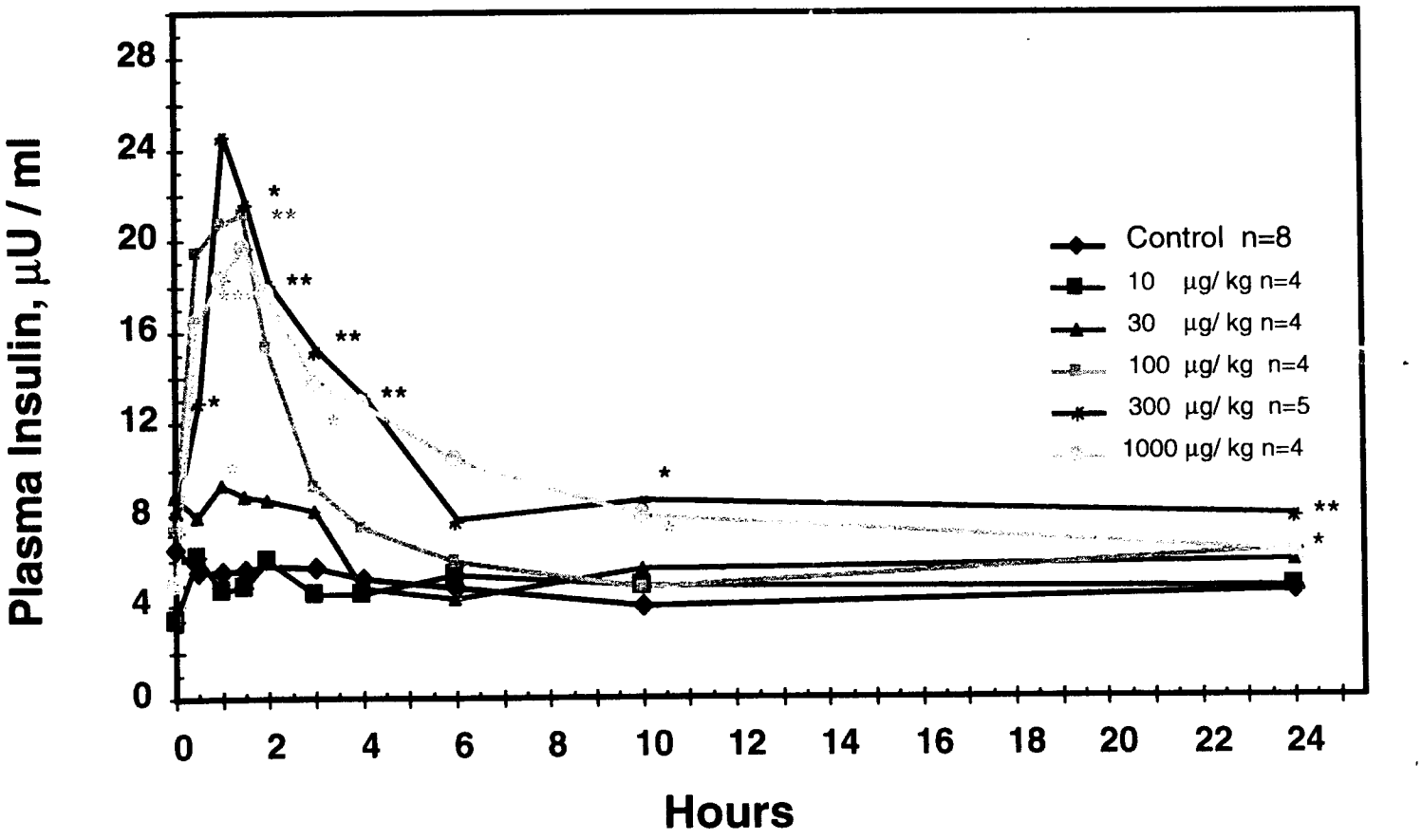
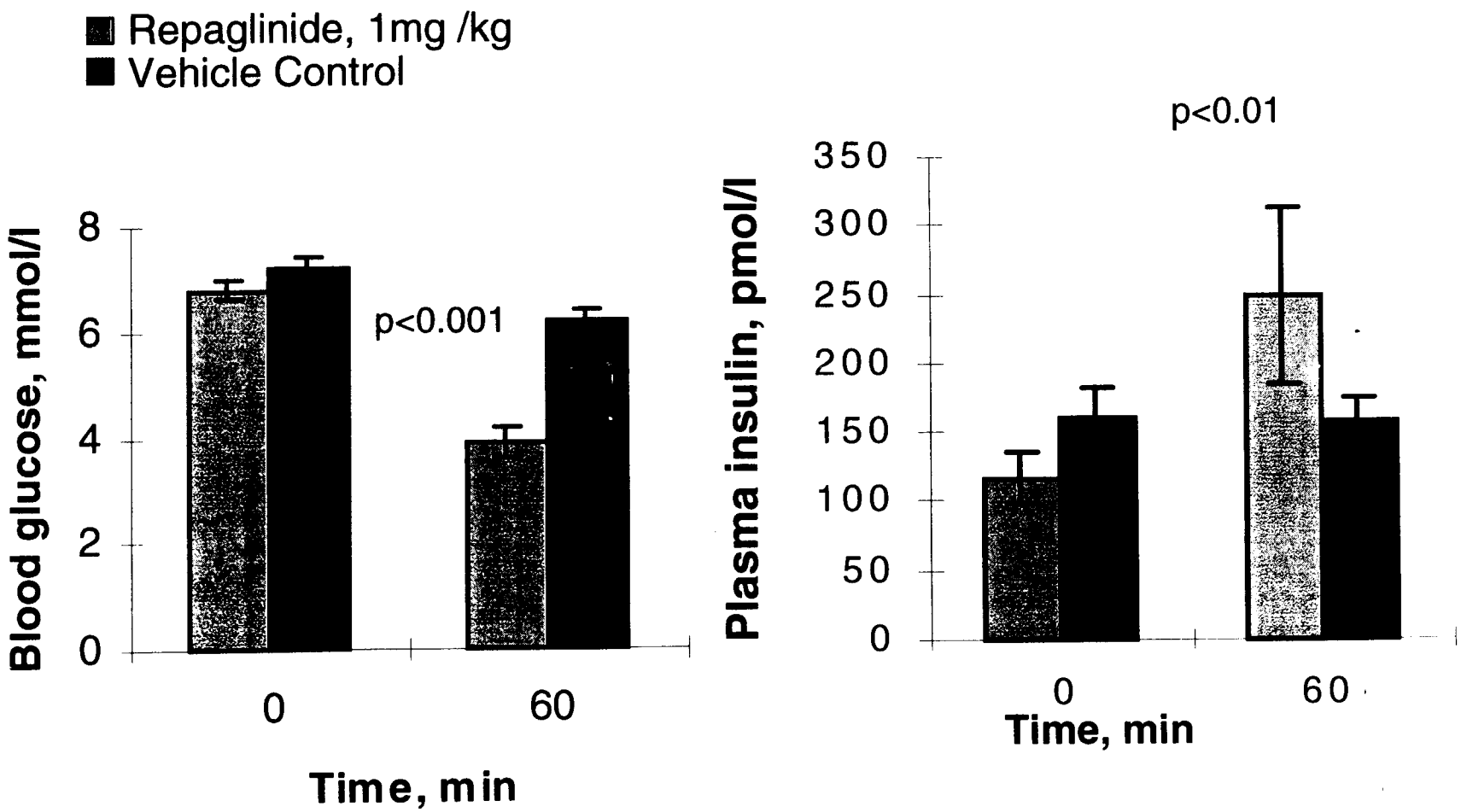
Dose Response, Fasted Dogs



Plasma Insulin Response, Fasted Dogs



Type 2 Rat Model (Low dose STZ)



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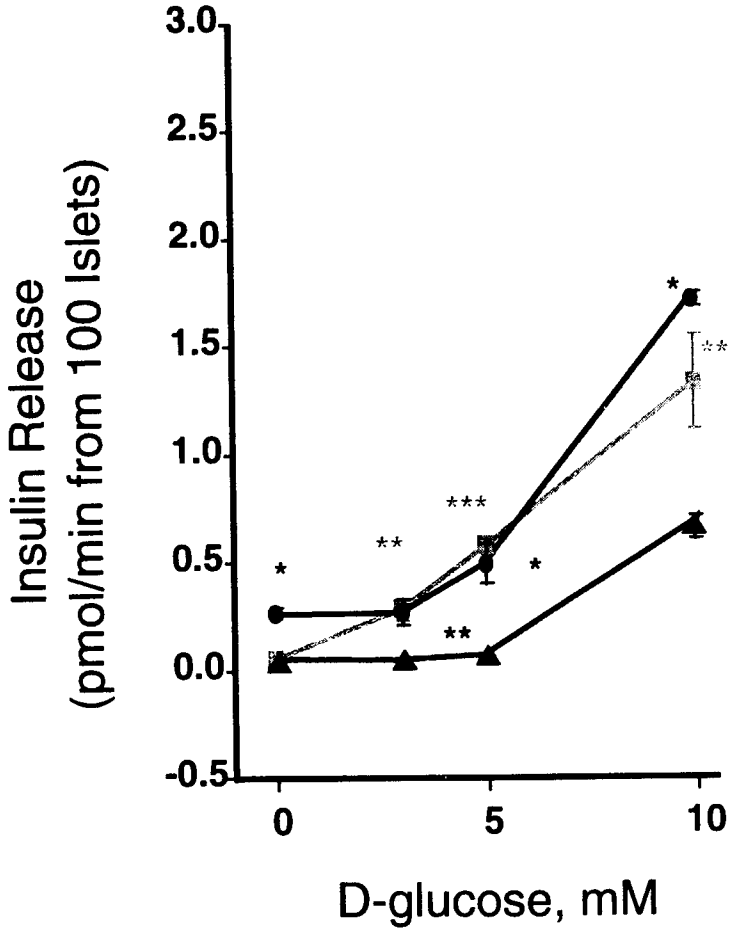
Glucose Dependent Insulin Secretion



Perifused Mouse Islets

- Repaglinide, 40 nM
- **Glyburide, 200 nM**
- **Control**

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Receptor Binding Studies

Differentiation of sites in whole βTC3-Cells

- Using two radioligands:
  [^{3}H]repaglinide and [^{3}H]glyburide
- Using potassium channel modulators:
  (+)-PPP
  haloperidol
  (+)-pentazocin
  DTG: di-orthotolyl-guanidine

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Three Binding Sites Identified:

1. High affinity site for repaglinide (3.6 nM), lower affinity for glyburide, (+)-PPP insensitive
   Corresponds to the *in vivo* potency
2. Low affinity for repaglinide (549 nM), high affinity for glyburide (25.2 nM), (+)-PPP sensitive
3. Common high affinity site for repaglinide and glyburide (8.2 nM), (+)-PPP sensitive

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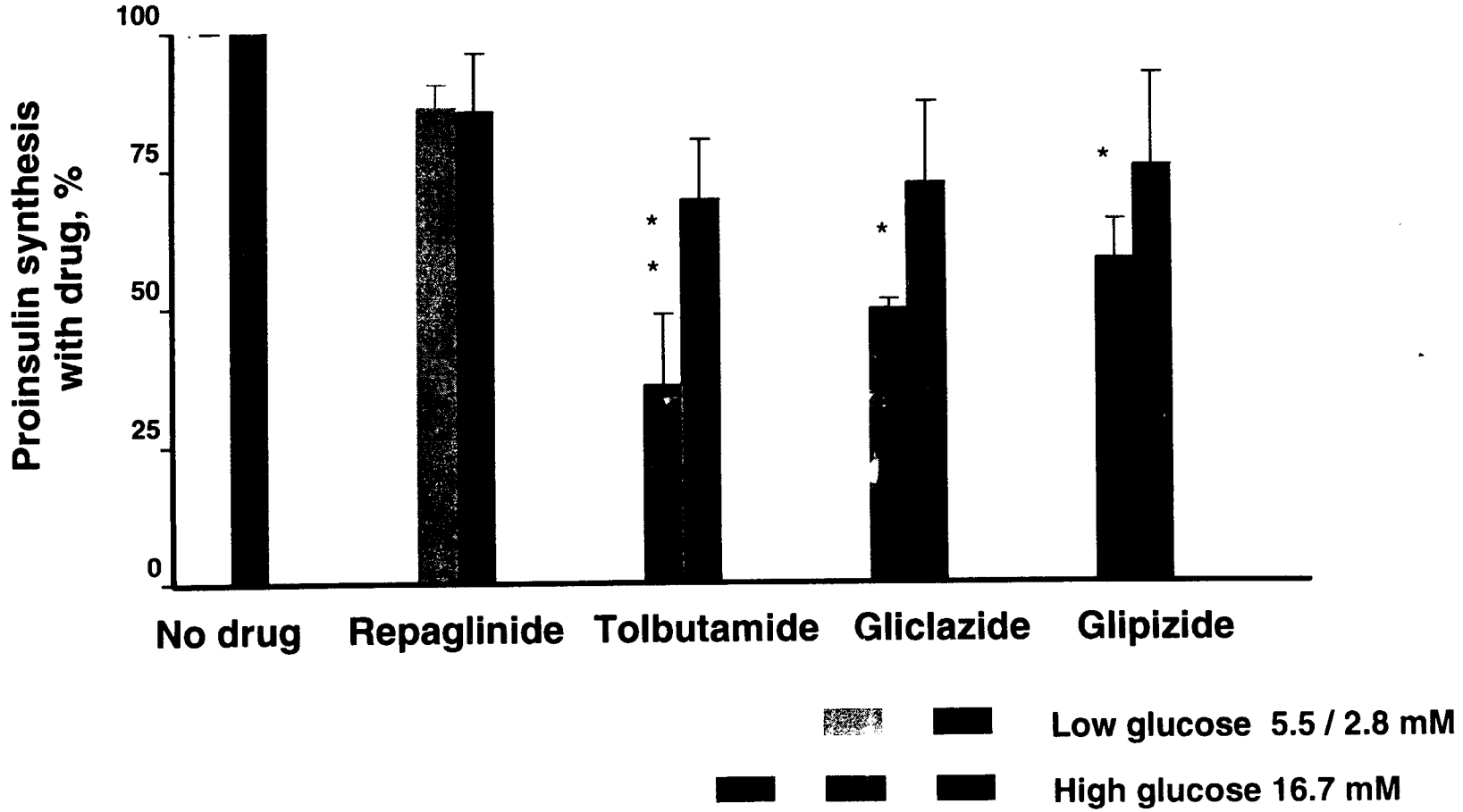
Binding Sites IC_{50} (βTC3 cells)

	[^{3}H] Repaglinide	[^{3}H] Glyburide
Repaglinide	3.4 nM	34000 nM
Glyburide	15 nM	26 nM
Glipizide	20 nM	71 nM
Glibornuride	47 nM	760 nM
Tolbutamide	ND	71000 nM

No Suppression of Biosynthetic Activity



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Exocytosis in Patch Clamped Mouse β-cells

- No exocytosis with 100 nM - 5000 nM repaglinide

Contrary to clinically relevant concentrations of:

Glyburide	100 nM
Glipizide	1000 nM
Tolbutamide	100000 nM

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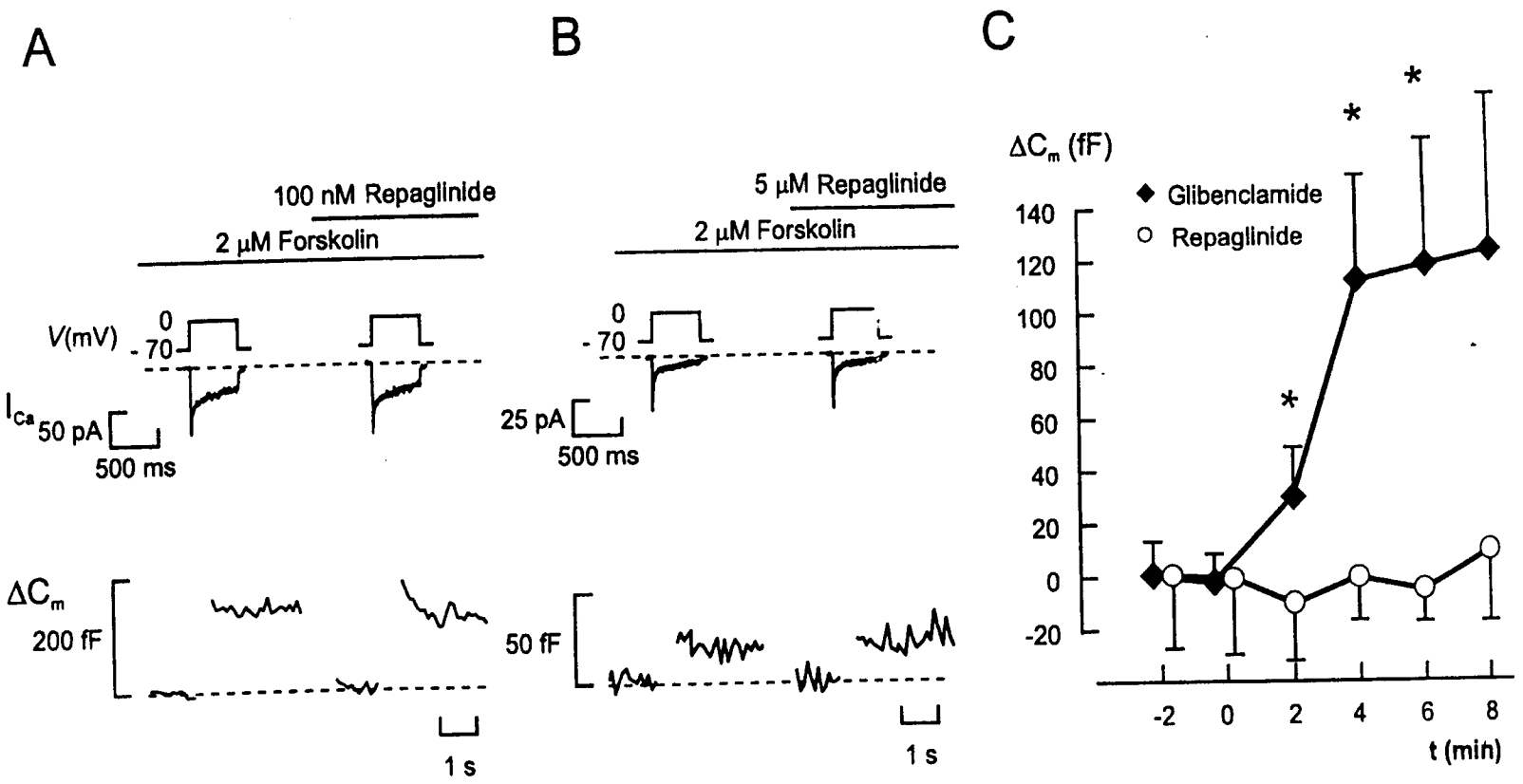
No Direct Exocytosis in Patch-clamped β-Cells



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Conclusion Preclinical Pharmacology

1. Potent insulin secretagogue compared to OHAs in fasted dogs, normal rats, fed, fasted and glucose loaded rats
2. Acts exclusively via the ATP-sensitive potassium channel (tissue selective) and does not cause direct exocytosis of insulin
3. Distinct binding sites
4. Glucose dependent insulin secretion, (no secretion at 0 mM glucose)
5. Without inhibition of proinsulin biosynthesis
6. Without peripheral effects

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Pharmacology Profile

- New chemical entity (NCE), benzoic acid derivative
- Oral insulin secretagogue, distinct β-cell binding sites
- No direct exocytosis, no suppression of protein synthesis

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Preclinical Safety

Frederick Reno, Ph.D.

Novo Nordisk

Safety Pharmacology Screening

- Central nervous (mice, rats)
- Cardiovascular (rats, rabbits, guinea pigs, pigs)
- Urinary volume (rats)
- Respiratory (guinea pigs, rabbits)
- Gastrointestinal (rats)
- Smooth muscle (guinea pigs)
- Ligand binding assays (rats, hamsters)

No organ system toxicities predicted at clinical doses

Toxicology Studies

Animal	N	Weeks	Dose Range (mg/kg/day)*
Mouse			
Chronic	140	8,13	30 - 1500
Carcino	500	104	50 - 500
Rat			
Acute	40	-	1000 - 3000
Chronic	340	13, 52	2 - 120
Carcino	600	104	15 - 120
Repro	574	3-6	0.5 - 80
Rabbit			
Repro	84	2	0.1 - 0.9
Dog			
Acute	4	-	300, 1000
Chronic	32	52	0.05 - 50

* Maximum clinical dose = 0.32 mg/kg/day

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Overall Conclusions

- No clinically relevant laboratory or histopathological changes
- Not genotoxic or immunogenic
- Not teratogenic
  - —Non-teratogenic limb effect
- Not tumorigenic at 50x human AUC
  - —Benign liver & thyroid tumors in male rats

Reproduction Findings

- Limb deformation in pups of dams at AUC 25x human
- High exposure safety margins, not seen up to 6x human AUC
- Safe gestational period defined (71x human AUC studied)
- Class effect, mechanism probably low serum glucose

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Mouse Carcinogenicity Study

- Not tumorigenic at exposure 71 to 169 times human AUC in males and females

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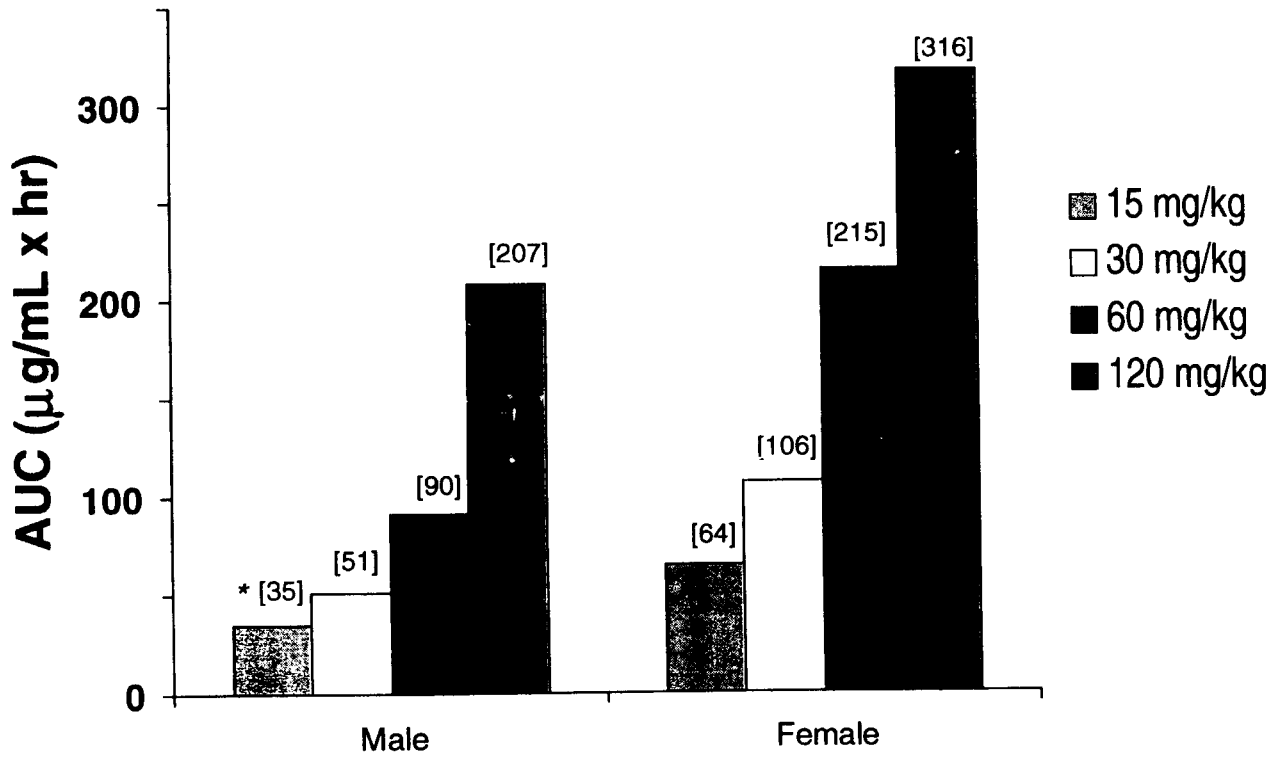
Rat Carcinogenicity Exposure



*[ ] = multiple of human exposure; cf to1.005 µg/mL•hr of 4 mg acx4

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Rat Carcinogenicity Study

- No increased tumors at 50 x human AUC
- 90 - 200 x human AUC increased benign thyroid tumors in males
- 200 x human AUC increased benign liver tumors in males

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Mechanism of Thyroid Tumors

- Known mechanism for rat thyroid tumors
  - —Decreased plasma T_3
  - —Increased TSH $\rightarrow$ proliferation
- No comparable mechanism in humans
  - —No clinical change in T_3 uptake, T_4, or TSH

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Carcinogenicity Conclusions

- Not genotoxic
- High exposure safety margin
- Thyroid tumor mechanism specific for rats
- Mouse carcinogenicity study - negative
- No clinical risk

Nonclinical Pharmacokinetics

- Rapid absorption (T_{max} < 1 hour)
- Highly bound to plasma proteins (95 - 99%)
- Plasma levels in female rodents 2-3 x males, as frequently seen in rodents
- Excreted via bile, only 8% radiolabel in urine
- Metabolized by glucuronidation and/or oxidative pathways of liver
- Metabolite profile similar between 5 animal species and man

Preclinical Profile

- New chemical entity (NCE), benzoic acid derivative
- Oral insulin secretagogue, distinct β-cell binding sites
- No direct exocytosis, no suppression of protein synthesis
- Not mutagenic, teratogenic or carcinogenic
- No clinically relevant preclinical safety changes

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Clinical Pharmacology

Poul Strange, M.D., Ph.D.

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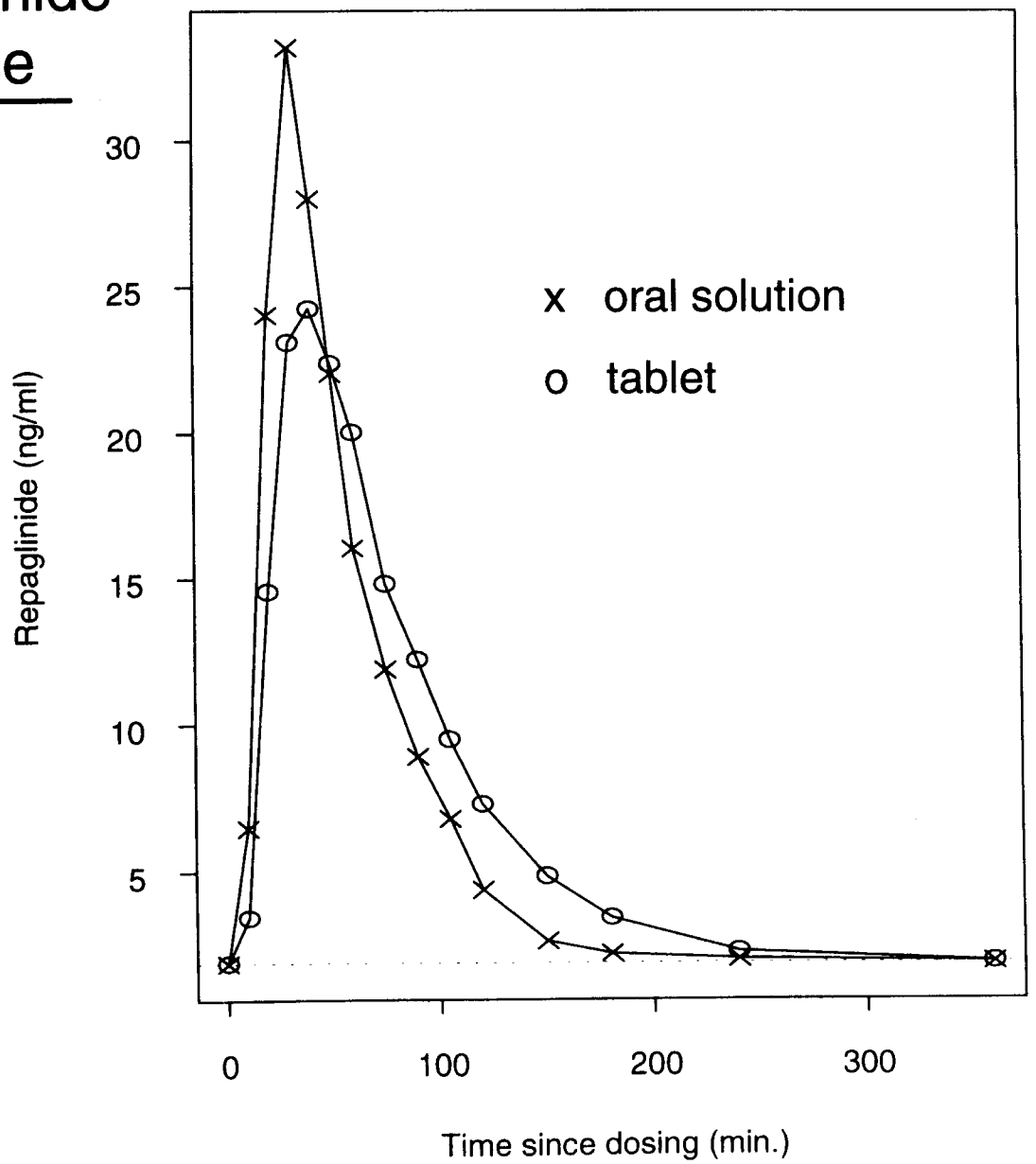
Serum Repaglinide After 2 mg Dose



Absorption and Distribution

- Rapidly absorbed from gastrointestinal tract
  T_{max}: 0.7 hour (0.3 - 1), unchanged by food
- Marginal decrease in AUC with food
- Rapid elimination from blood stream:
  t½ = 1 hour (0.7 - 2.93); CL = 38 L/hour
- Absolute bioavailability: 56%
- Volume of distribution at steady state: 31 L
- 98% plasma protein bound

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Metabolism and Excretion

- >60% of plasma concentration is parent compound
- No chiral conversion *in vivo*
- Metabolized primarily by CYP3A4
- Metabolites do not contribute significant activity
- 90% of dose excreted in the feces by biliary secretion
- Major metabolite is dicarboxylic acid in feces (72%)
- 8% excreted in urine as metabolites

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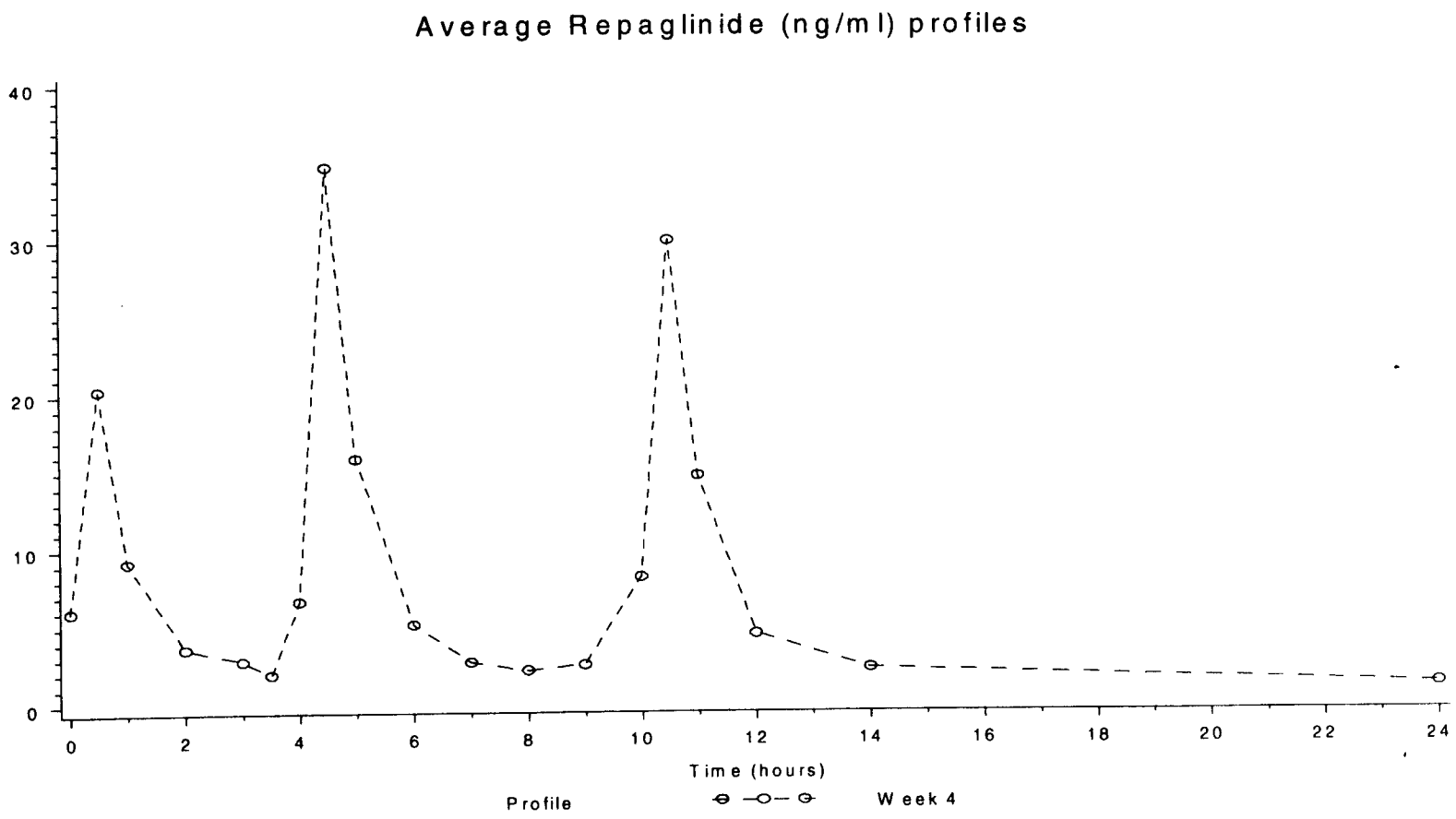
Initial Meal Related Response Profiles (004)



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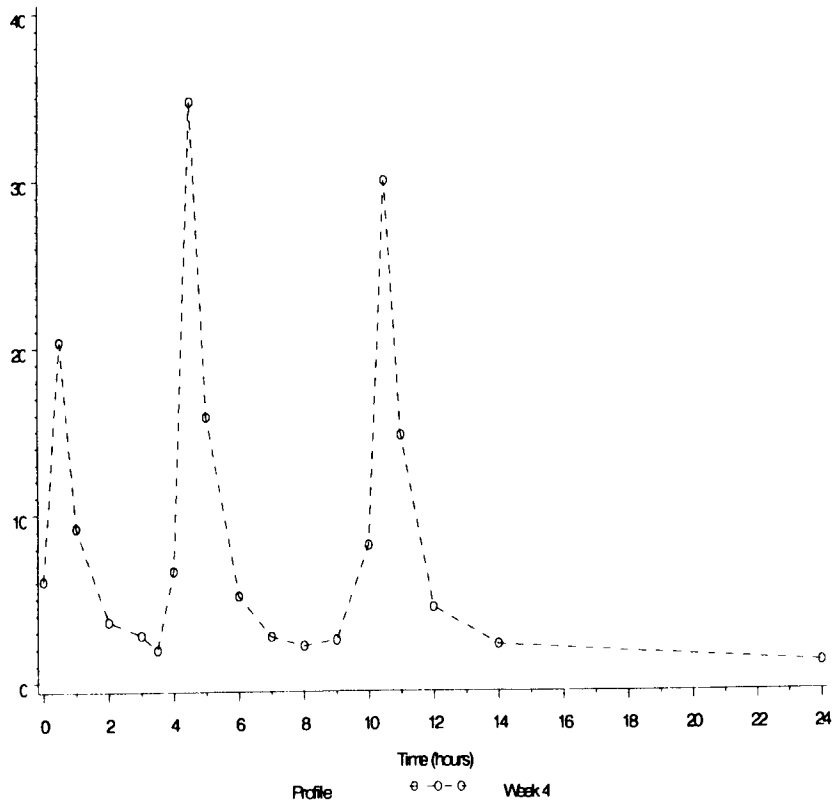
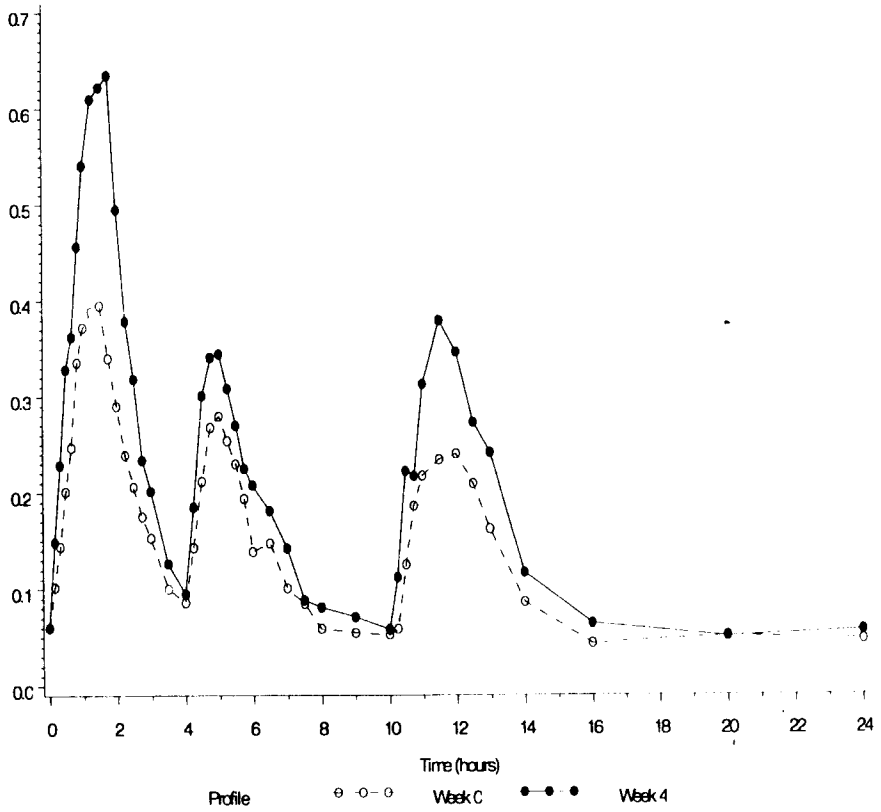
Initial Meal Related Response Profiles (004)

Average Repaglinide (ng/ml) profiles



Average Insulin (nmol/l) profiles



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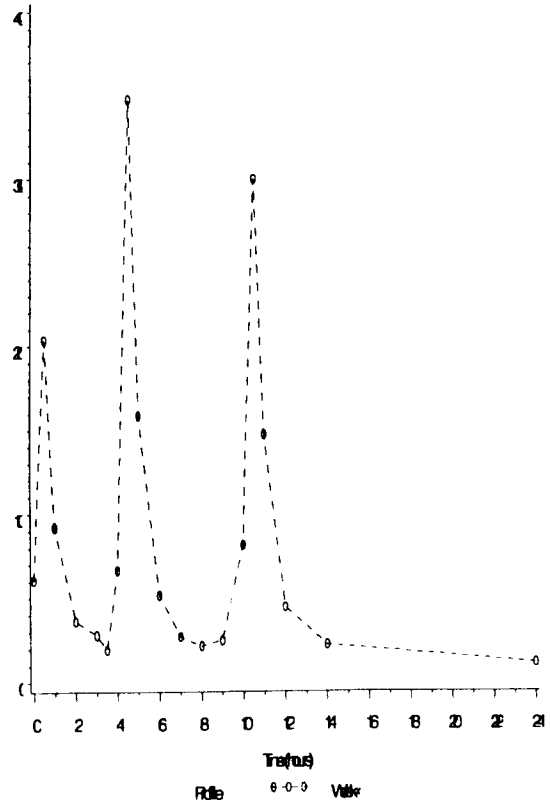
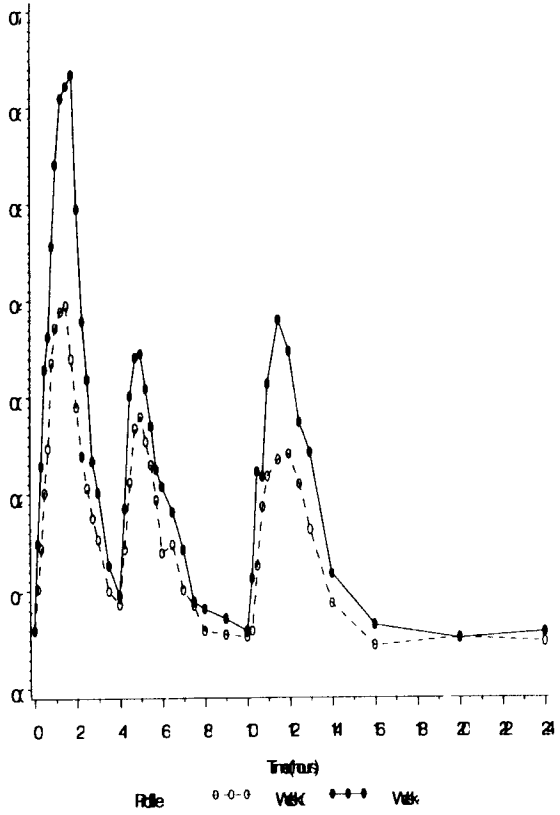
Initial Meal Related Response Profiles (004)

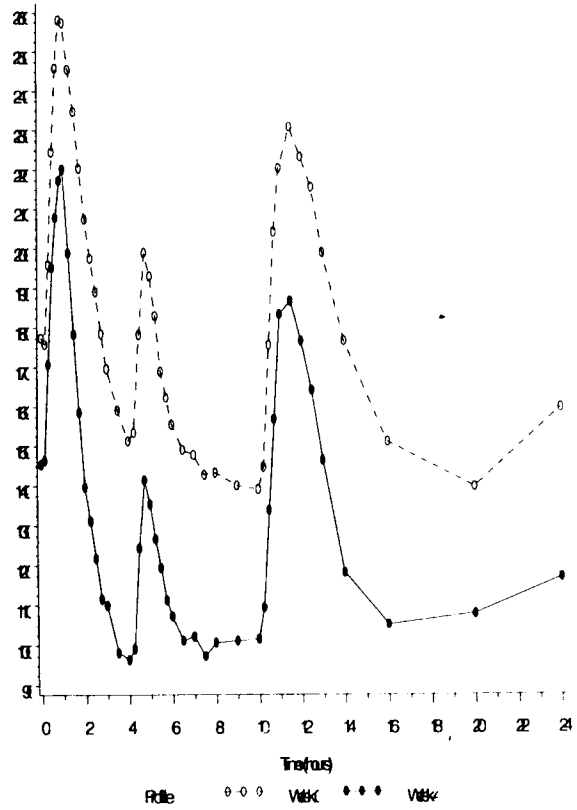
Average Repaglinide (ng/ml) profiles



Average Insulin (nmol/l) profiles



Average BG (mg/dl) profiles



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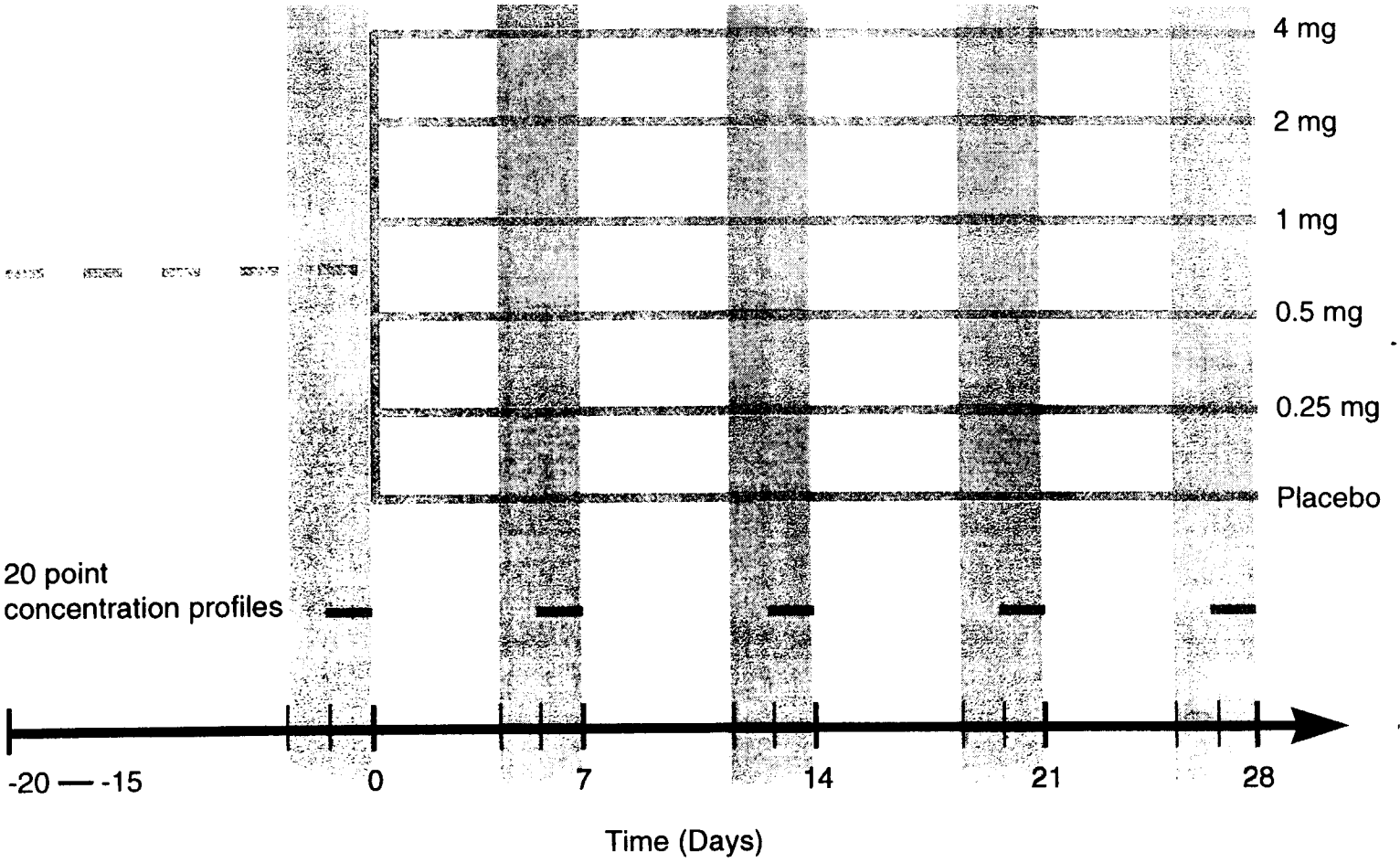
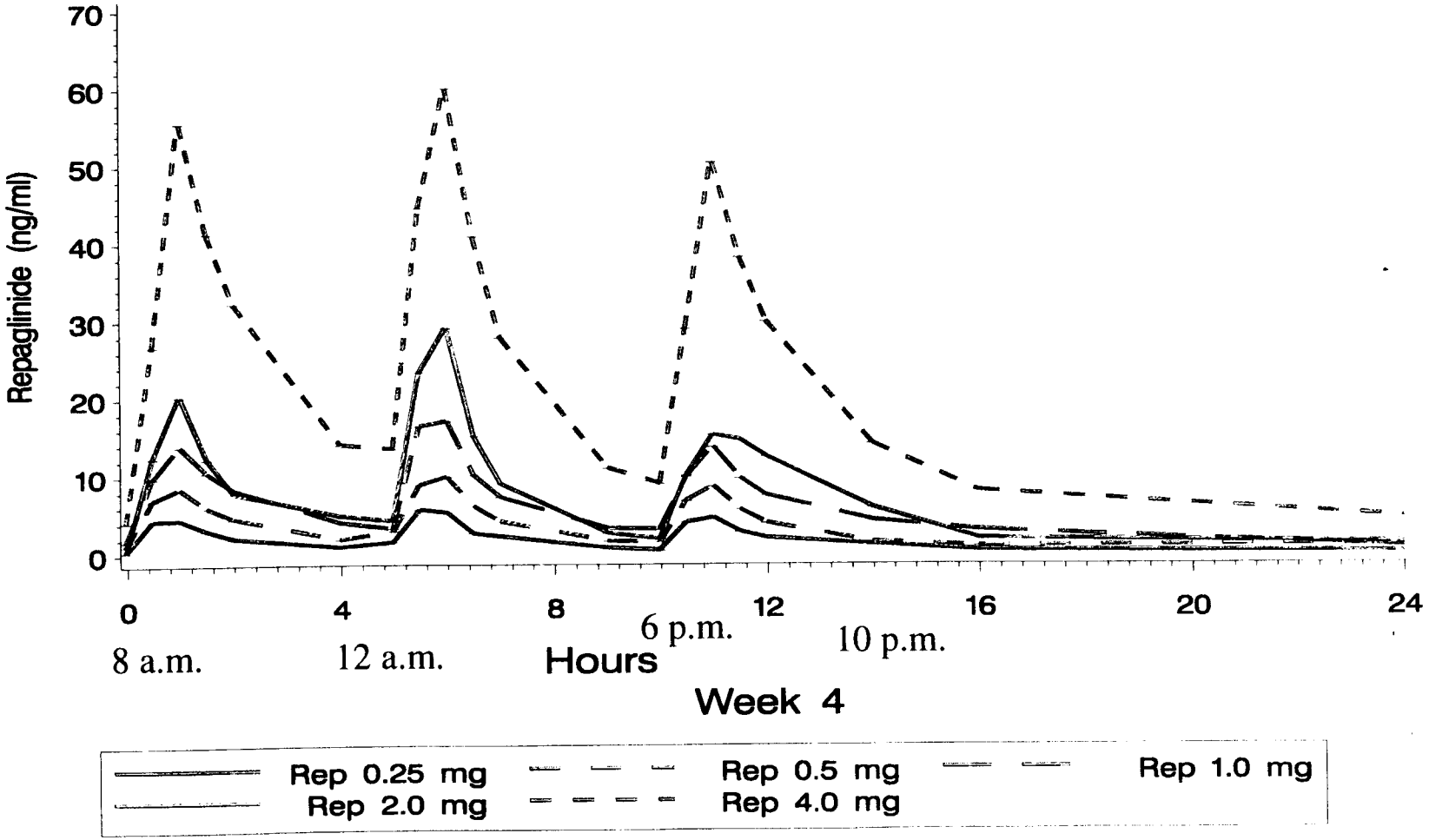
Dose-Response Study (064)

- 2-3 week stabilization without OHA
- FPG between 180 and 300 mg/dl
- Randomization to five dose levels
  (0, 0.25, 0.5, 1.0, 2.0 and 4.0 mg)
- Doses 15 minutes before each of three meals
- Weekly 58-hour stay in Clinical Research Unit
- Standard meals during CRU visits
- 20-point repaglinide, insulin, and glucose concentration profiles determined

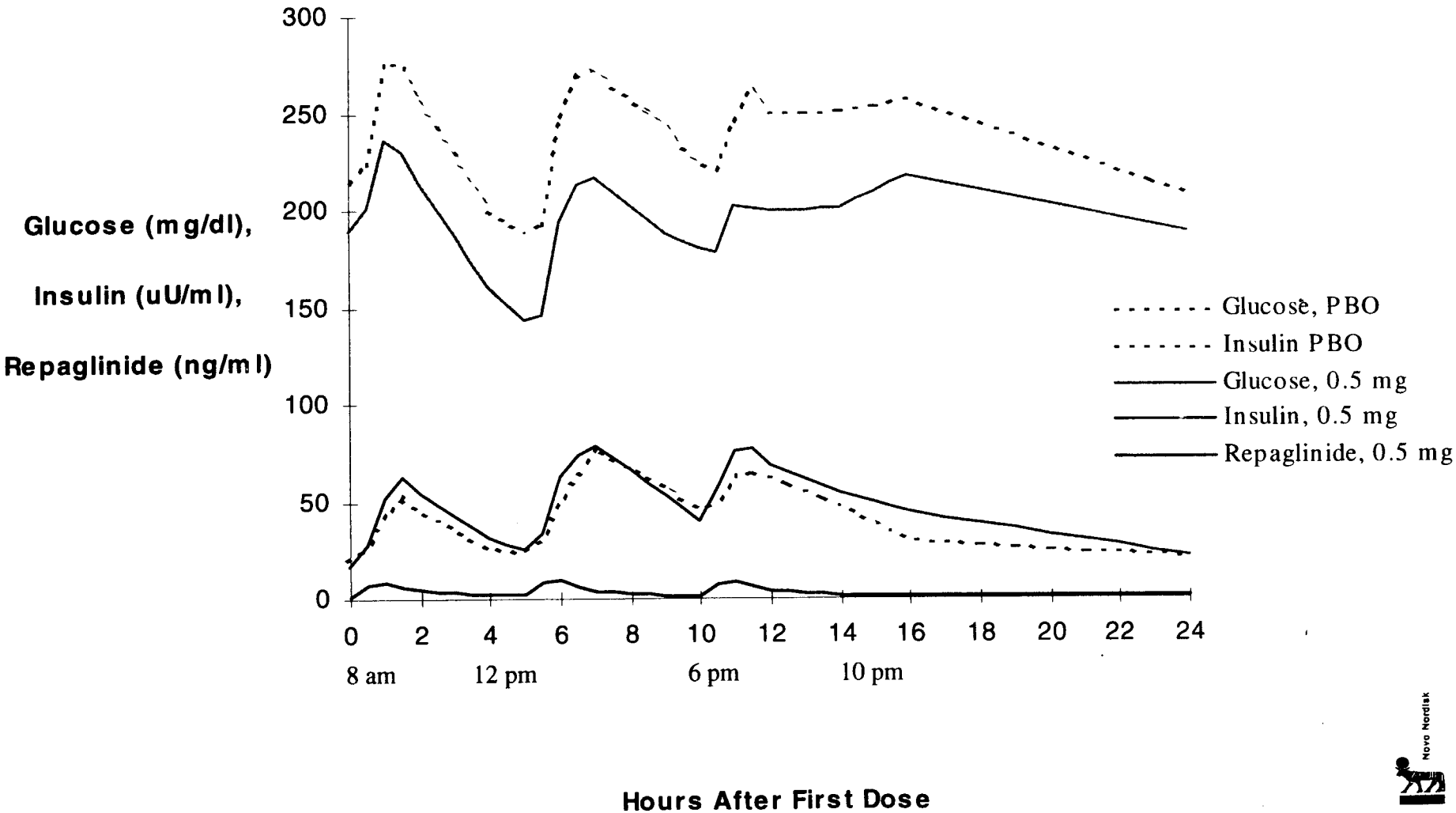
Dose Response Study (064)



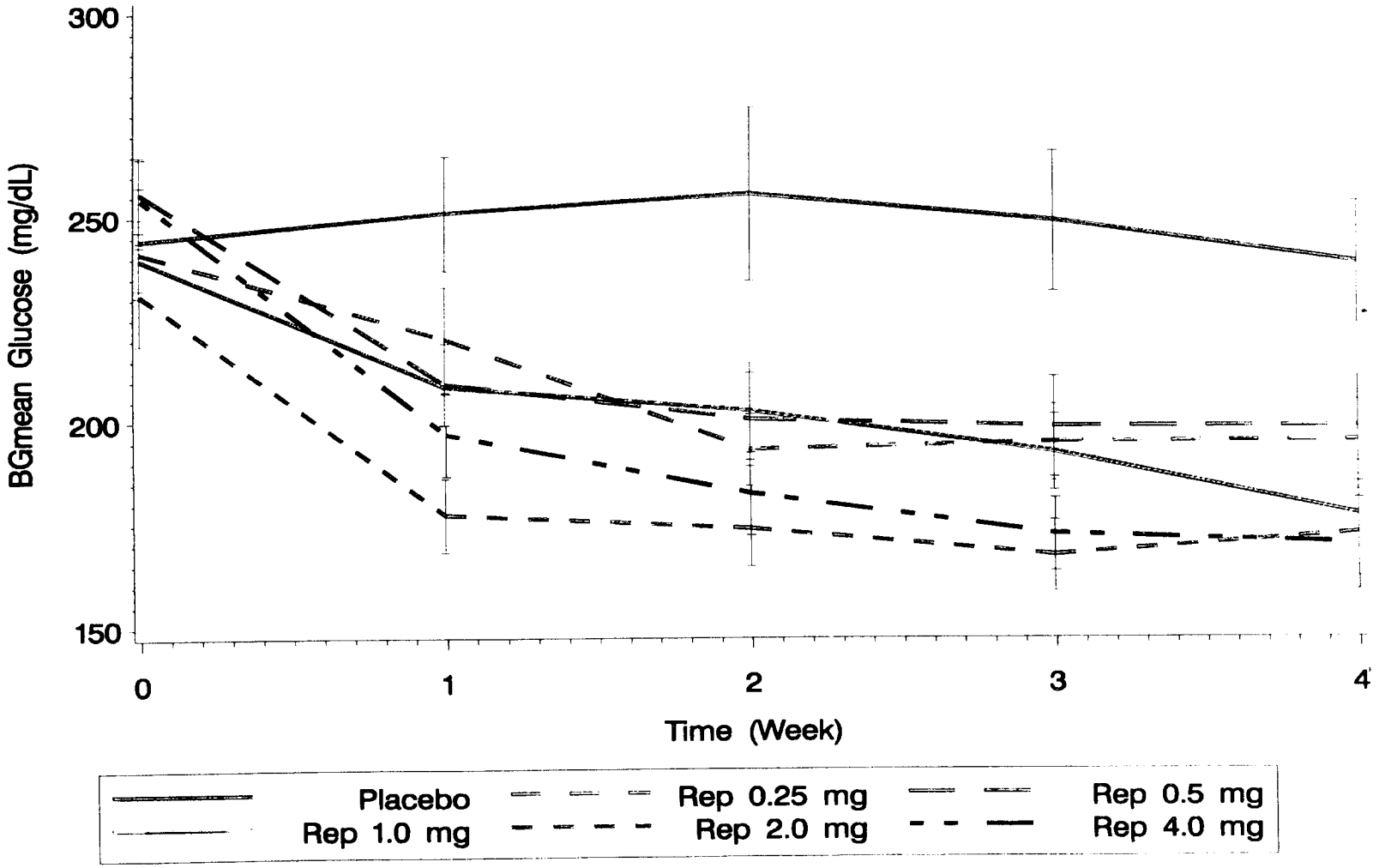
Drug Concentration Profiles (064)



Steady State Pk/PD, 0.5 mg a.c. x 3



Kinetics of BG Response by Dose (064)



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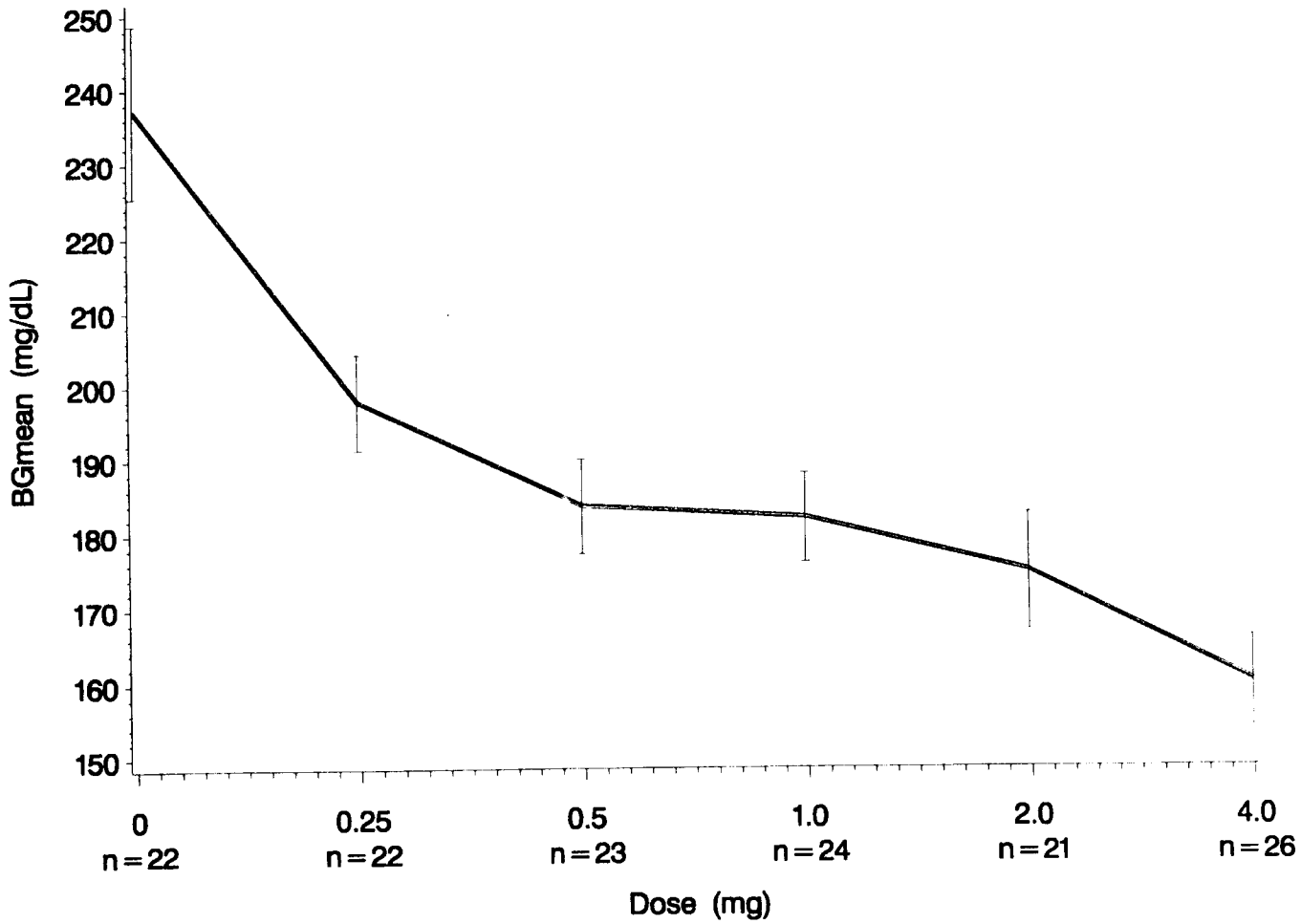
Blood Glucose Dose Response (064)



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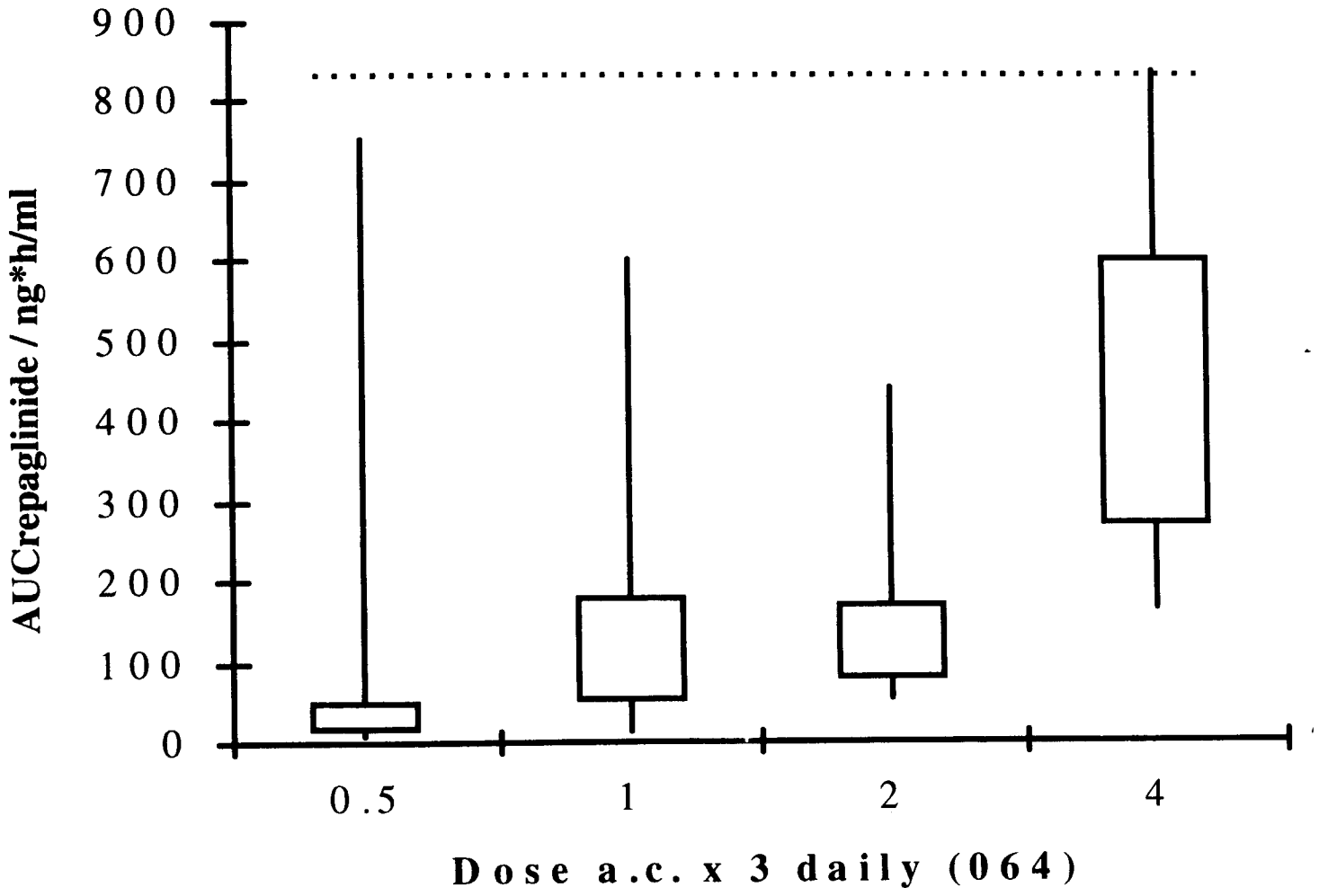
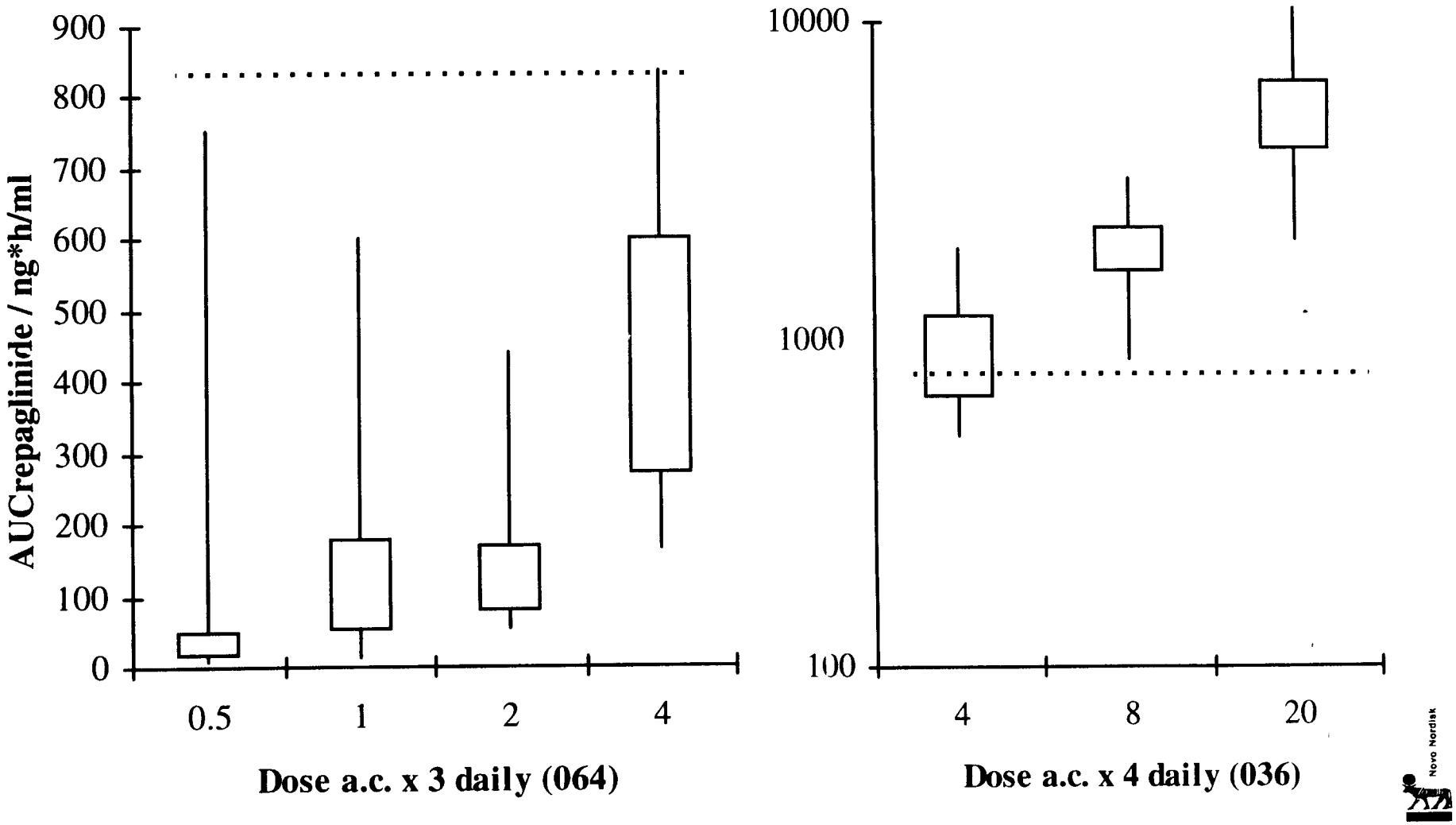
AUC vs. Dose in Type 2 Diabetes



AUC vs. Dose in Type 2 Diabetes



Special Populations Studies (2 mg dose)

	Repaglinide AUC [mean (range) (ng*h/ml)]
◆ Elderly:	
— 12 young healthy	49 (12-302)
— 12 elderly healthy	67 (26-189)
◆ Liver dysfunction:	
— 12 healthy	92 (12-213)
— 12 Child Pugh B,C	369 (57-968)
◆ Renal dysfunction:	
— 6 healthy	31 (18-66)
— 6 mild/moderate	75 (20-497)
— 6 severe	80 (39-285)

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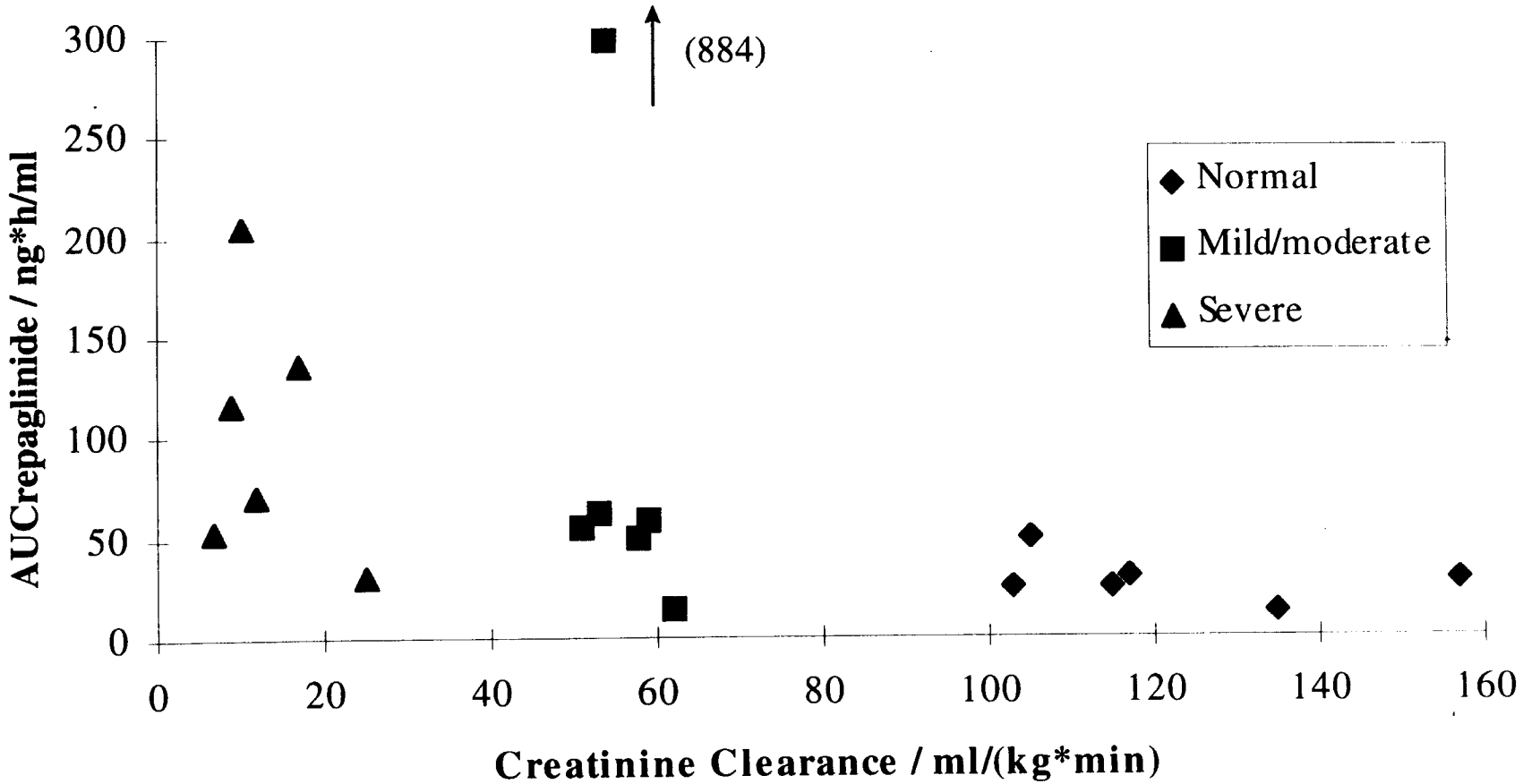
AUC vs. Renal Dysfunction



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Drug Interaction Pharmacokinetics Summary

- Digoxin
  - —No influence on profile
- Warfarin
  - —No influence on profile or dynamics
- Theophylline
  - —No influence on profile
- Cimetidine
  - —No influence on repaglinide profile

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Preclinical Profile

- New chemical entity (NCE), benzoic acid derivative
- Oral insulin secretagogue, distinct β-cell binding sites
- No direct exocytosis, no suppression of protein synthesis
- Not mutagenic, teratogenic or carcinogenic
- No clinically relevant preclinical safety changes

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Clinical Pharmacology Profile

- Rapid onset (T_{max}= 0.7 hours), rapid plasma clearance
- Enhances insulin response to meals
- Clinically significant blood glucose response
- Effective in doses from 0.5 mg
- 100-fold AUC repaglinide over dose range recommended
- Excreted via the bile
- No significant interaction with digoxin, warfarin, theophylline, cimetidine
- Dose adjustment required only for liver dysfunction

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PRANDIN (Repaglinide) TABLETS
NDA 20-741

Efficacy

Poul Strange, M.D., Ph.D.

Novo Nordisk

Placebo Controlled Trials

Trial	Doses	Weeks	Patients Exposed Rep	Pla	Total
033	Titration 0.25-8 mg (a.c.x3)	18	66	33	99
064	Fixed Dose 0.25 v 0.5 v 1.0 v 2.0 v 4.0 mg (a.c.x3)	4	120	23	143
065	Fixed Dose 1 v 4 mg (a.c.x3)	24	289	72	361
		Totals	475	128	603

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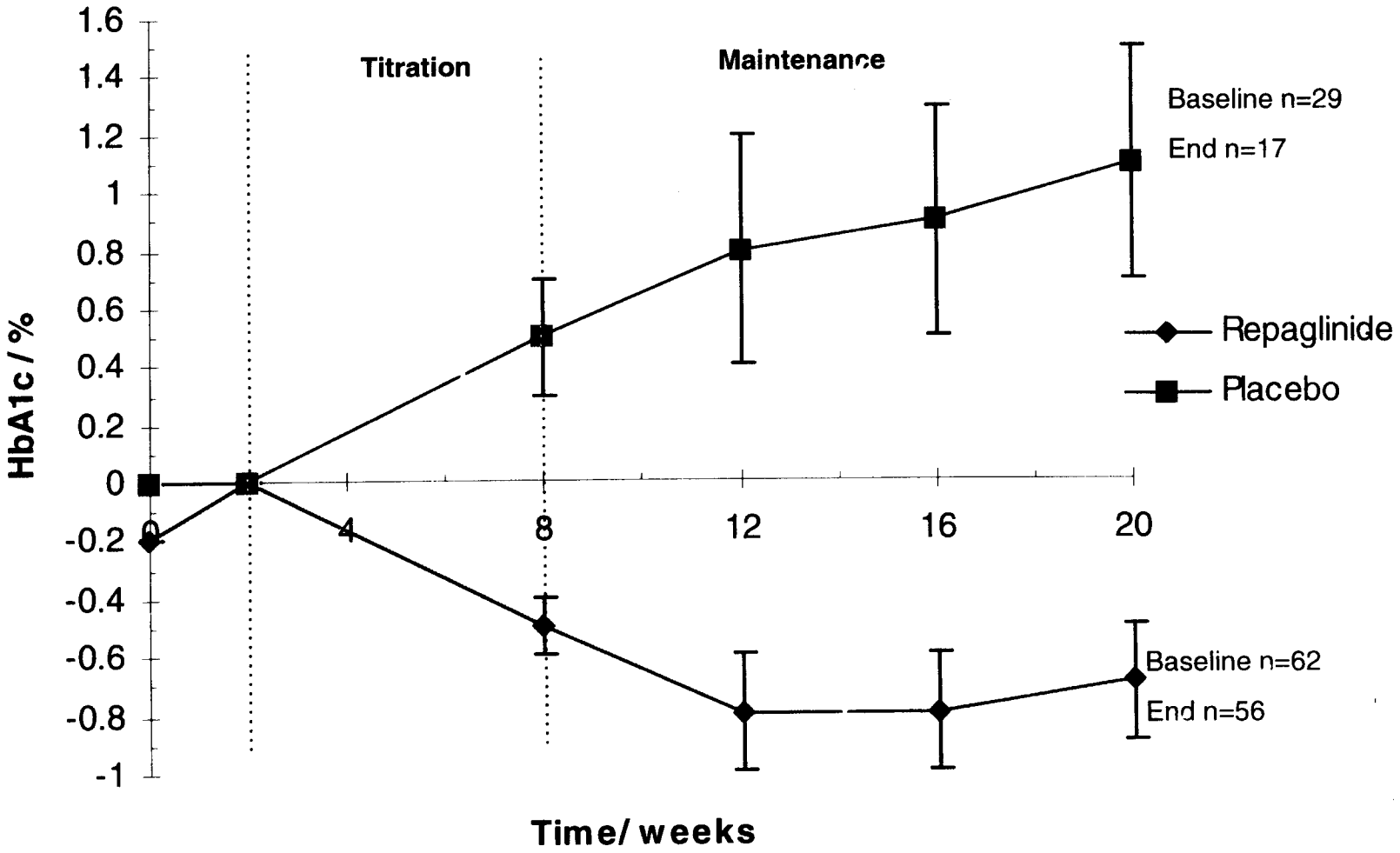
HbA_{1c} Response vs. Placebo (033, all patients)



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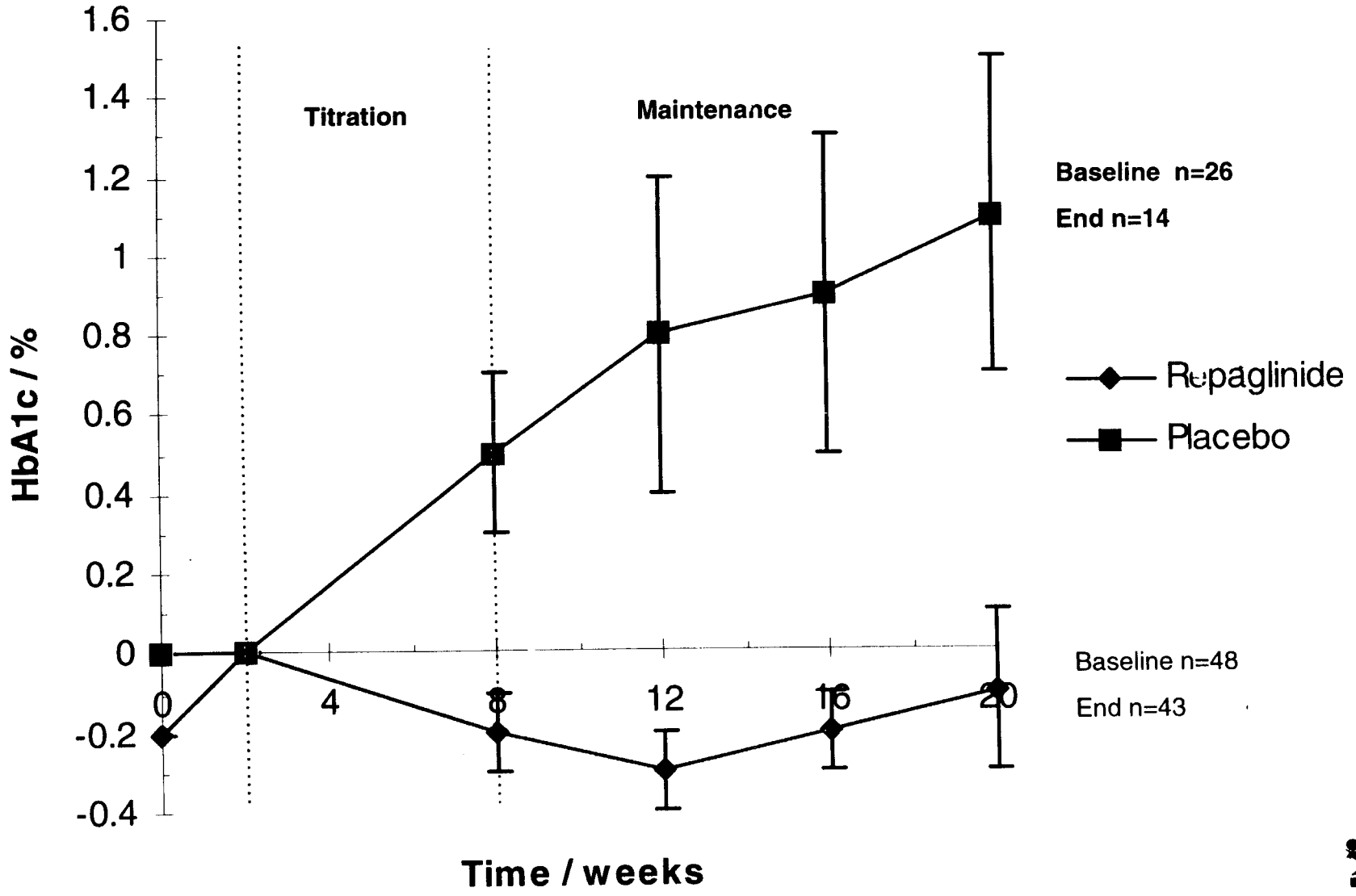
HbA_{1c} Response vs. Placebo (033, previously treated)



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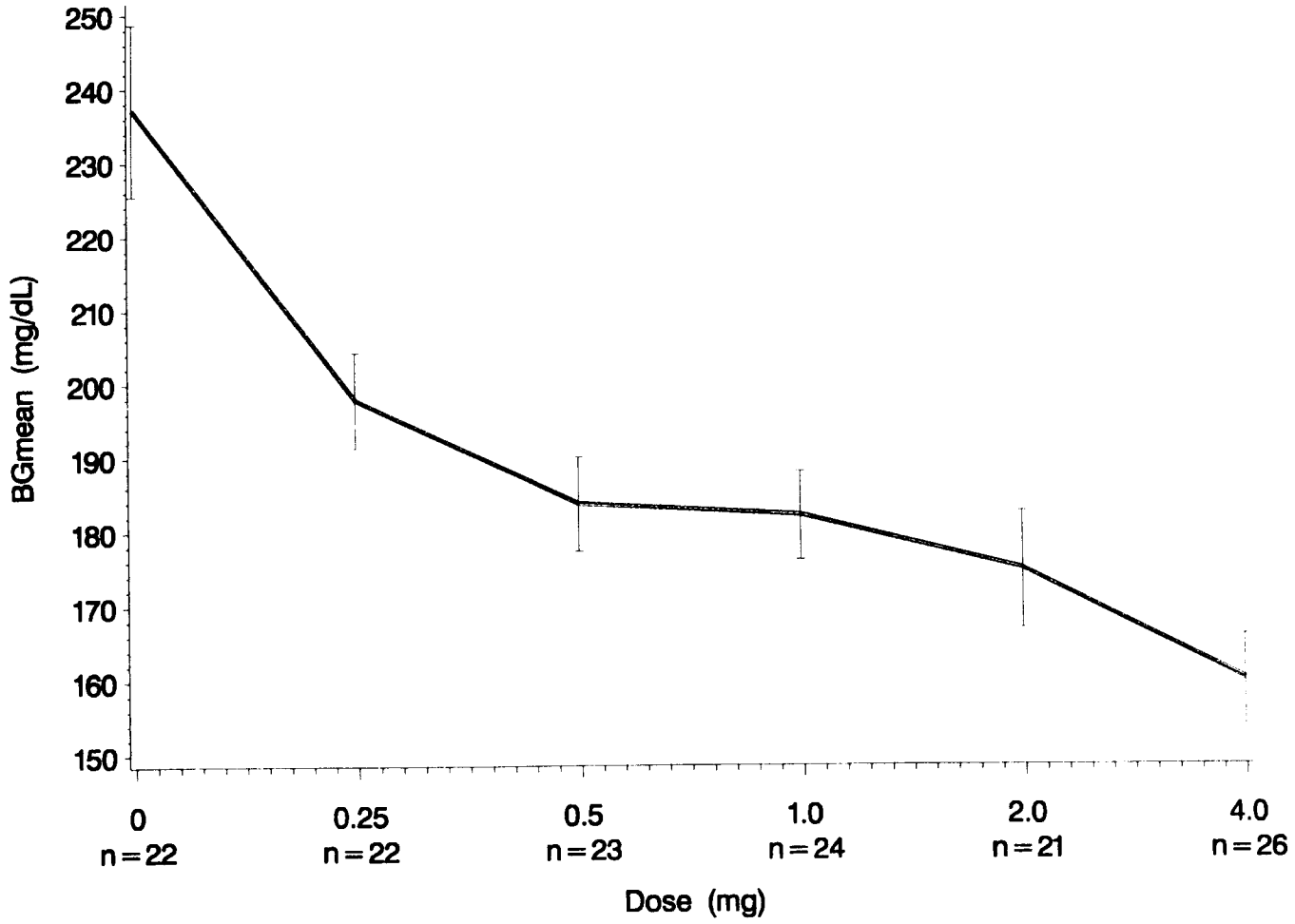
Blood Glucose Dose Response (064)



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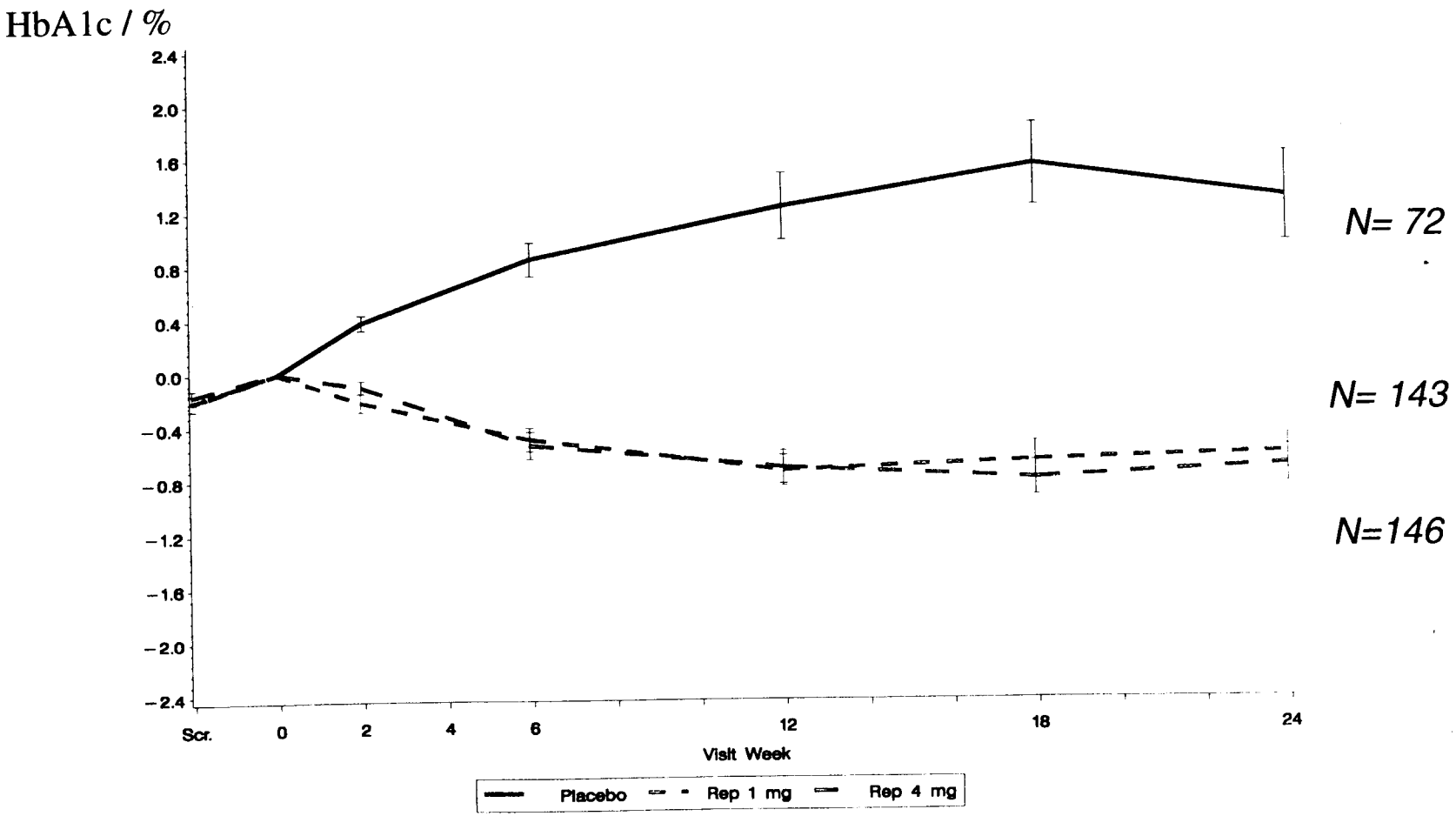
HbA_{1c} Response vs. Placebo, All Patients (065)

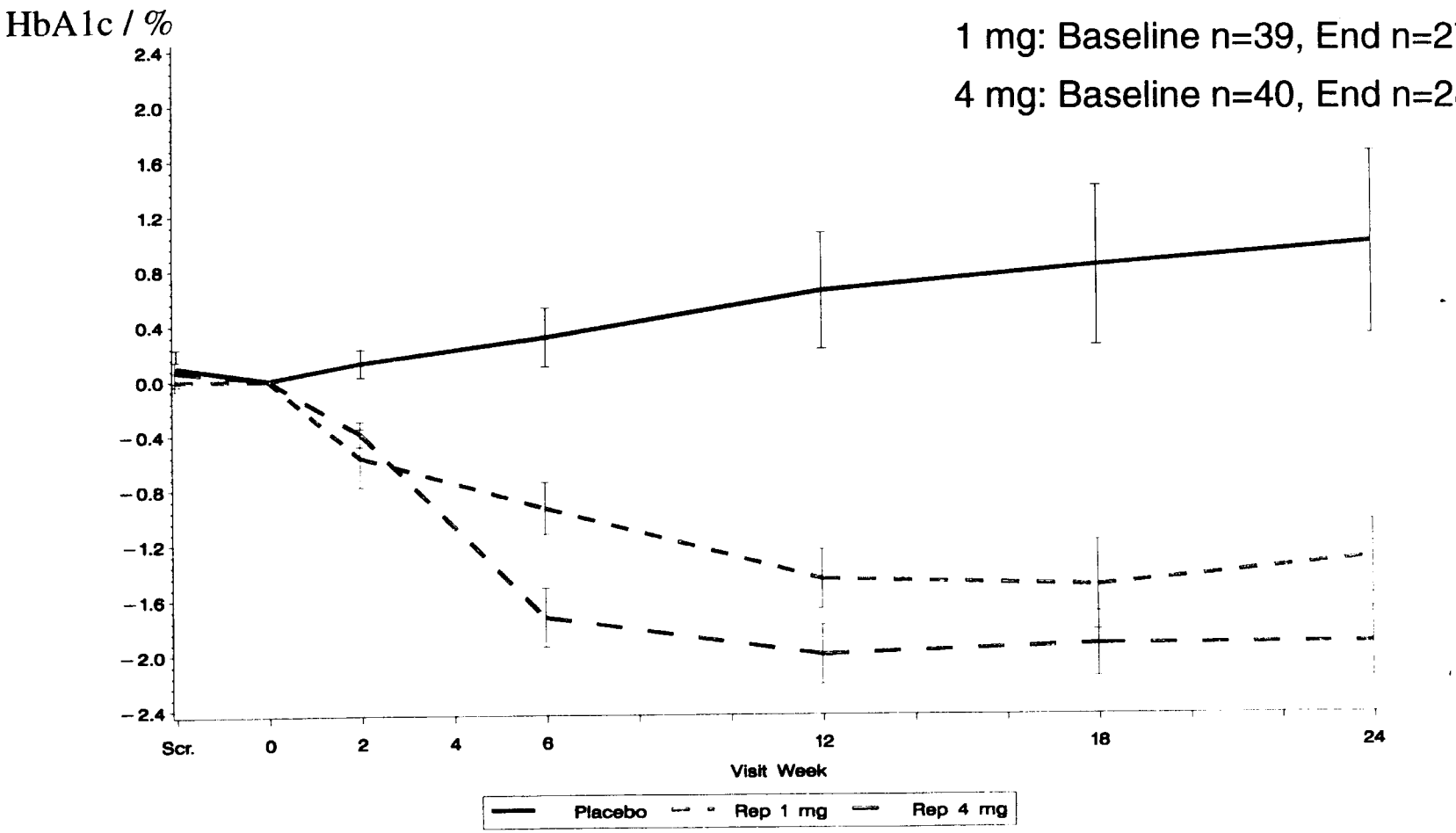


HbA_{1c} Response vs. Placebo, Naïve (065)

Placebo: Baseline n=17, End n=9

1 mg: Baseline n=39, End n=27

4 mg: Baseline n=40, End n=28



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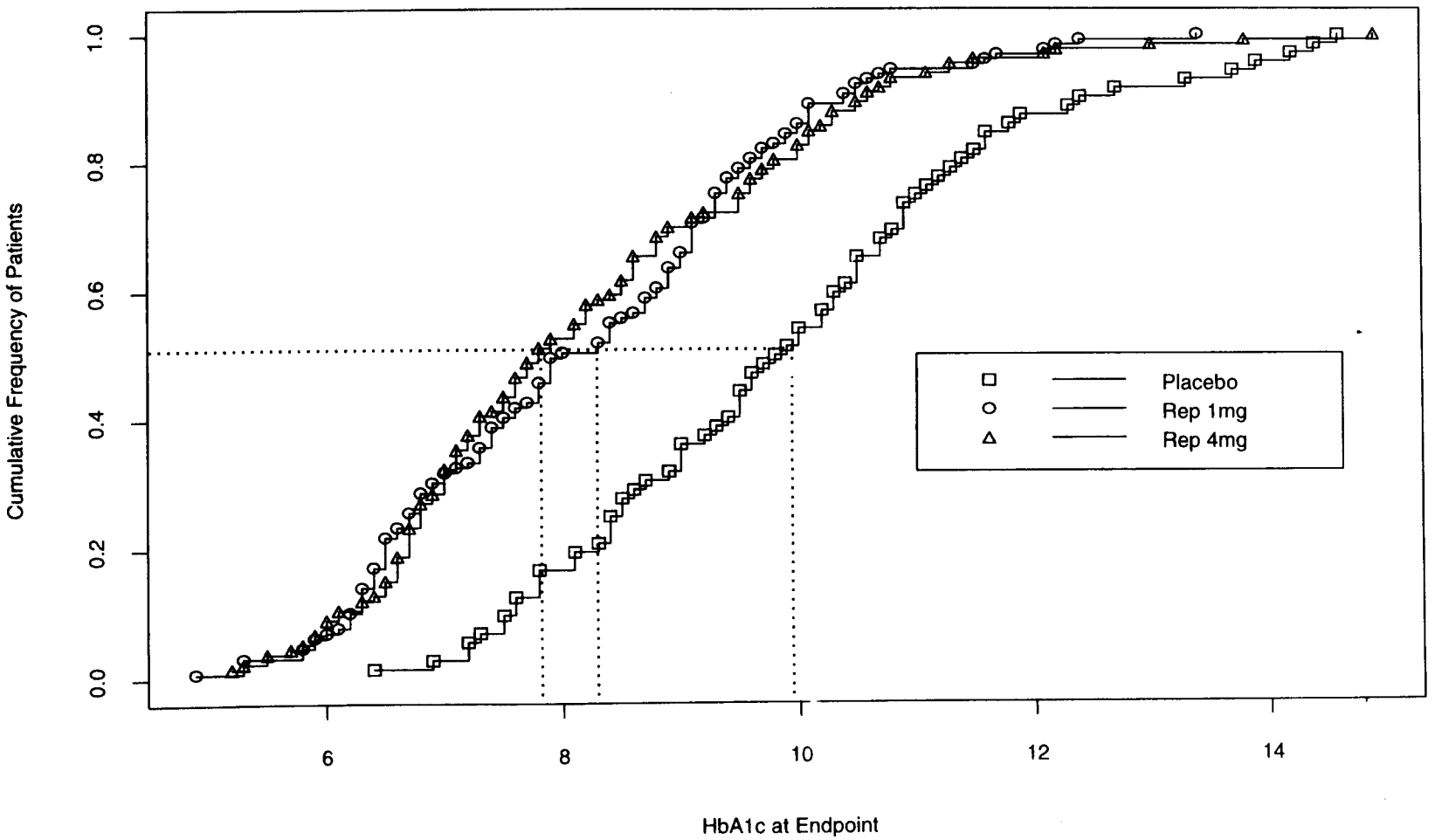
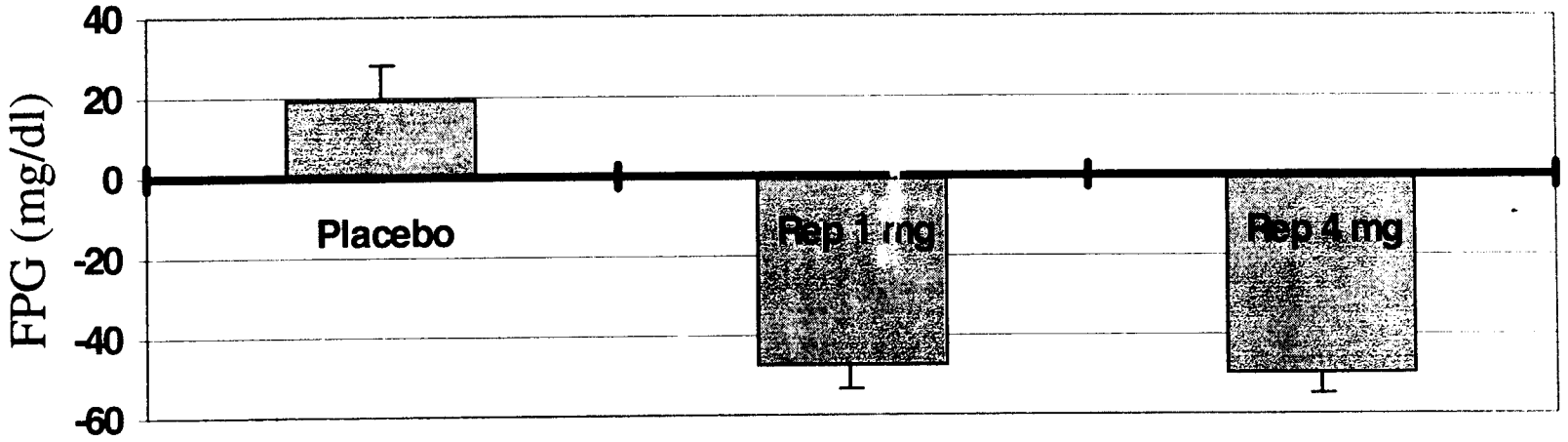
Cumulative Frequency of HbA_{1c} at 6 mos (065)



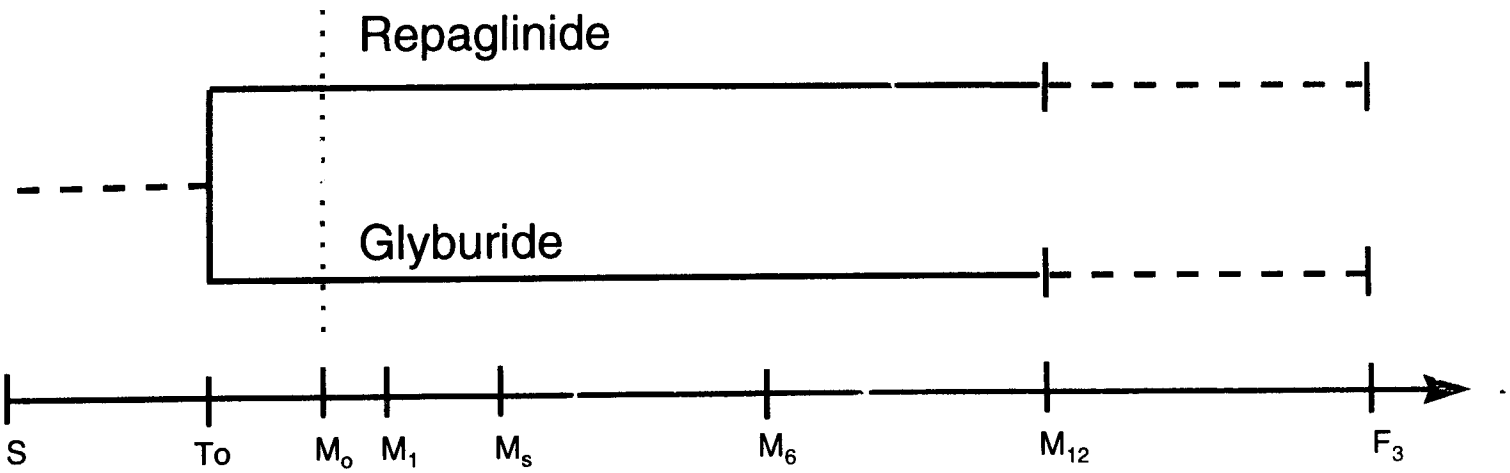
Novo Nordisk

Fasting Plasma Glucose vs. Placebo (065)



Novo Nordisk

1-year Repaglinide v. Glyburide (049)



Demographics & Baseline Characteristics

	Age (y)	Sex-M/F %	Dur. Diabetes	BMI (kg/m^2)	% OHA naïve	HbA_{1c} %
Repaglinide	58	67/33	7.2	29	13	8.7
Glyburide	59	66/34	8.3	29	13	8.9

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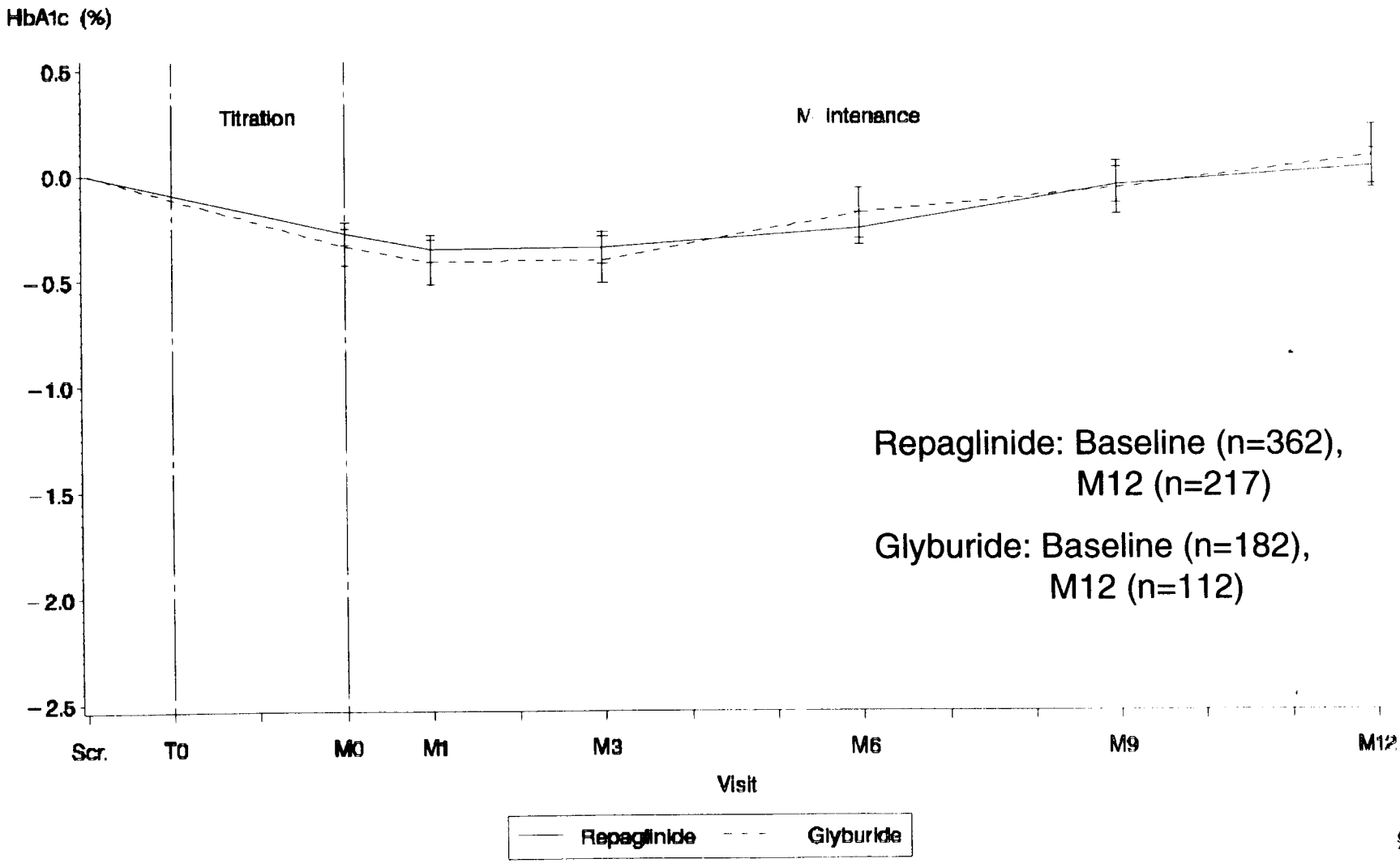
HbA_{1c} in 1-year Comparator (049)



Repaglinide: Baseline (n=362),
M12 (n=217)

Glyburide: Baseline (n=182),
M12 (n=112)

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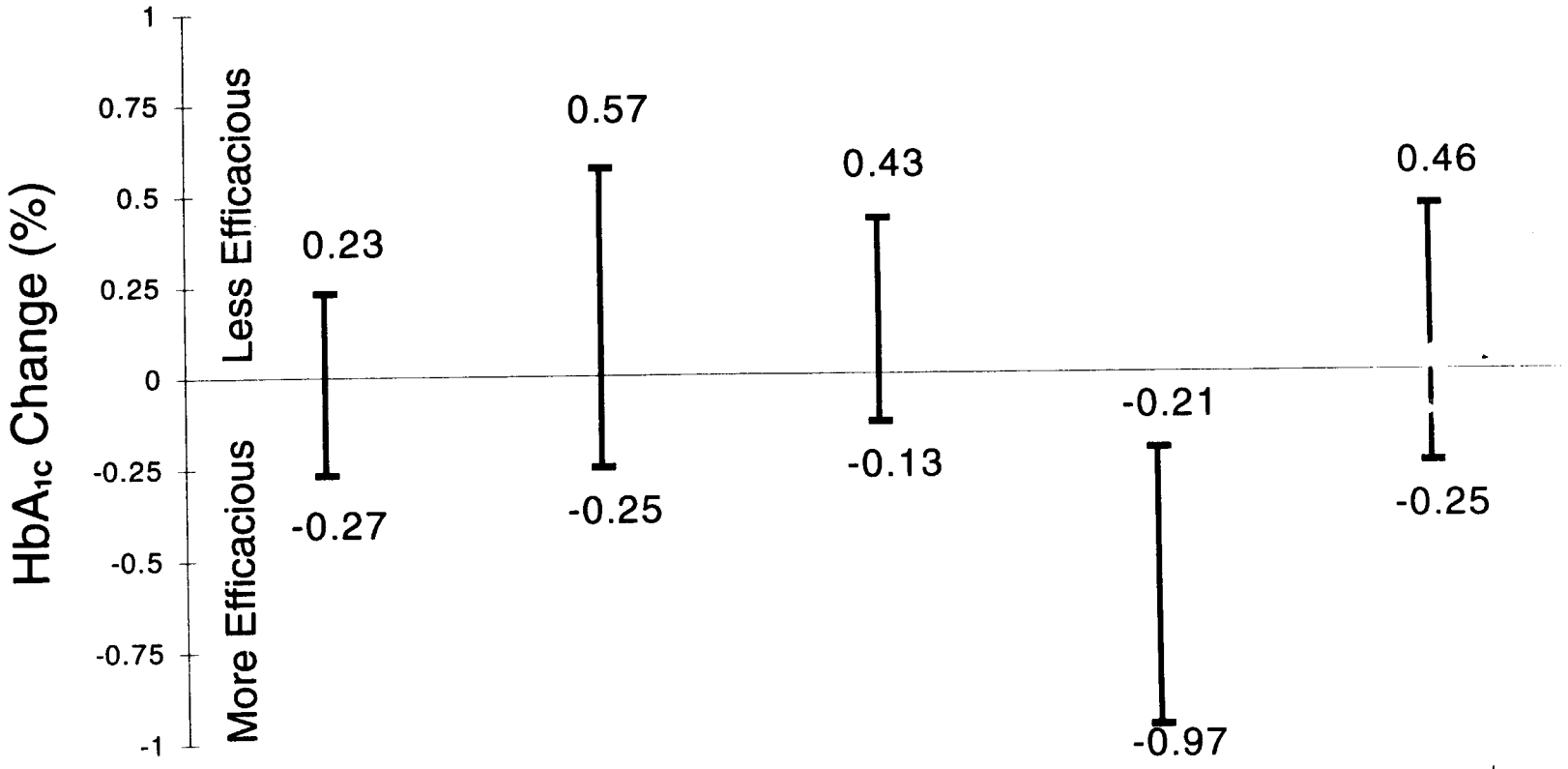
HbA_{1c}(%) in 1-year Comparator Trials



Comparator:	049/USA Glyburide	046/UK Glyburide	050/D-NL Glyburide	048/Scand Glipizide	047/F-I-B Gliclazide
	N = 544	N = 262	N = 425	N = 256	N = 305

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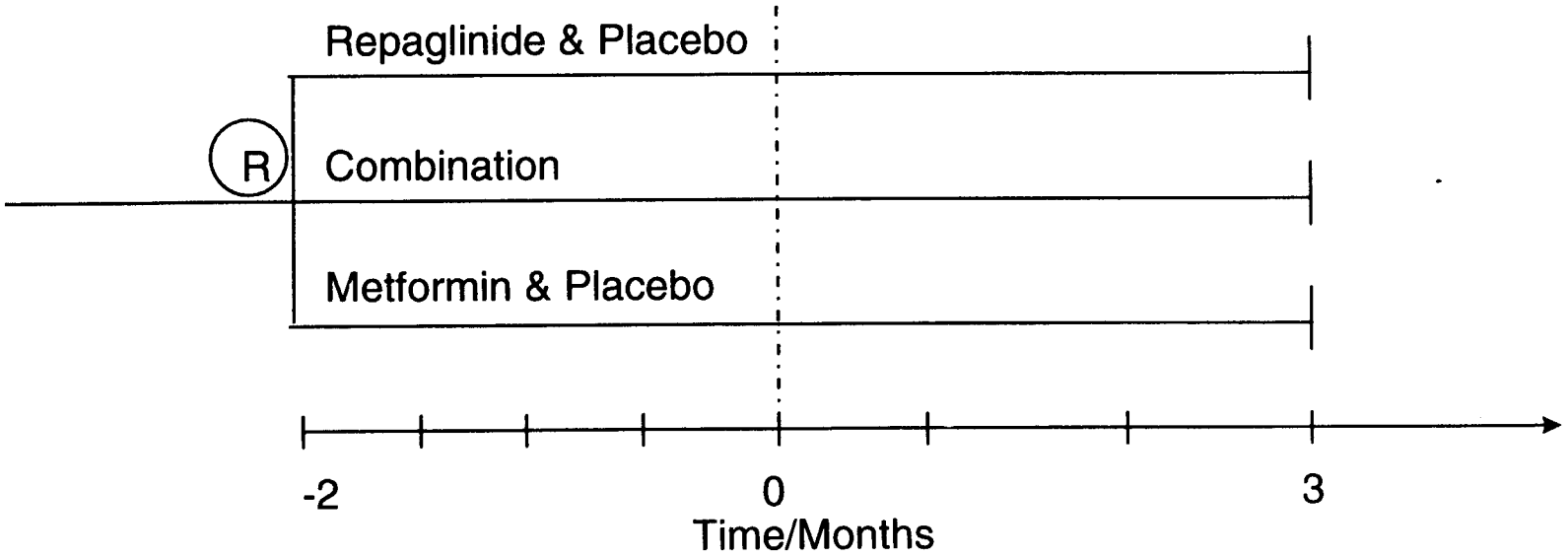
Repaglinide and Metformin Combination (053)

Type 2 diabetes currently inadequately treated
with metformin monotherapy
Age 40 - 75 years
HbA_{1C} > 7.1%

83 subjects
9 centers
FPFV: JUL '95
LPLV: JUL '96



HbA_{1C}	X					X	X				X	
FPG	X	X	X	X	X						X	

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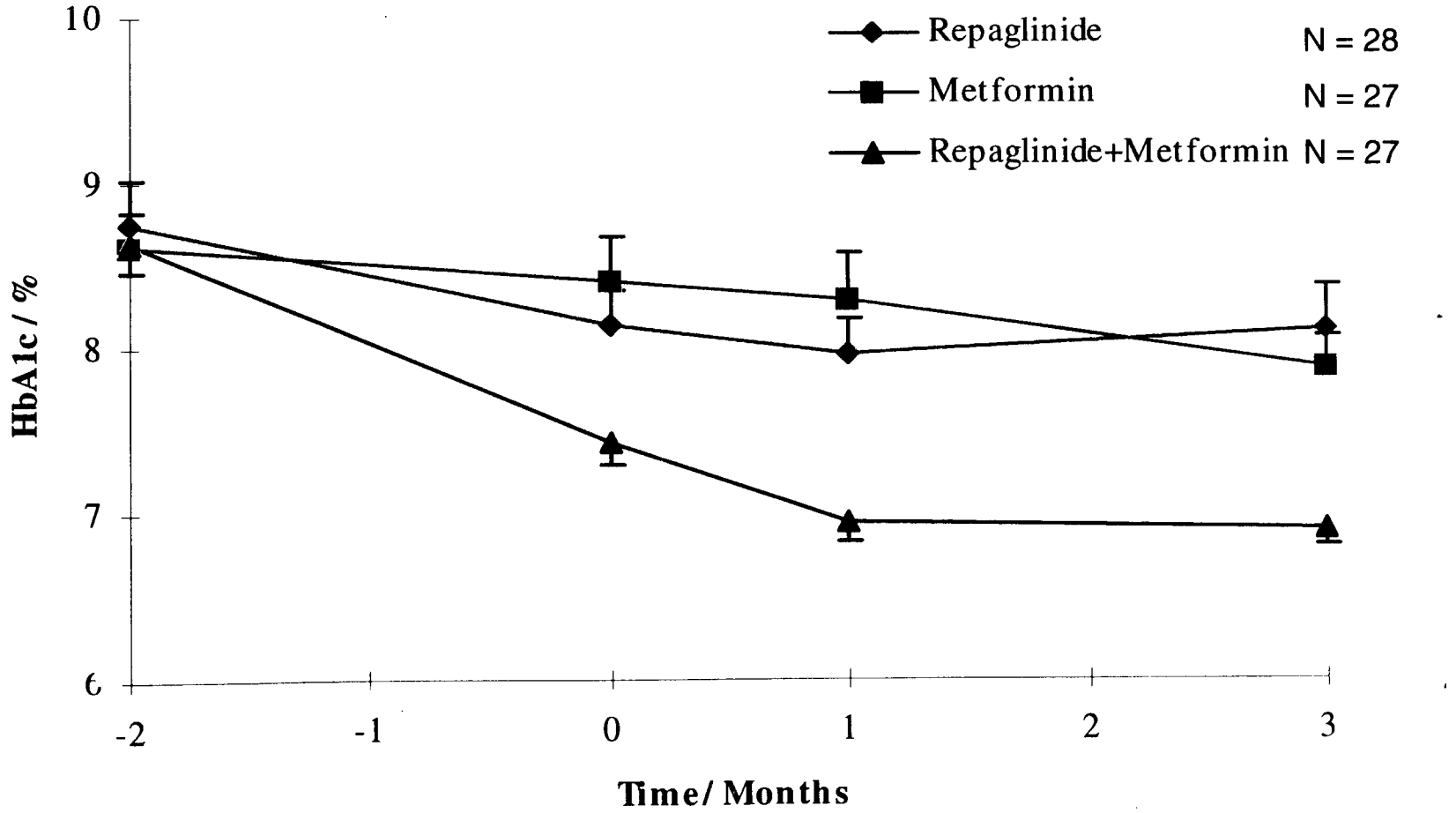
Metformin Combination Study (053)



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Clinical Pharmacology Profile

- Rapid onset (T_{max}= 0.7 hours), rapid plasma clearance
- Enhances insulin response to meals
- Clinically significant blood glucose response
- Effective in doses from 0.5 mg
- 100-fold AUC repaglinide over dose range recommended
- Excreted via the bile
- No significant interaction with digoxin, warfarin, theophylline, cimetidine
- Dose adjustment required only for liver dysfunction

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Efficacy Profile

- BG response within 1 week (40-80 mg/dl)
- Dose-response 0.5 - 4 mg a.c. x 3
- Significant difference vs placebo
  (titration and fixed dose)
- Improves glucose control 1.6-2.9% HbA_{1c}
- Maintenance of glycemic control > 1 yr
- Substantial addition to metformin

Novo Nordisk

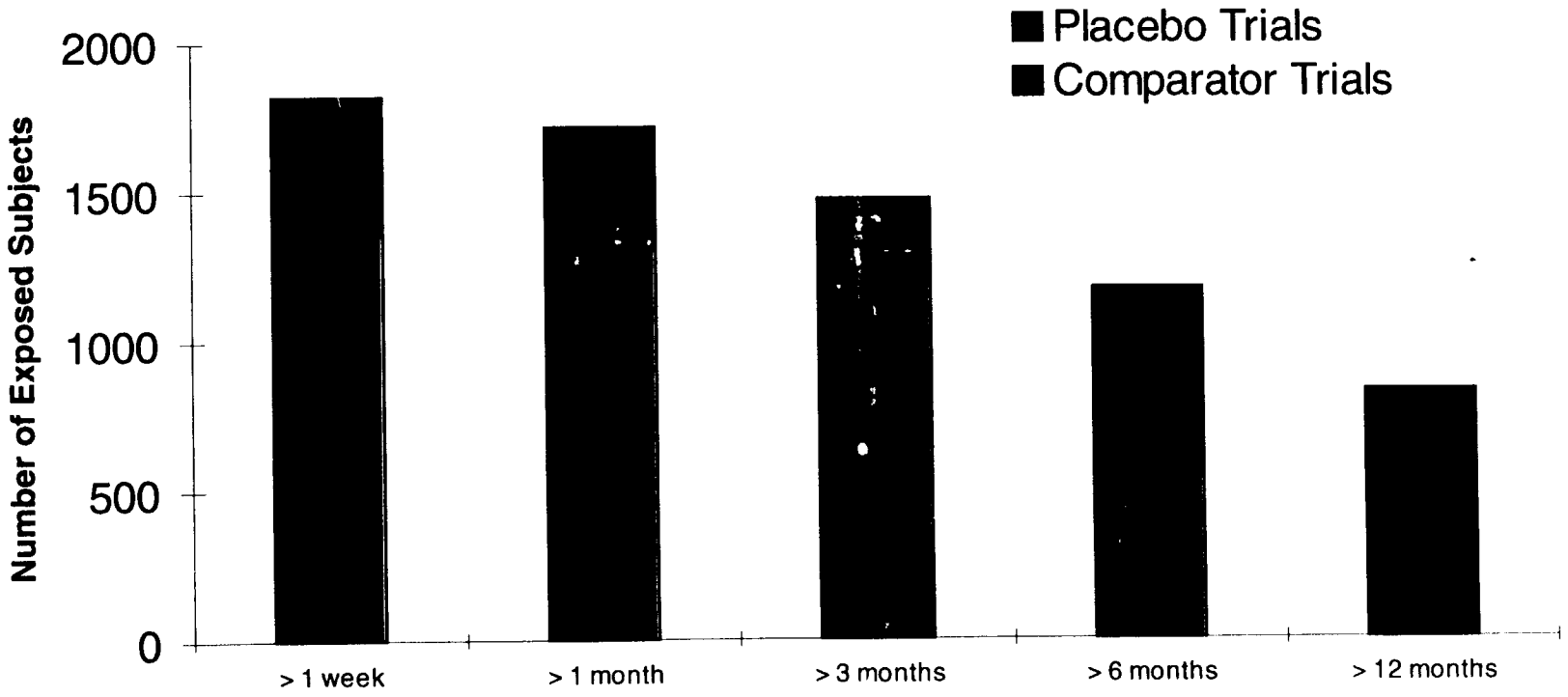
PRANDIN (Repaglinide) TABLETS
NDA 20-741

Clinical Safety

Martin Edwards, M.D.

Novo Nordisk

Duration of Exposure in Controlled Trials



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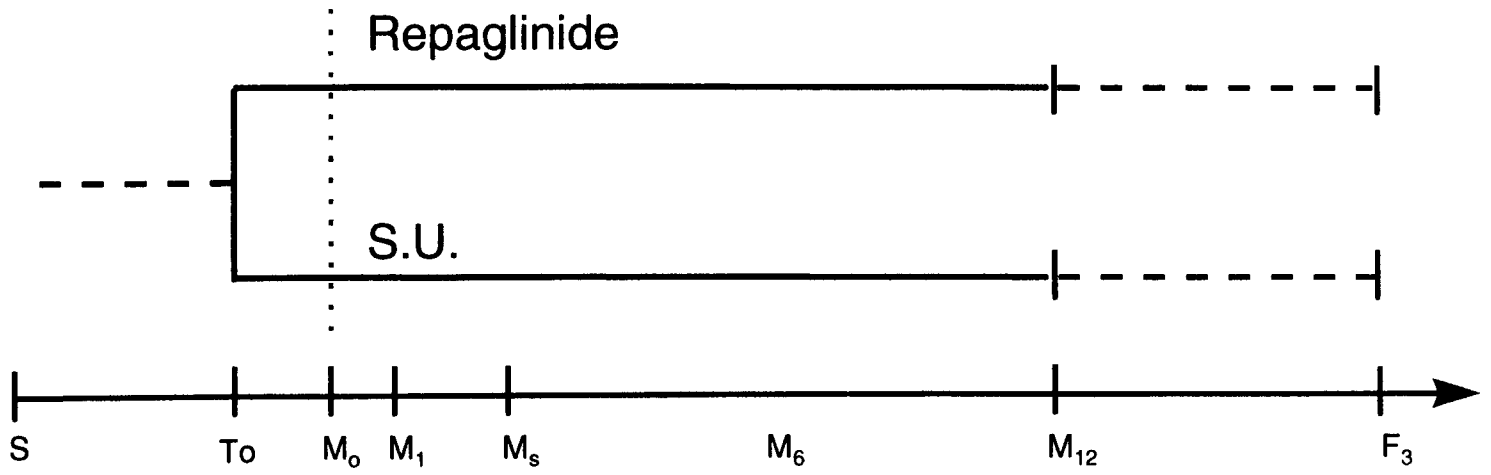
1-Year Repaglinide vs. S.U. (046-050)



1-Year Comparator Trials

Trial	Rep	Patients Exposed Gly	Glip	Glic	Total
049	383	193			576
046	178	85			263
050	286	139			425
048	175		81		256
047	206			99	305
Totals	1228	417	81	99	1825

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Exposure by Age, Gender and Race

	USA Studies			European Studies	
	Repaglinide	Placebo	Glyburide	Repaglinide	Comparator
No. Treated	855	131	193	994	531
Age >65	23%	18%	29%	24%	26%
Female	34%	33%	34%	38%	34%
Race					
Caucasian	75%	72%	80%	96%	96%
Hispanic, Other	15%	15%	11%	1%	1%
Black	9%	12%	8%	1%	2%
Asian	1%	1%	1%	1%	1%

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Discontinuations

	Placebo Trials		1-yr Comparator Trials	
	Repl.	Plac.	Rep.	Comp.
N =	472	131	1228	597
% completed	79	53	66	68
% discontinuing				
Adverse Event	4.6	7.6	13.3	14.1
Hypoglycemia	0.6	0	1.4	2.8
Hyperglycemia/ Ineffective Therapy	7.2	30.5	9.5	9.0
Other	8.6	8.9	9.8	6.1

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Symptomatic Adverse Event Profile

	033, 065		046-50	
	Rep	Placebo	Rep	Act Comp
# exposed	352	108	1228	597
% of patients with events	76	67	78	79
Hyperglycemia	1	6	5.0	5.0
Headache	11	10	5.0	4.9
Dizziness	7	8	3.1	4.0
Fatigue	6	7	4.3	2.2
Upper Resp Tract Infect	16	8	10.3	8.9
Rhinitis	3	3	7.3	8.0
Bronchitis	2	1	6.0	6.5
Sinusitis	6	2	2.7	3.4
Influenza-like symptoms	0	0	8.1	8.7
Abdominal pain	2	4	4.6	4.7
Diarrhea	5	2	4.4	5.2
Back pain	5	4	6.1	6.2
Arthralgia	6	3	2.7	3.7
Unspecified pain sympt	0	0	5.5	5.9
Injury, accidental	2	4	3.9	5.4

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Ascending Tolerance Trial in Type 2 Diabetes Patients

Repaglinide dosing tested: 4 mg a.c. x 4 - 20 mg a.c. x 4

Adverse events reported	Repaglinide (N=15)	Placebo (N=5)
Chest pain		1
Dizziness	1	
Diarrhea	1	
Nausea		1
Headache	1	
Anemia		1

Repaglinide was safe and well-tolerated (Adverse events appeared at lower dose levels only)

No clinically relevant changes of liver enzymes were observed

No clinically relevant changes of ECG intervals occurred

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Hypoglycemia in 1-Year Trials

All Patients	Rep	Glyb	Glip	Glic
# exposed	1228	417	81	99
% w hypo	16	20	19	15
% hypo d/c	1.5	2.6	2.5	4.0
% hypo w BG	50	45	93	73
% w BG < 45	13	27	29	18
Mean hypo BG	63	56	59	51

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Serious Cardiovascular Events

	PRANDIN™	Glyburide	Glipizide
Total Exposed	1228	417	81
Serious CV Events	51 (4%)	8 (2%)	5 (6%)
Cardiac Ischemic Events	29 (2%)	5 (1%)	4 (5%)
Deaths due to CV Events	6 (0.1%)	2 (0.1%)	0

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Cardiac Deaths - 1-Year Comparator Trials

	Repaglinide	Comparator
Treatment Years	1087	538
Myocardial infarction	5	1
Cardiac failure	1	0
Heart block	0	1
Cardiac arrest	0	1

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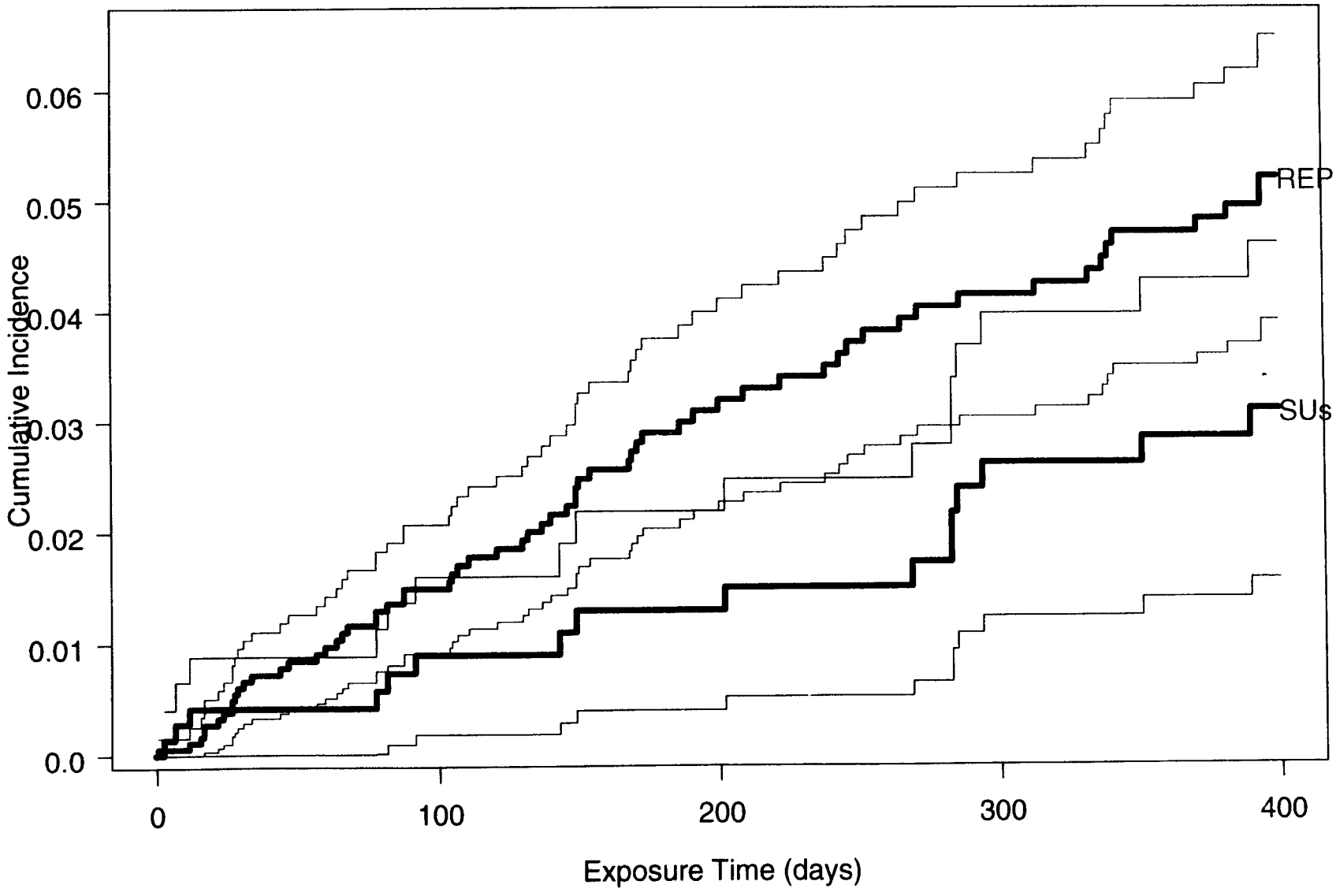
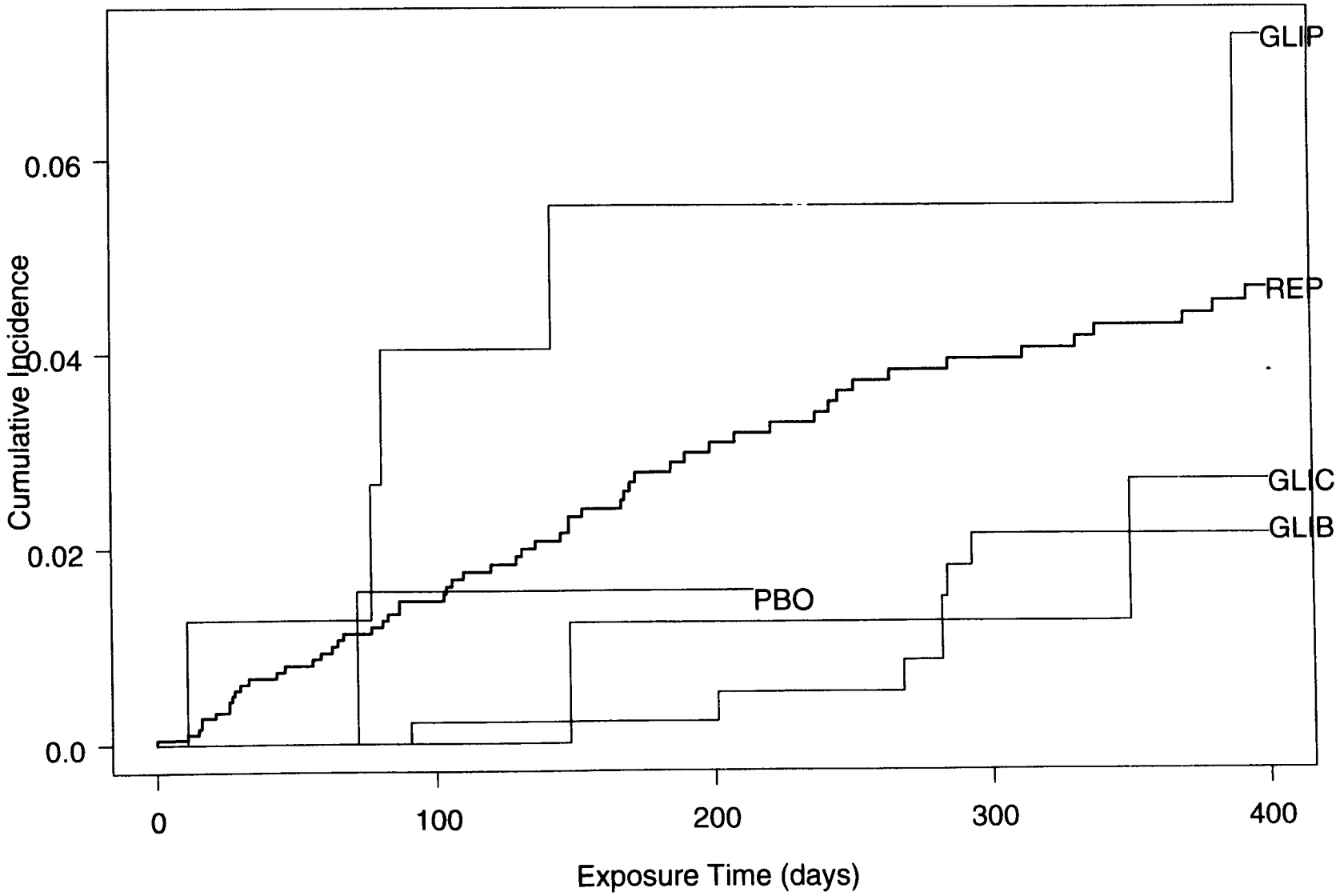
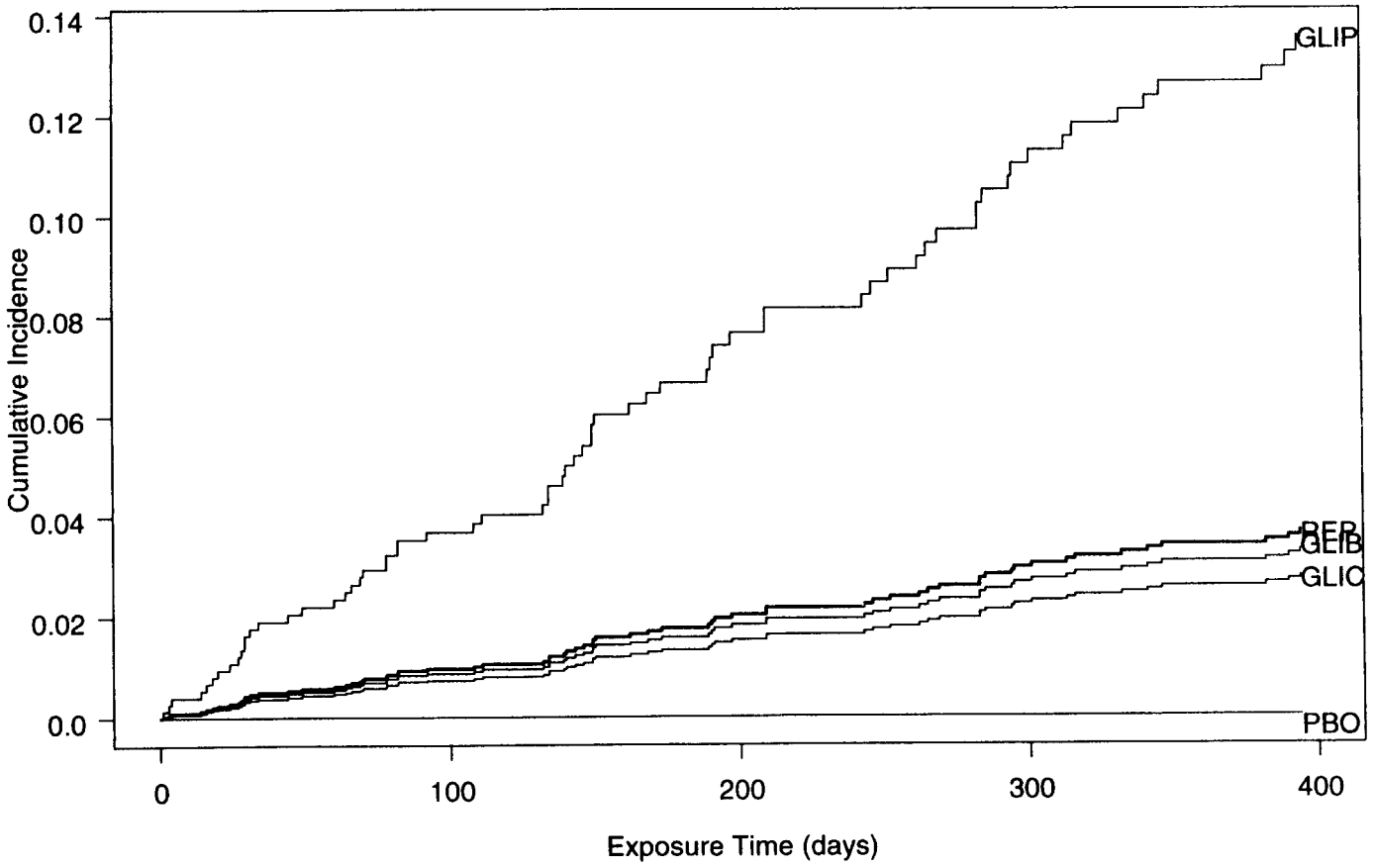
CV Serious Adverse Events



Serious CV Events, Cumulative Incidence Unadjusted



Acute Ischemic Cardiovascular Events



Cumulative Risk Adjusted for Trial & Country
& Standardized to AGEE/DCD/049/USA

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Covariates for Cardiovascular Analysis

- Age: Risk increased by 3.7% (2%-6%) per year, P<0.01
- Gender: Males/Females relative risk: 0.86 (0.65-1.13), P=0.27
- CV Medical History: Risk 1.54 (1.14-2.07), P<0.01
- Baseline ECG: Risk for Abnormal ECG at baseline with 1.75(1.27-2.41), P<0.01
- Hypoglycemia: Risk of subjects with Hypoglycemic event 1.62(1.14-2.30), P<0.01

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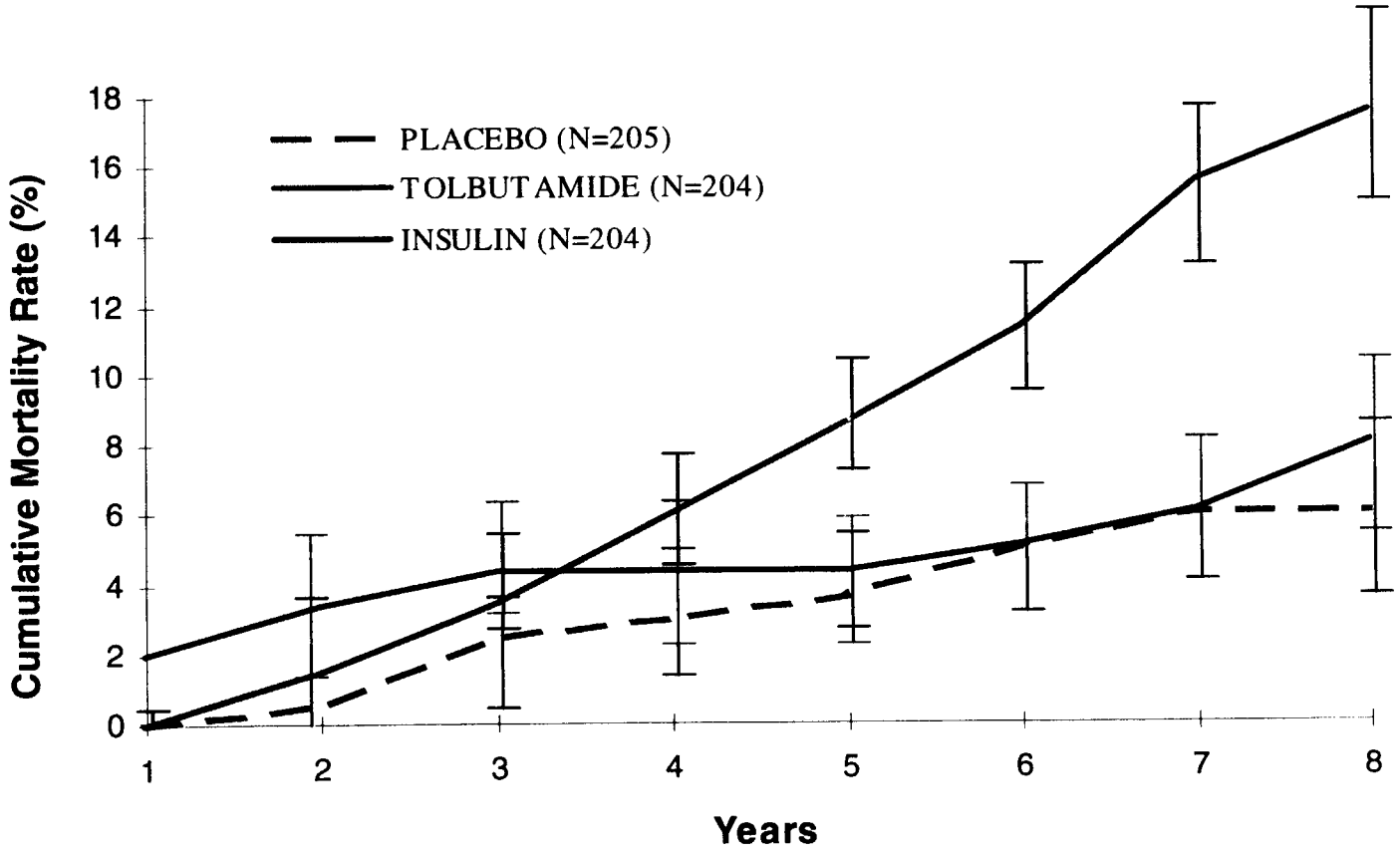
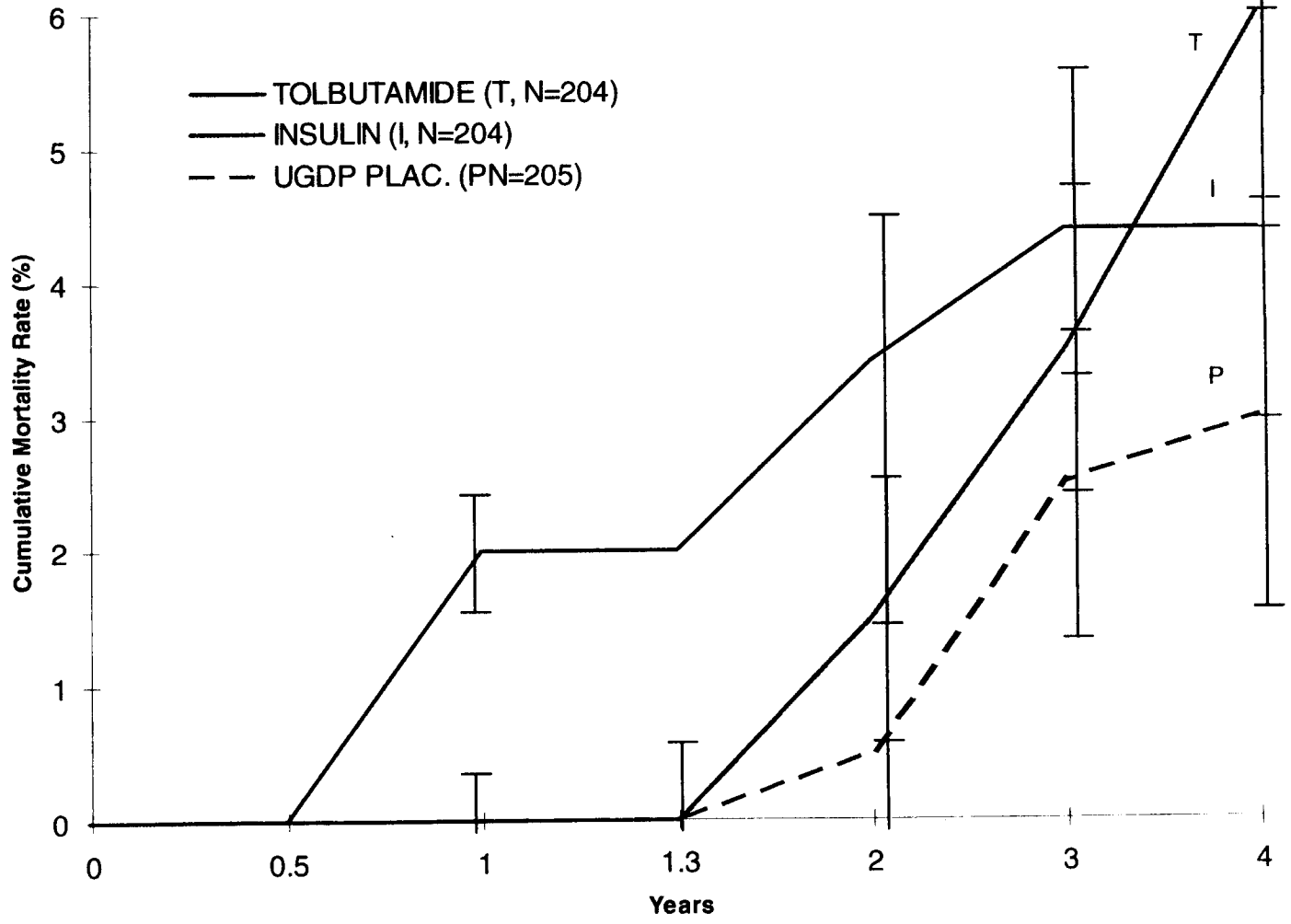
Diabetes CV Mortality in UGDP Study



Novo Nordisk

Diabetes CV Mortality in UGDP Study



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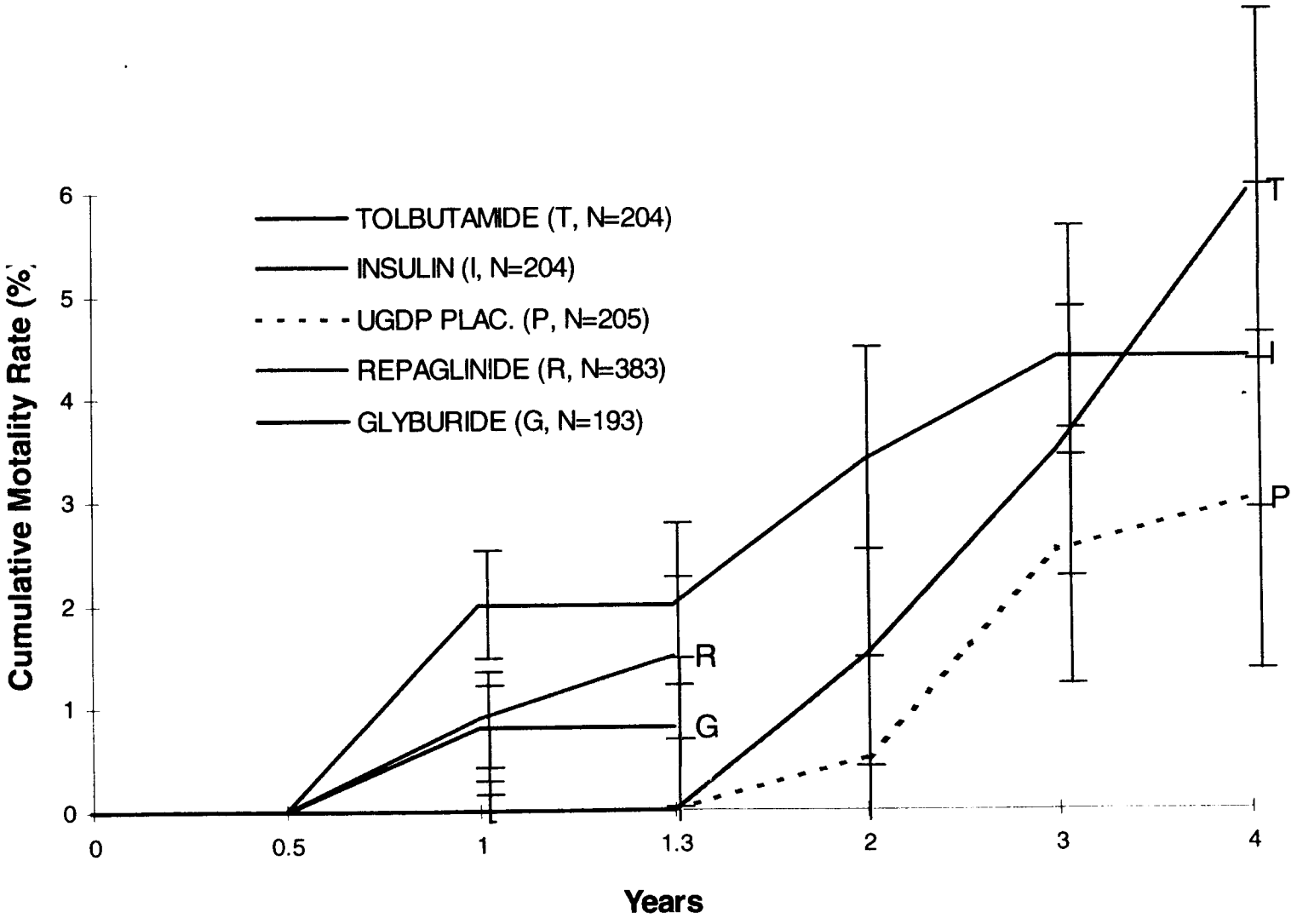
Diabetes CV Mortality in Repaglinide vs UGDP



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Safety Profile

- No excess mortality vs comparators
- Overall safety profile comparable to approved OHAs
- Acceptable to good hypoglycemia profile
- Overall CV profile is comparable to sulfonylureas
- A small increase in nonfatal CV events in comparison to Glyburide
- No safety precautions requiring dose adjustments in special populations
- Wide therapeutic index

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Preclinical Profile

- New chemical entity (NCE), benzoic acid derivative
- Oral insulin secretagogue, distinct β-cell binding sites
- No direct exocytosis, no suppression of protein synthesis
- Not mutagenic, teratogenic or carcinogenic
- No clinically relevant preclinical safety changes

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Clinical Pharmacology Profile

- Rapid onset (T_{max}= 0.7 hours), rapid plasma clearance
- Enhances insulin response to meals
- Clinically significant blood glucose response
- Effective in doses from 0.5 mg
- 100-fold AUC repaglinide over dose range recommended
- Excreted via the bile
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- BG response within 1 week (40-80 mg/dl)
- Dose-response 0.5 - 4 mg a.c. x 3
- Significant difference vs placebo
  (titration and fixed dose)
- Improves glucose control 1.6-2.9% HbA_{1c}
- Maintenance of glycemic control > 1 yr
- Substantial addition to metformin

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The Repaglinide Answer to the Clinical Need

Wayman Wendell Cheatham, M.D.

Peter Damsbo, M.D.

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Diabetes In The USA

- Approximately 18 Million Individuals With Diabetes Mellitus (2 Million Added By Revised Diagnostic Criteria)
- 16 Million Individuals With Type 2 Diabetes Mellitus
- Less Than 1/2 Are Under Any Form of Therapy

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The Graying Of Diabetes

- Today, 58% Of Individuals With Diabetes Are > 60 Years Of Age - 10 Million People
- By 2010, 24 Million Individuals Will Have Diabetes Mellitus (Aging "Baby Boomers")
- By 2010, 64% of Individuals With Diabetes Will Be > 60 Years of Age - 15 Million People

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Inadequate Therapy

- Hemoglobin A_{1c} Goal - 7.0% or Below
- Intervention Indicated - 8.0% or Above
- Average Hemoglobin A_{1c} In Individuals With Diabetes - 9.1%

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Possible Reasons For Inadequate Therapy

- Delayed Diagnosis
- Low Sensitivity to Seriousness of Disorder
- Fear of Hypoglycemia with Effective Rx
- Non-compliance
- Primary Failure Without Induction of Alternate Rx
- Secondary Failure Without Induction of Alternate Rx

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The Clinical Dilemma

- Near normalization of blood glucose has become a clinical aim to prevent late diabetic complications.
- Inability to reach near normal blood glucose with OHAs is not solely due to primary or secondary failure, but often a chosen underdosing to avoid inducing hypoglycemia.
- Thus, long term complications may be traded for avoidance of hypoglycemia in the present.

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Need Continues, 1994

"Severe hypoglycemia is the major complication of sulfonylurea therapy... Elderly patients are more susceptible to hypoglycemia, particularly when they have a tendency to skip meals or when renal function is impaired."

Ref.: Medical Management of Non-Insulin-Dependent (Type II) Diabetes; (Third Edition) p.41. ***ADA-CEP*** *1994.*

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Repaglinide Pharmacology & Pharmacokinetics

Related to Hypoglycemia

Pharmacology (animal models)

- Reduced effect on insulin release at low blood glucose
- No direct exocytosis (contrary to SU's)

Pharmacokinetics (human data)

- Short action, insulin reverts to control levels between doses and meals
- Meal related dosing; "no meal- no dose"

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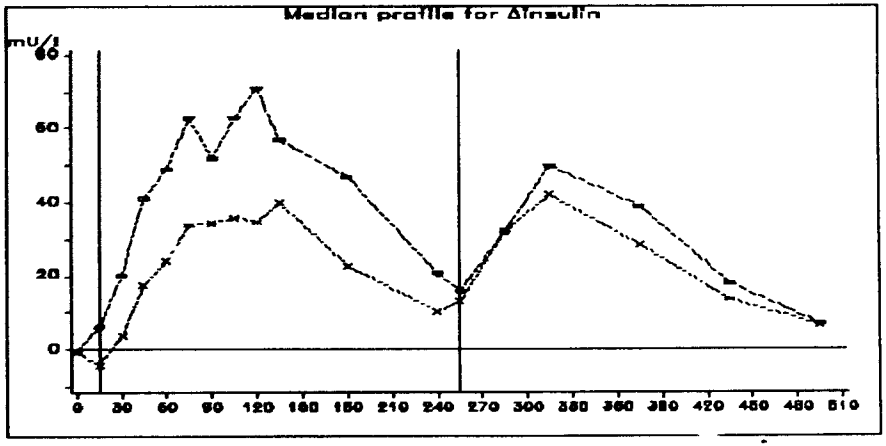
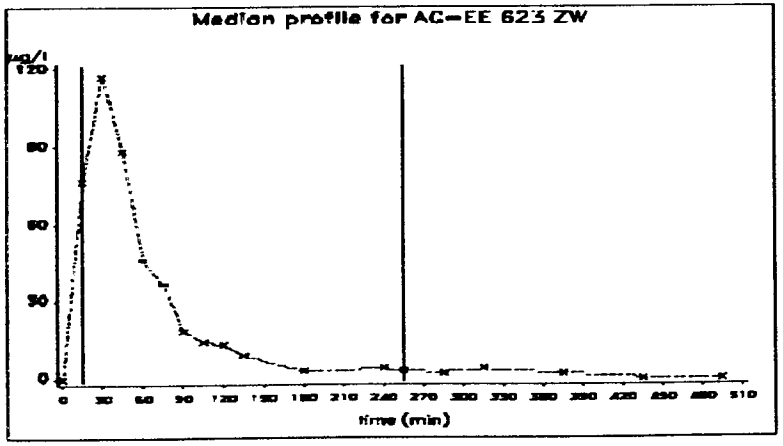
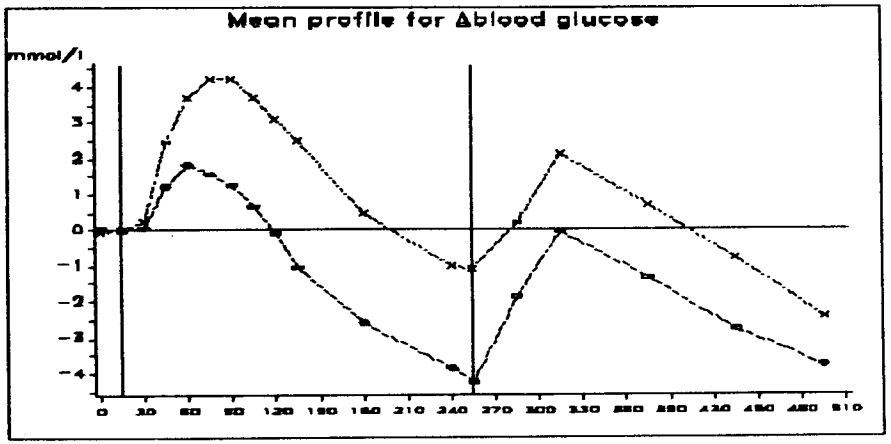
PK/PD Profile of 4 mg Repaglinide

Short action - insulin reverts to control levels between doses and meals







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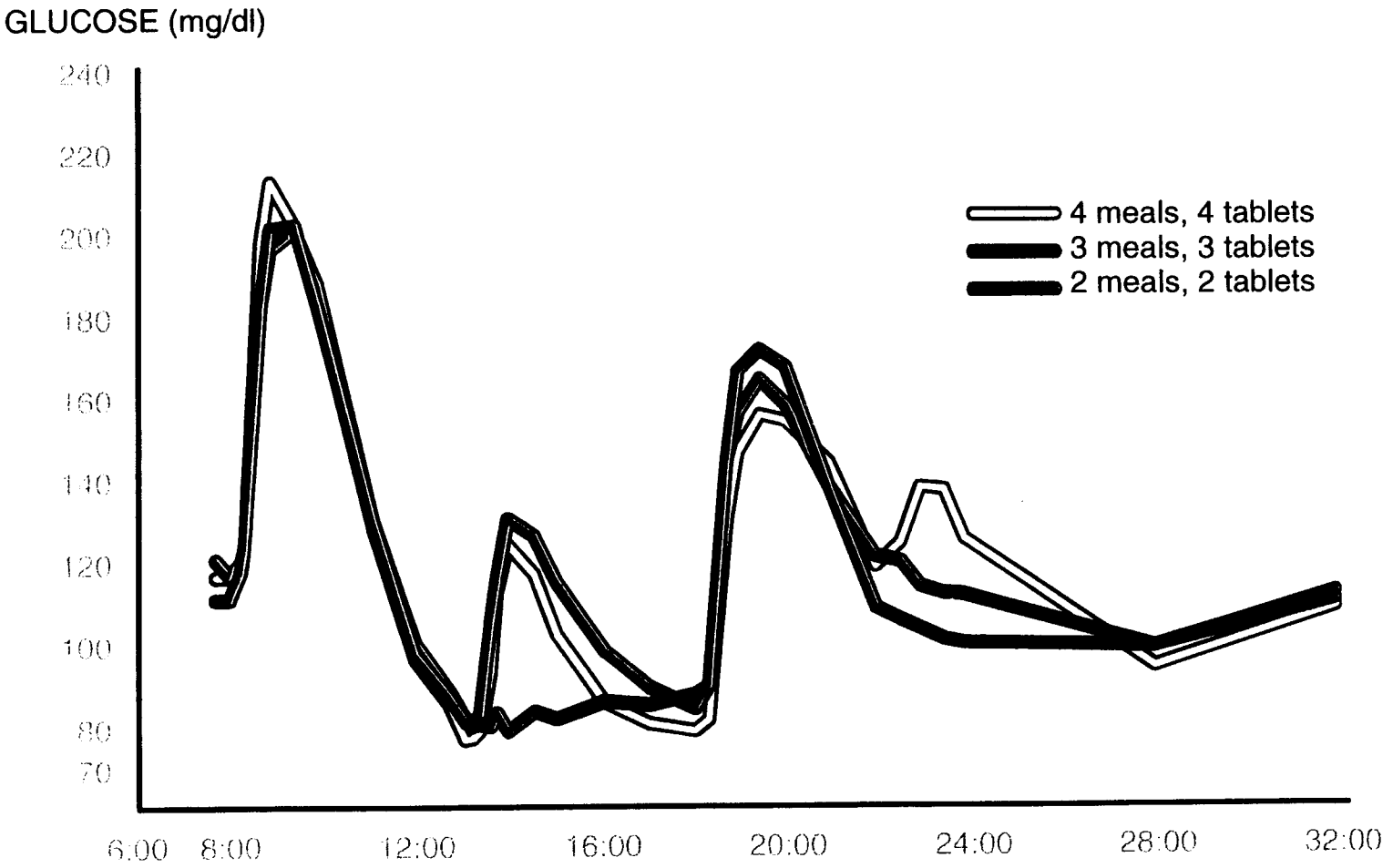
Fixed/Mixed Concept



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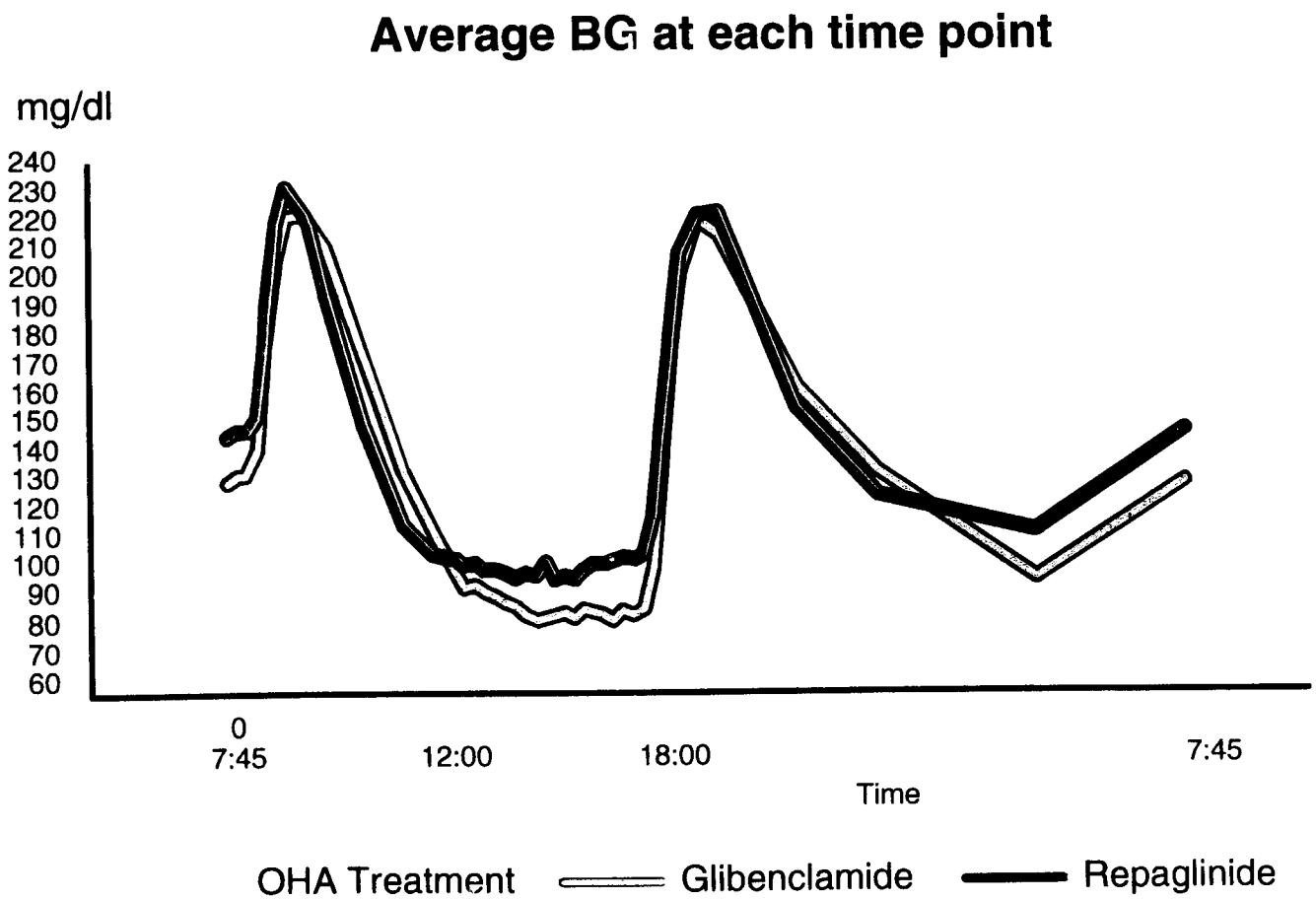
"Skip-a-Meal" Study



Hypoglycemic Events When a Meal is Skipped

Glyburide	6 patients
Repaglinide	0 patients

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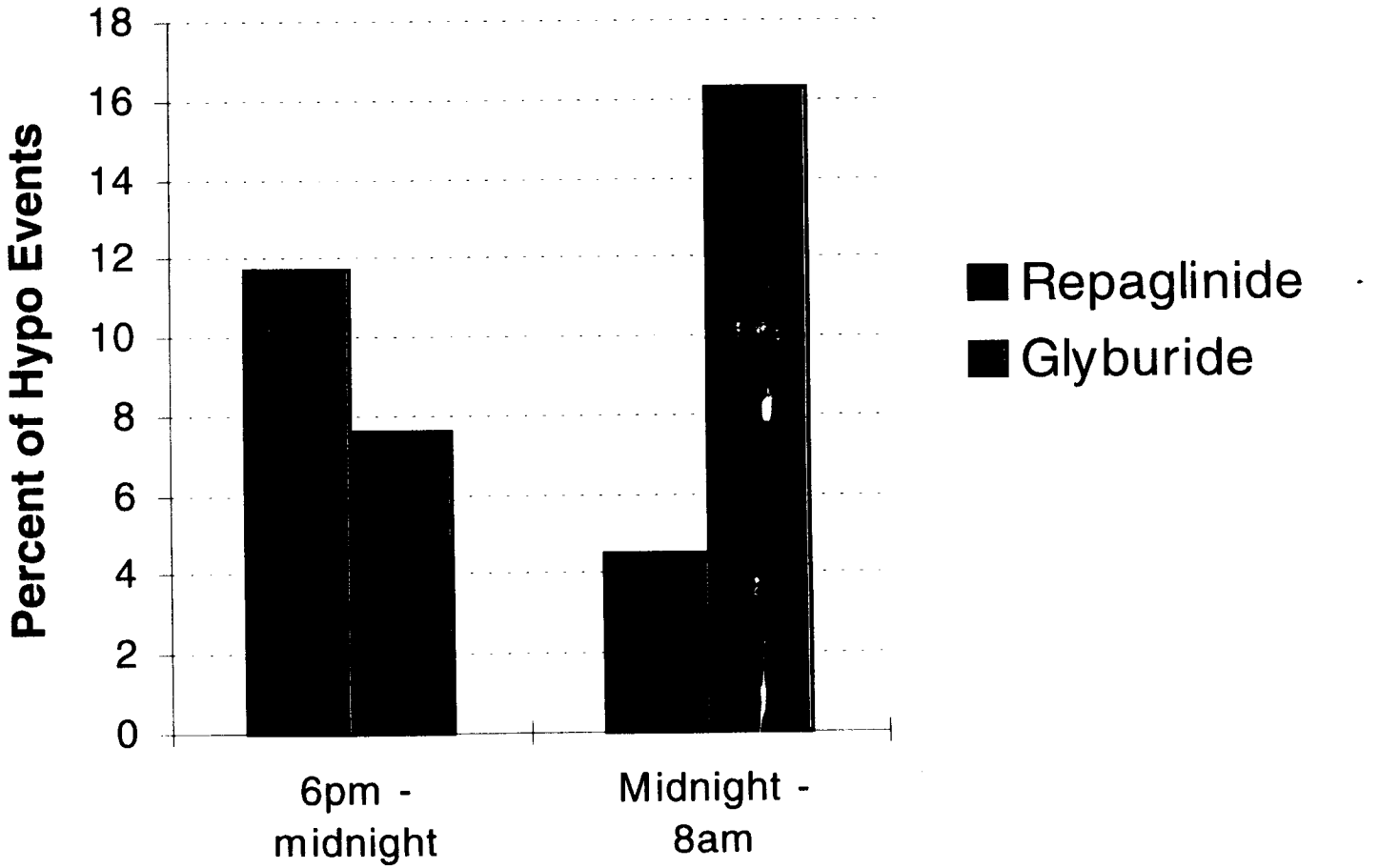
Nocturnal Hypoglycemia in 1-yr Comparator Trials (for 179 Repaglinide Events vs 92 Glyburide Events)



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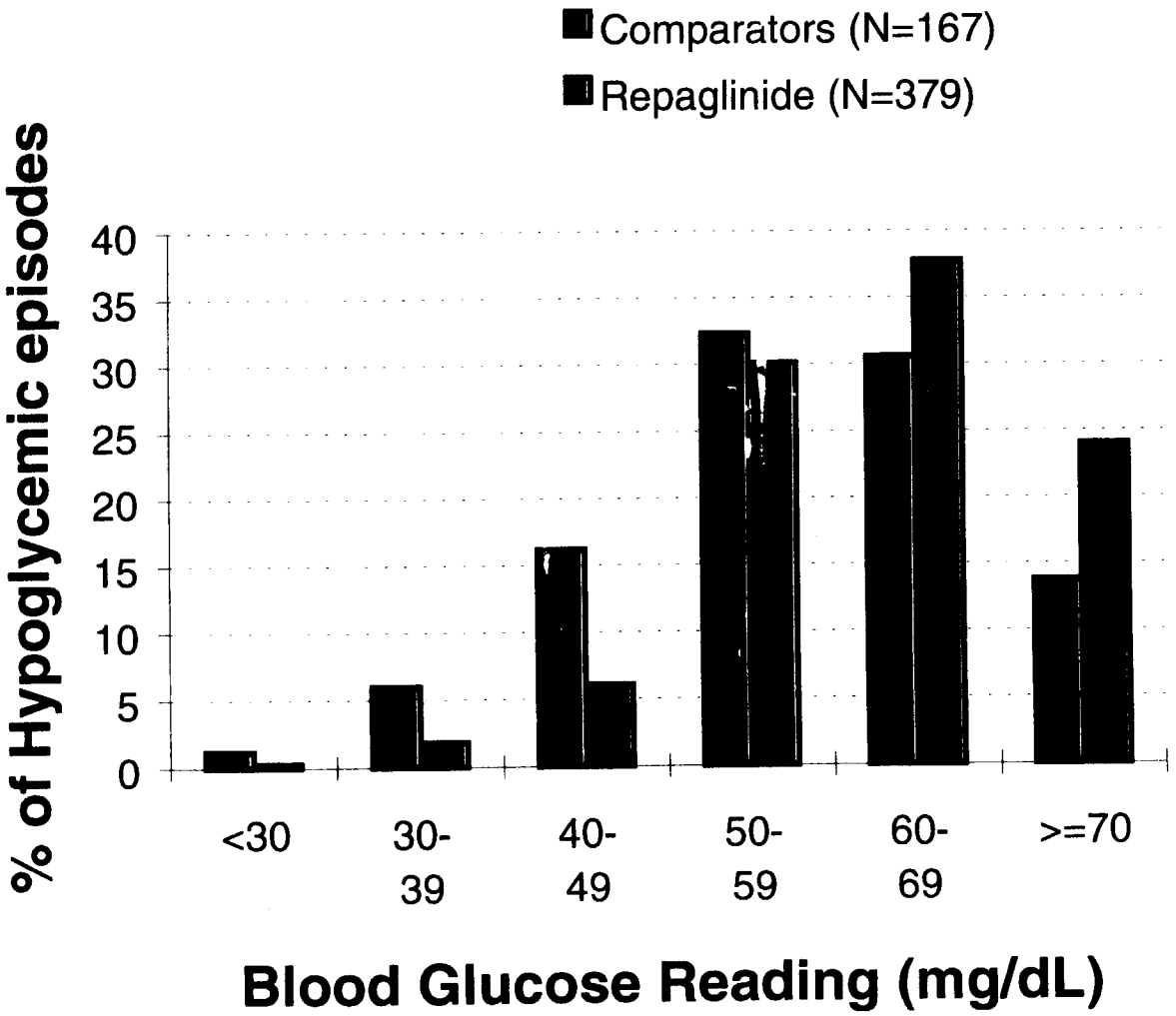
Hypoglycemia by Blood Glucose Monitoring

1-year trials



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Hypoglycemia in 1-Year Trials

All Patients	Rep	Glyb	Glip	Glic
# exposed	1228	417	81	99
% w hypo	16	20	19	15
% hypo d/c	1.5	2.6	2.5	4.0
% hypo w BG	50	45	93	73
% w BG < 45	13	27	29	18
Mean hypo BG	63	56	59	51

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Hypoglycemia in 1-Year Trials

Elderly (>65 yrs)	Rep	Glyb	Glip	Glic
# exposed	343	131	30	19
% w hypo	16	18	17	5
% hypo d/c	1.5	4.6	0.0	0.0
% hypo w BG	45	63	100	0
% w BG < 45	8	33	60	0
Mean hypo BG	68	55	50	N/A

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Hypoglycemia Summary

- No reported hospitalizations, coma or deaths
- Severe reactions (assistance required) less often than comparators
- Fewer nocturnal hypoglycemic events
- Discontinuations less often than comparators
- No increased frequency in elderly (>65) compared to younger patients

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Conclusion

- Preprandial treatment with Repaglinide leads to significantly improved glycemic control—yet the risk of low blood glucose values and severe hypoglycemic events is low.

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Risk/Benefit Profile of Prandin

- Fast onset insulin release with meals
- Flexibility of dosing dependent on meals - not meals dictated by dosing
- Dosing compliance related to meals
- "Physiologic" insulin profile before meals and at night
- Lower insulin "coverage" at night
- Rapid insulin response and decrease in BG
- Symptomatic hypoglycemia events not severe or serious
- Efficacy response within one week (FPG)
- Glycemic control over 1 year (HbA_{1c})
- Long term natural history not yet studied (primary, secondary failure, β cell sparing)
- Type 2 complications to be defined; CV risk comparable to range expected

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PRANDIN™ (Repaglinide) TABLETS
NDA 20-741

Phase IV CV Study

Gerald A Faich, M.D.

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Repaglinide - Safety Analysis Conclusions

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- Overall safety profile comparable to approved OHAs
- Acceptable to good hypoglycemia profile
- Overall CV profile is comparable to sulfonylureas
- A small increase in nonfatal CV events in comparison to Glyburide
- No safety precautions requiring dose adjustments in special populations
- Wide therapeutic index

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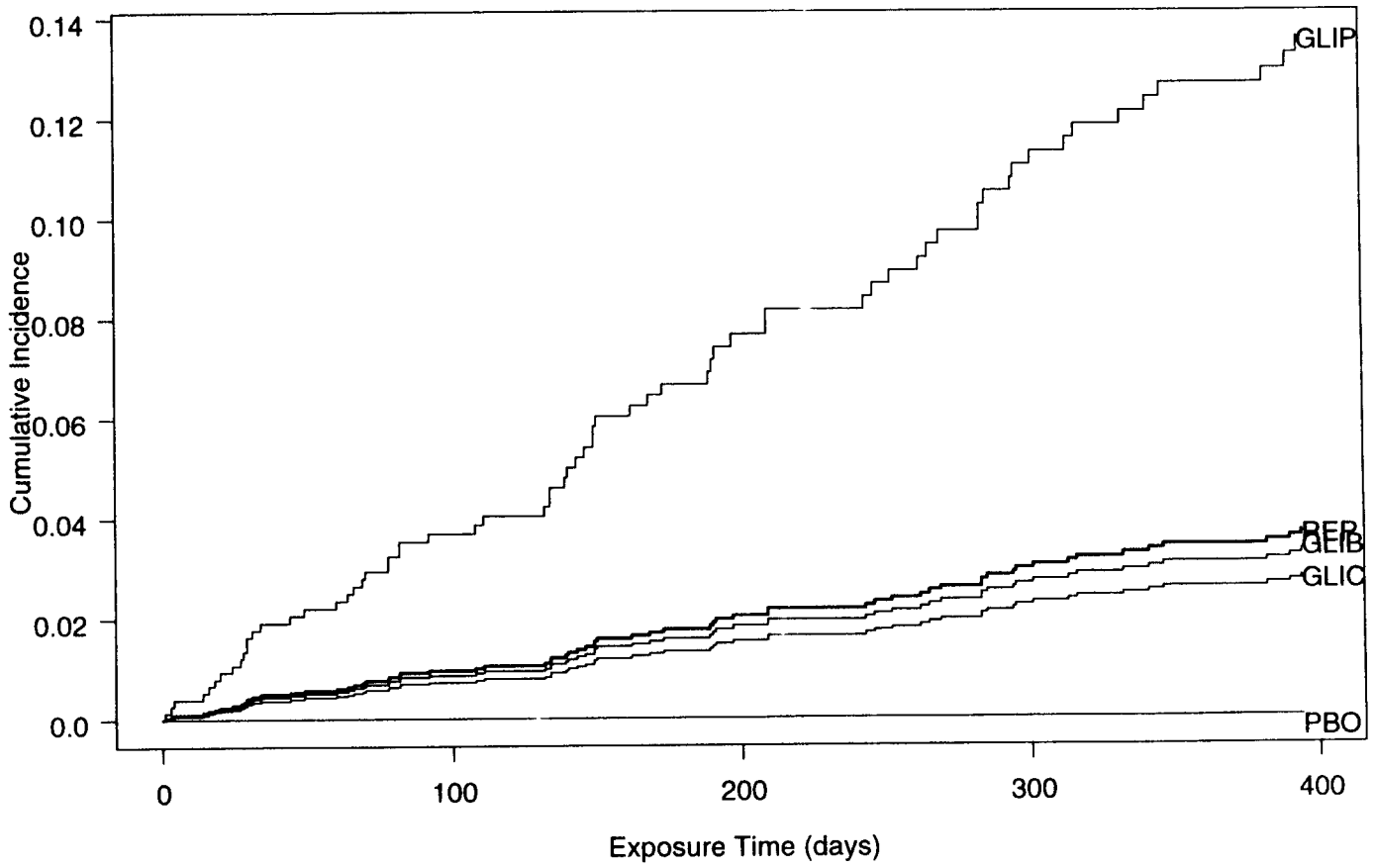
Acute Ischemic Cardiovascular Events



Cumulative Risk Adjusted for Trial & Country
& Standardized to AGEE/DCD/049/USA

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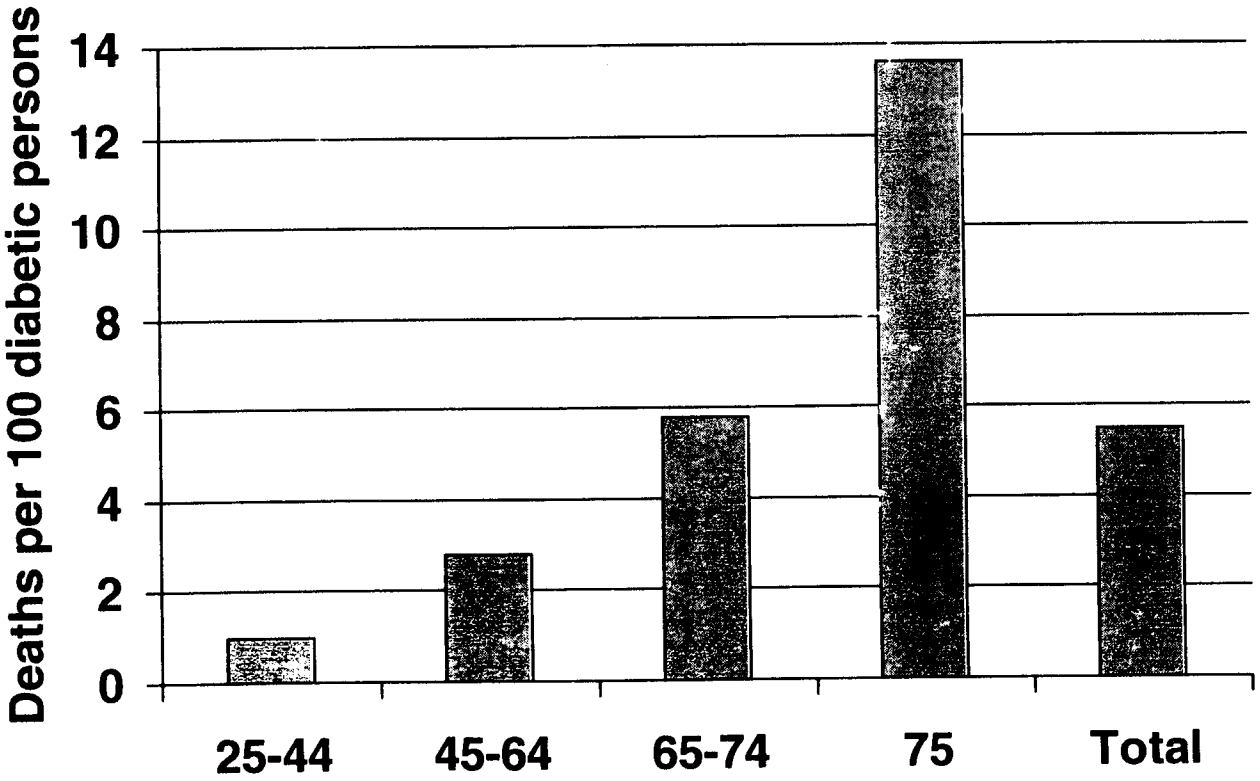
Death Rates by Age for Persons with Diabetes



NMFS, 1986 National Mortality Followback Survey: NHEFS, 1974-82

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Cardiovascular Event Rate inType 2 Patients

Ref	Age	F/UP duration (yr)	Study Design	Event	Annualized Event Rate
London/WHO	35-54	8	Cohort 497)*	IHD/CVD/PVD	4.3%
Multiple Risk Facto Intervention Trial	50-57	12	RCT (5163 men)	Total Mortality	1.6%
Early Treatment of Diabetic Retinopathy Study	>50	5	RCT (507)	MI/Stroke/ Vascular Death	4.5%
Aarhus Cohorte	60-74	8.5	Cohort (228)	Total Mortality	5.7%
Prospective Study of Microalbuminurea as Predictor of Mortality in NIDDM	66 (mean)	6.1	Cohort (246)	Total Mortality IHD/CVD Mortality	6.0% 2.6%
Finish 5 year Study of Atherosclerosis Disease in Diabetics and Nondiabetics	45-64	5	Cohort (109)	MI/Stroke/ Vascular death	4.8%
UKPDS	52 (mean)	9	RCT (5102)	MI/stroke/ sudden/IHD	2.3%
HOPE	≥55	1	RCT (3463)*	MI/stroke/CV death	4.6%
VACSDM	40-69	2.25	RCT (153)	CV death/MI/stroke amputation	5.8

*Includes some patients with IDDM

Novo Nordisk

Expert Consultant Group

- Sean Dinneen, M.D., M.S.C.
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Possible Approaches

- Passive Surveillance
  (considered inadequate to provide risk estimates due to underreporting etc.)
- Prescription/Event monitoring
  (good estimates, very confounder sensitive)
- Case/control study
  (cannot provide discontinuation data, long time to sufficient data with new drug)
- Randomized, Simplified Clinical Trial
  (large undertaking internal comparaptor, feasibility, resistant to confounders)

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Critical Issues for Phase IV Studies

- Representative Population
- The Right Endpoints
- Sufficient Power
- Timeliness

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Design Considerations

- What comparator(s) is (are) essential?
- Should the study population be restricted?
- What endpoints can be rigorously documented?
  - —(Cardiac hospitalizations and all cause mortality)
- Stopping rule and ethical issues
- Common treatment goals (blood glucose/HbA1c)
- What will be secondary endpoints:
  - —Therapeutic failure rates
  - —Serious hypoglycemia

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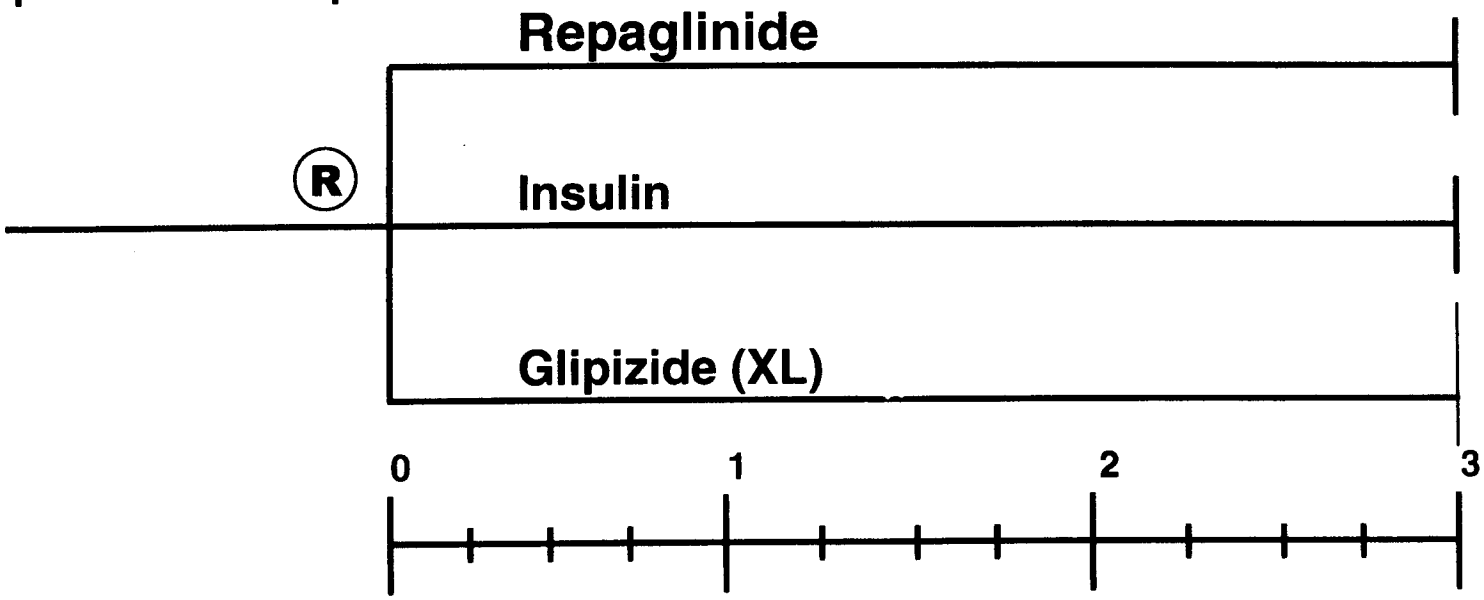
Study Size Determinants

- Number of comparators
- Level of statistical power (1-β=0.80)
- Relative risk target: RR=1.0 (0.7-1.3)
- Length of follow up (3-4 years)
- Higher risk subset vs. all patients?
  - —Assume event incidence 4% (3.5 -5%)/year
- Practical limitations, including timely results

Phase IV CV Trial

Tp 2, naïve or previous OHA
HbA1c > 7, ≥ 45 years
Representative Population

N= 5000-6000 pt
Open Label



HbA1c	x	x	x	x	
EKG	x				
Cardiac Events	[x]	→			
Drug therapy	[x]	→			
Severe Hypoglyc.	[x]	→			
DSMB Review		x	x	x	x	x

Elements of Study Design

- Randomized, simplified clinical trial
- Multicenter
- Exposure 3-4 years
- Comparators: Repaglinide, Insulin, Glipizide
- Primary endpoints
  - —Cardiac death
  - —Hospitalization for acute cardiac disease
  - —All cause mortality

Ideal Pharmacodynamics

- Adequate insulin response and level
- Intact feed back mechanism
- Insulin in response to glucose load
- Control sensitive to hypoglycemia
- Long term (natural) history improvement
- Prevention of complications

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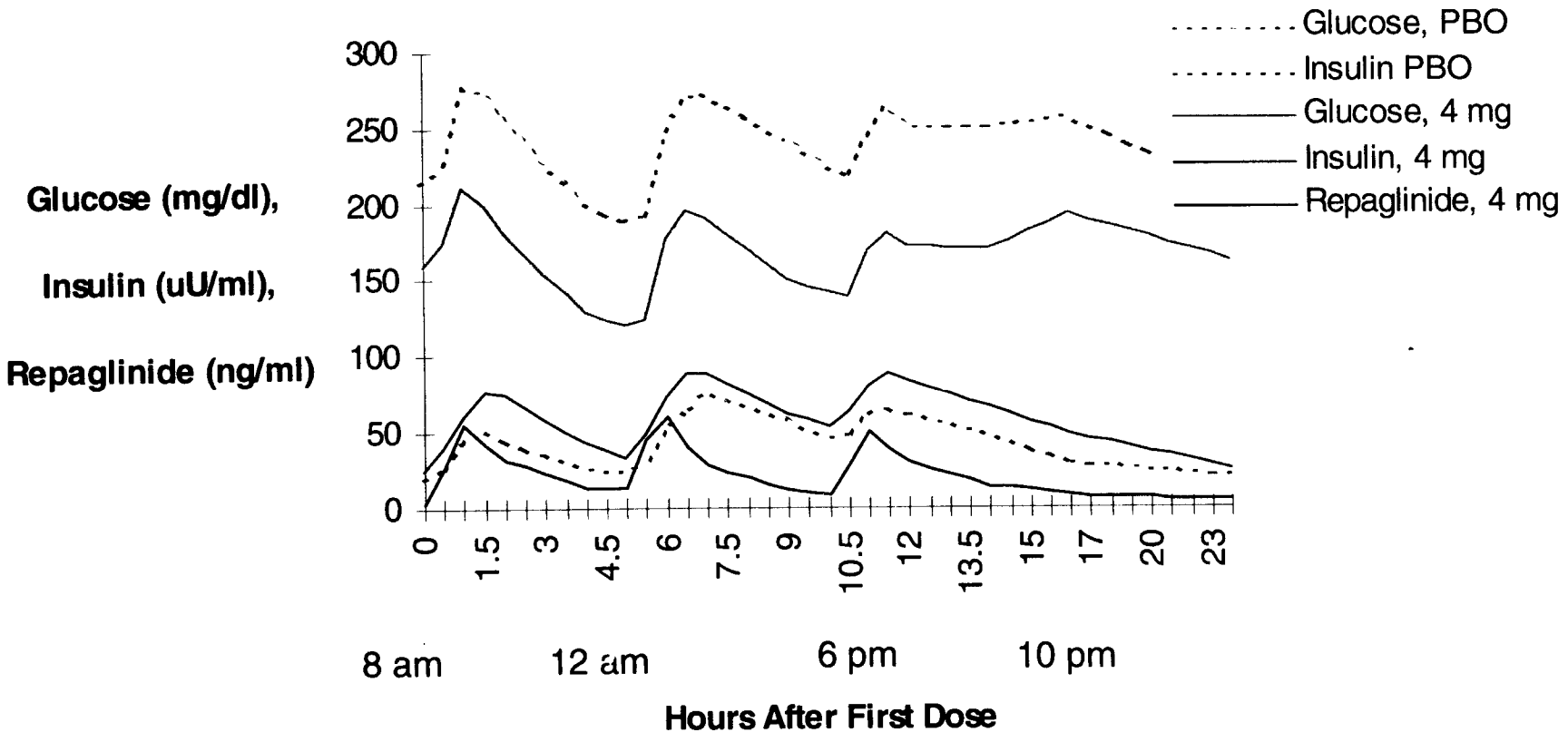
Steady State Pk/PD in Type II Diabetes Patients



Patient Controlled (Flexible) ~~Dosing~~

- Dose should be taken before each meal
- Dose to meal interval can be 30 to 0 minutes without change in PK or efficacy
- Dose should be skipped if no meal is planned/available
- Smaller doses give lower insulin response for a meal
- Doses can be taken 2, 3 or times a day
- Dose titration may not be required

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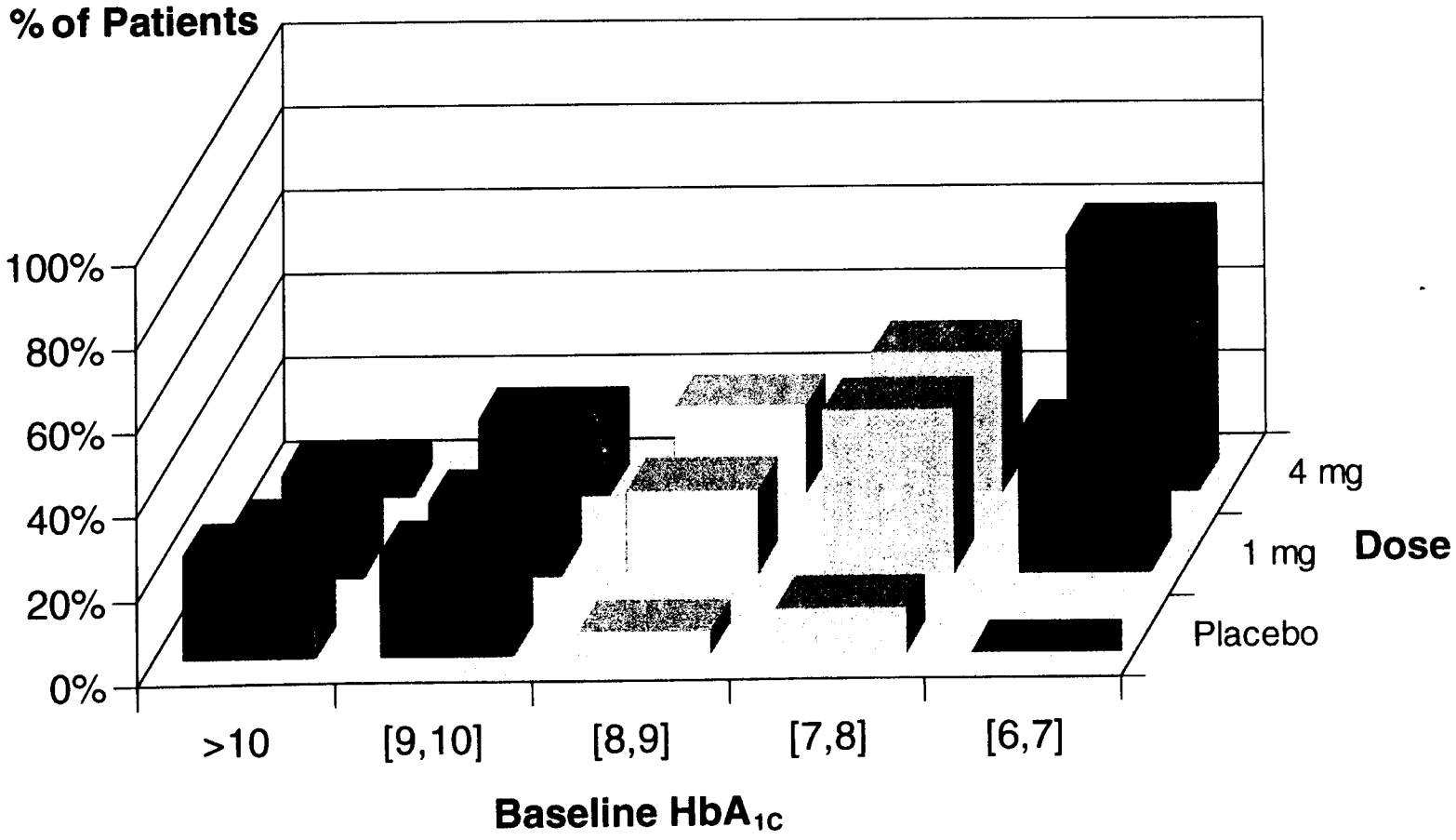
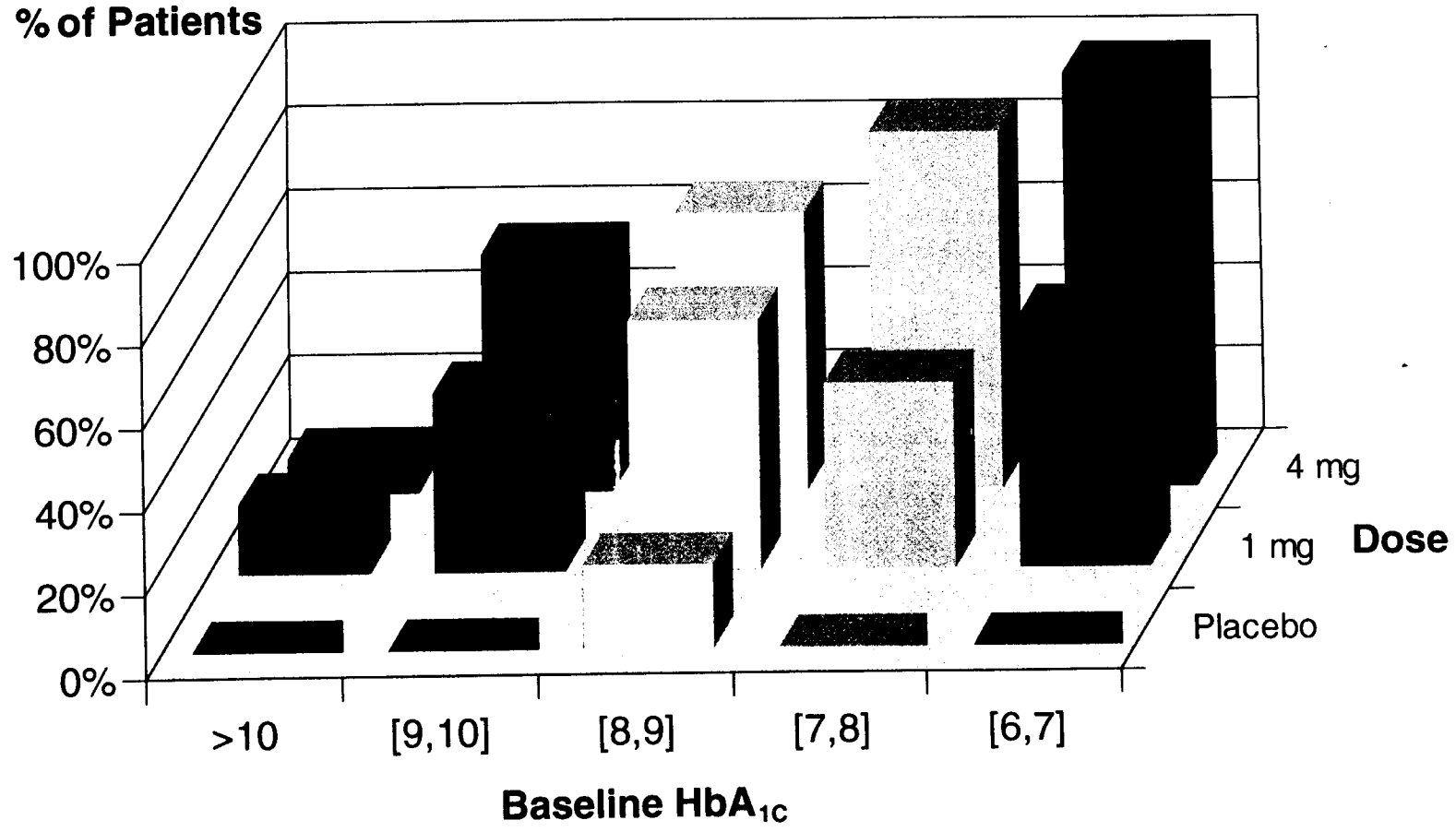
Hypoglycemia by Dose and HbA_{1C}

Previously Treated

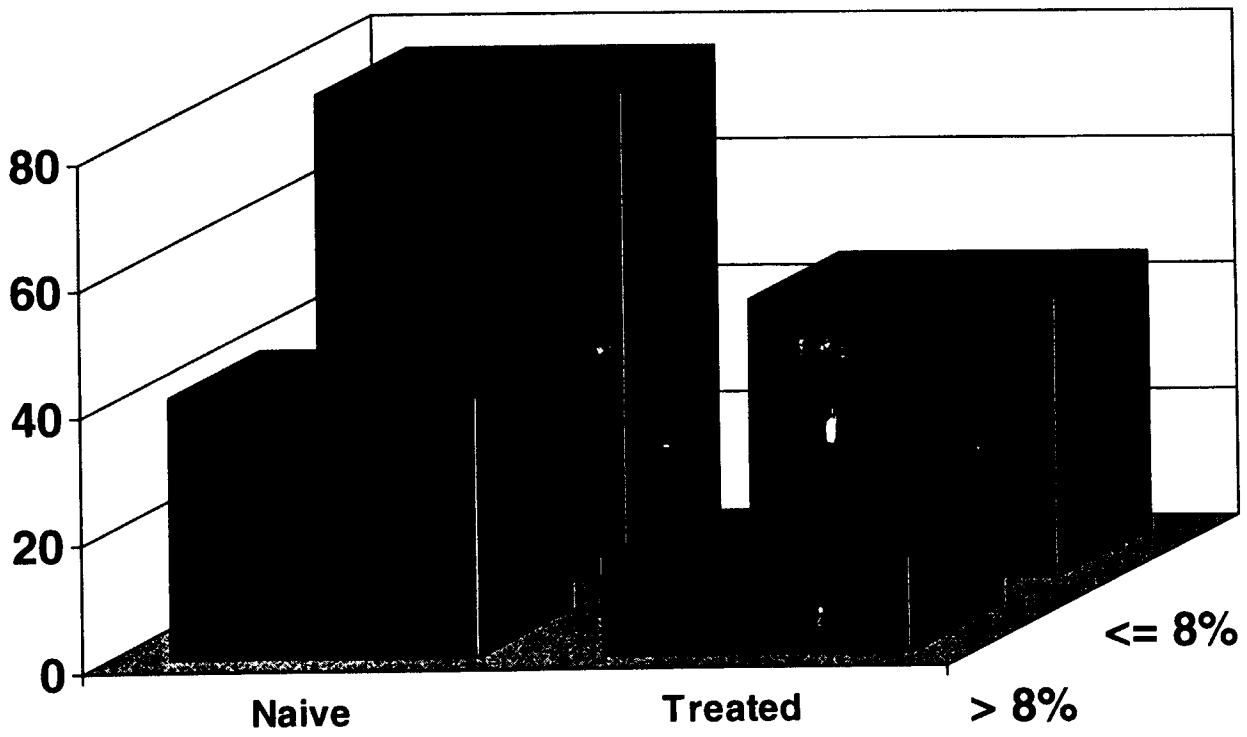


Hypoglycemia by Dose and HbA_{1C}

Naive



Hypoglycemic Predictors (065, 4 mg)



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Hypoglycemia by Initial Dose (1-YearTrials)

Dose at Start of Titration	Number of Patients	% with Hypoglycemia
0.5	616	21.1
1.0†	558	12.0
2.0‡	54	3.7

† At the discretion of the investigators, patients with FBG≥ 160 mg/dL while on previous SU therapy were allowed to start on 1 mg Repaglinide, a.c.x 3

‡ Patients in one trial, 050/D/NL, were allowed to start titration on 2 mg Repaglinide, a.c.x 3, if they had FBG levels >180 mg/dl

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Risk/Benefit Profile of Prandin

- Fast onset insulin release with meals
- Flexibility of dosing dependent on meals - not meals dictated by dosing
- Dosing compliance related to meals
- "Physiologic" insulin profile before meals and at night
- Lower insulin "coverage" at night
- Rapid insulin response and decrease in BG
- Symptomatic hypoglycemia events not severe or serious
- Efficacy response within one week (FPG)
- Glycemic control over 1 year (HbA_{1c})
- Long term natural history not yet studied (primary, secondary failure, β cell sparing)
- Type 2 complications to be defined; CV risk comparable to range expected

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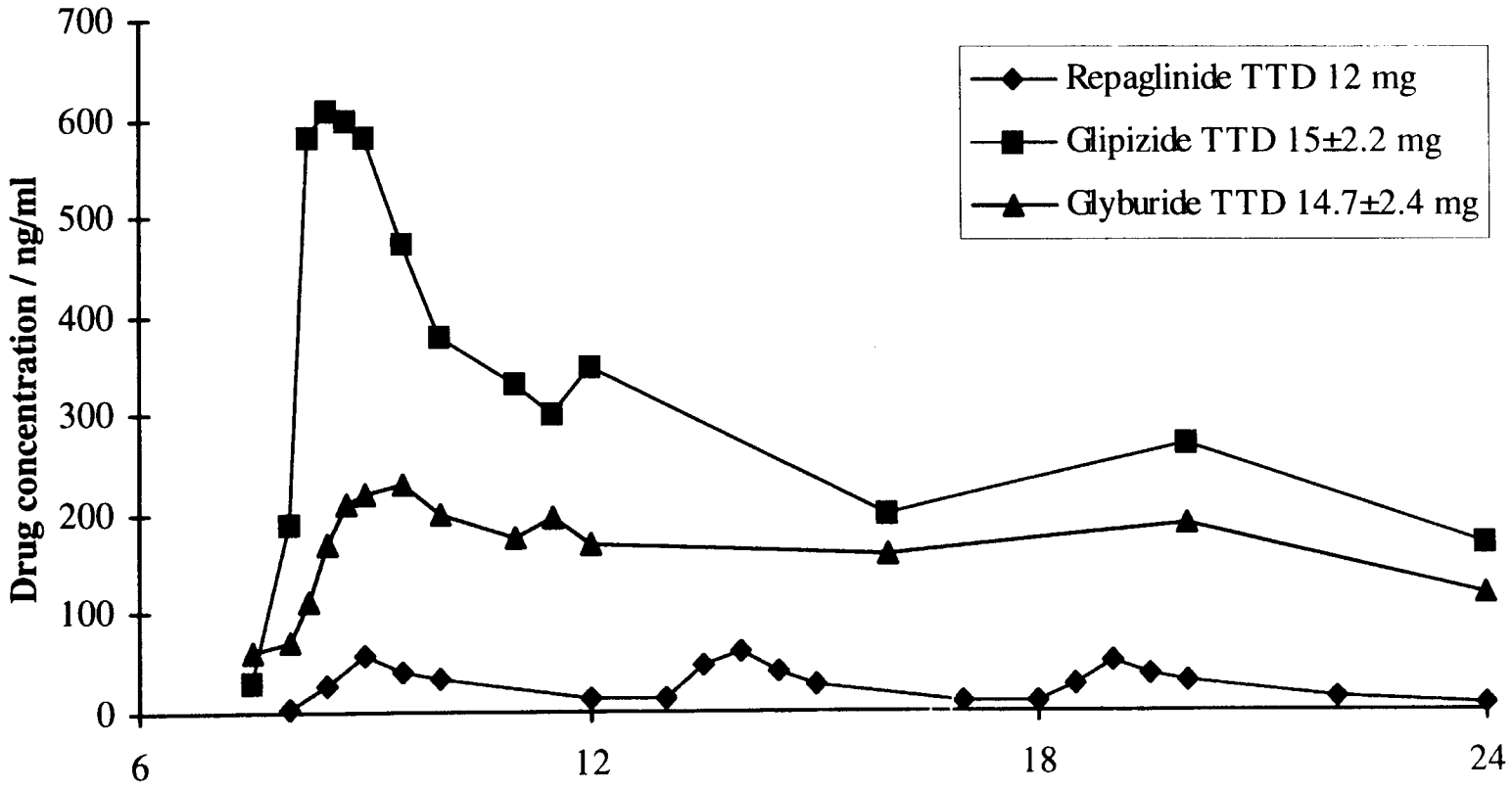
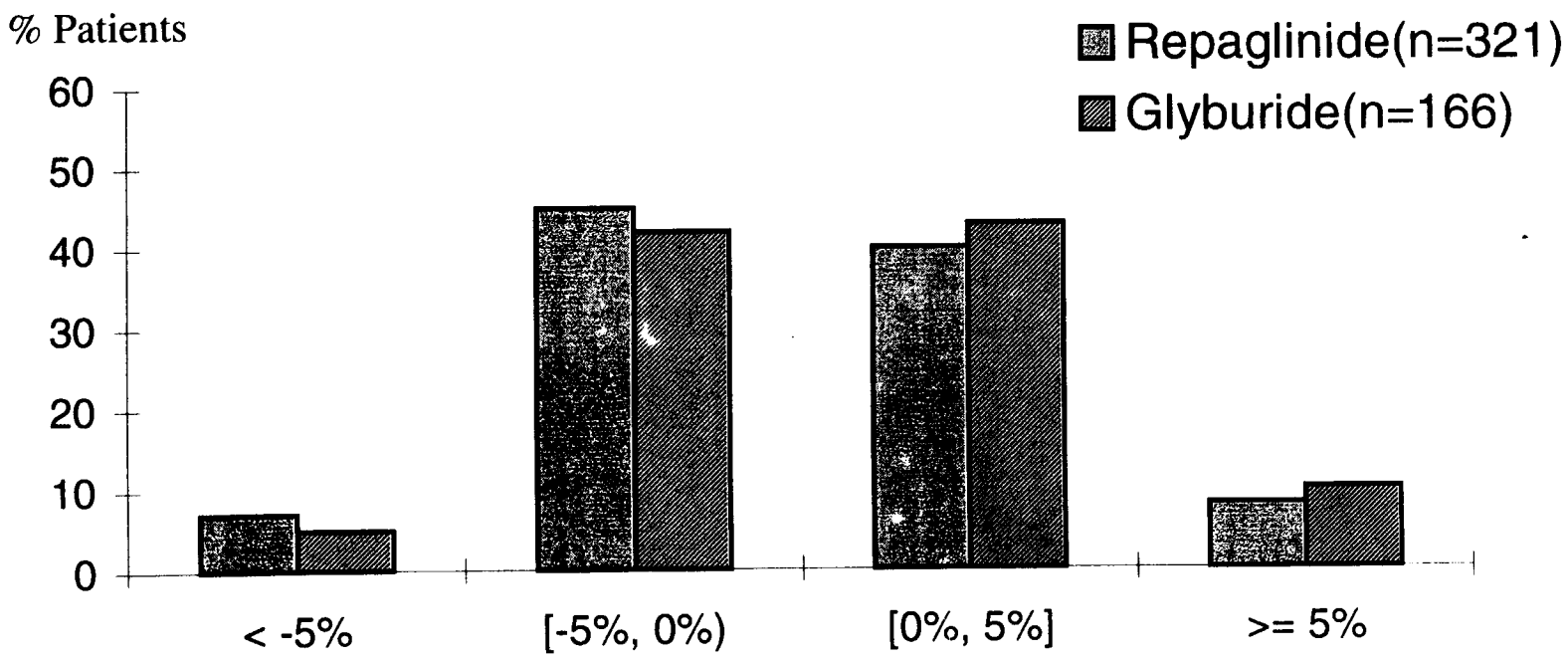
Insulin secretagogue bioavailability timing



Groop L et al. Diabetes Care. 1987;10: 671-8. and 064/USA.

Weight Change 049 - All Patients



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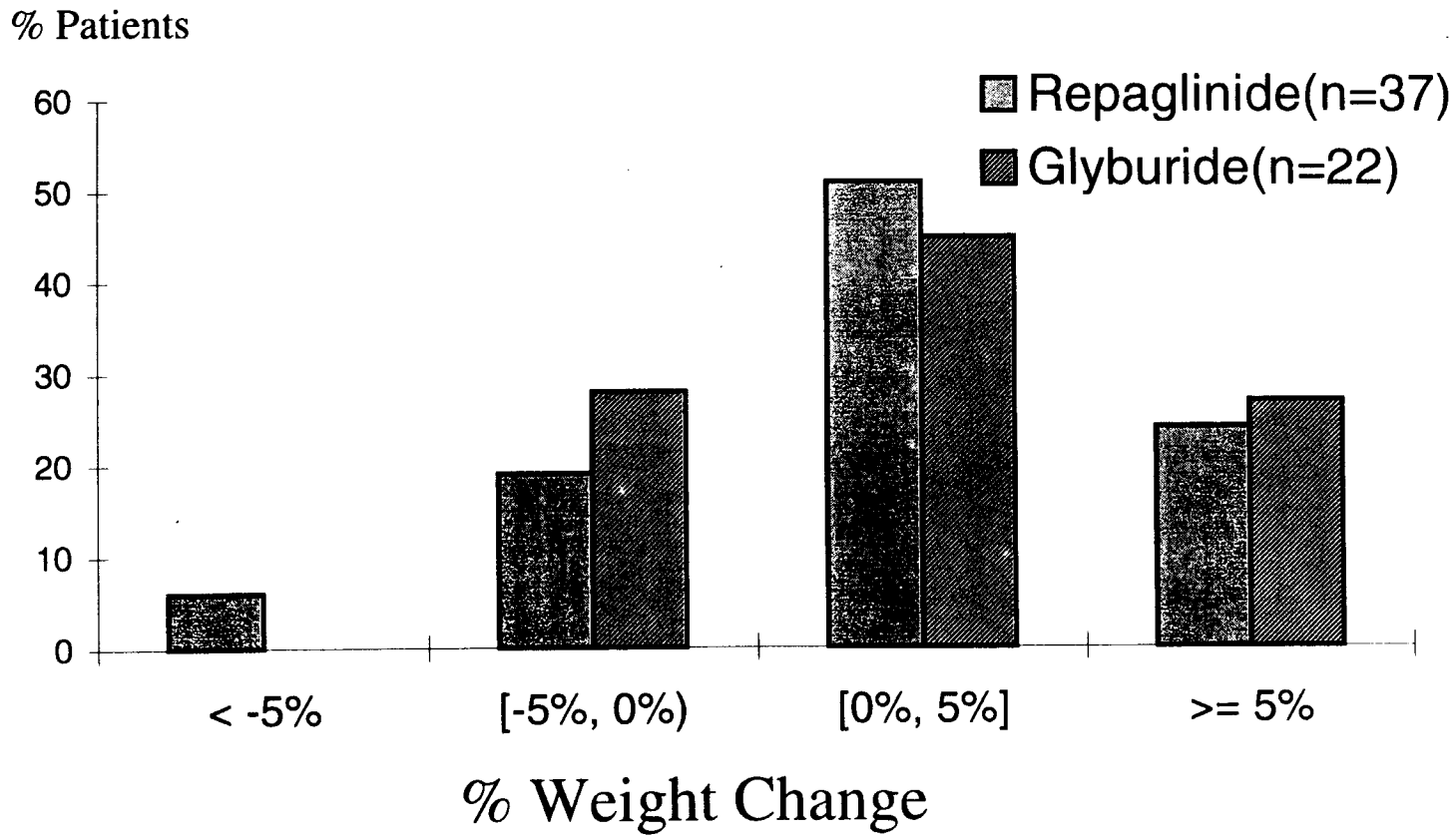
Weight Change 049 - Naïve Patients



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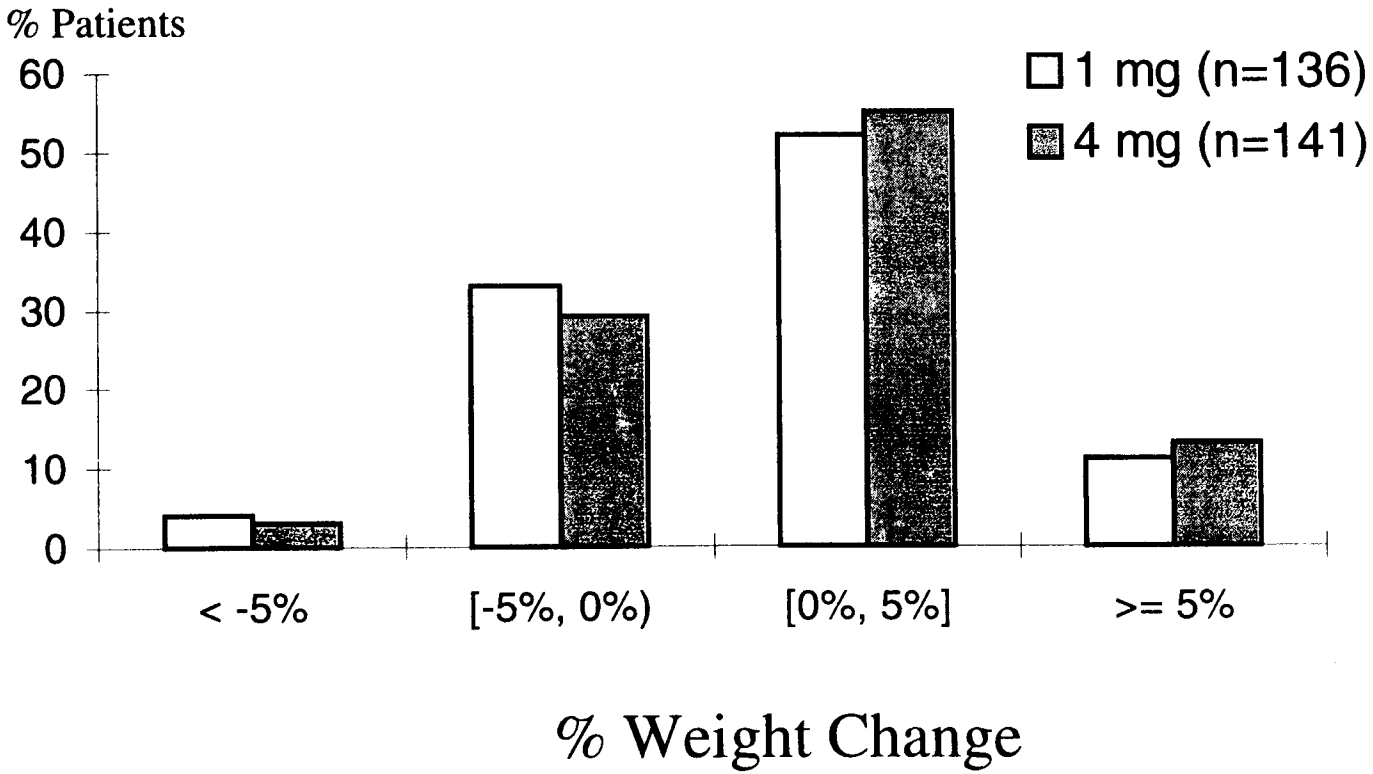
Weight Change 065 - All Patients



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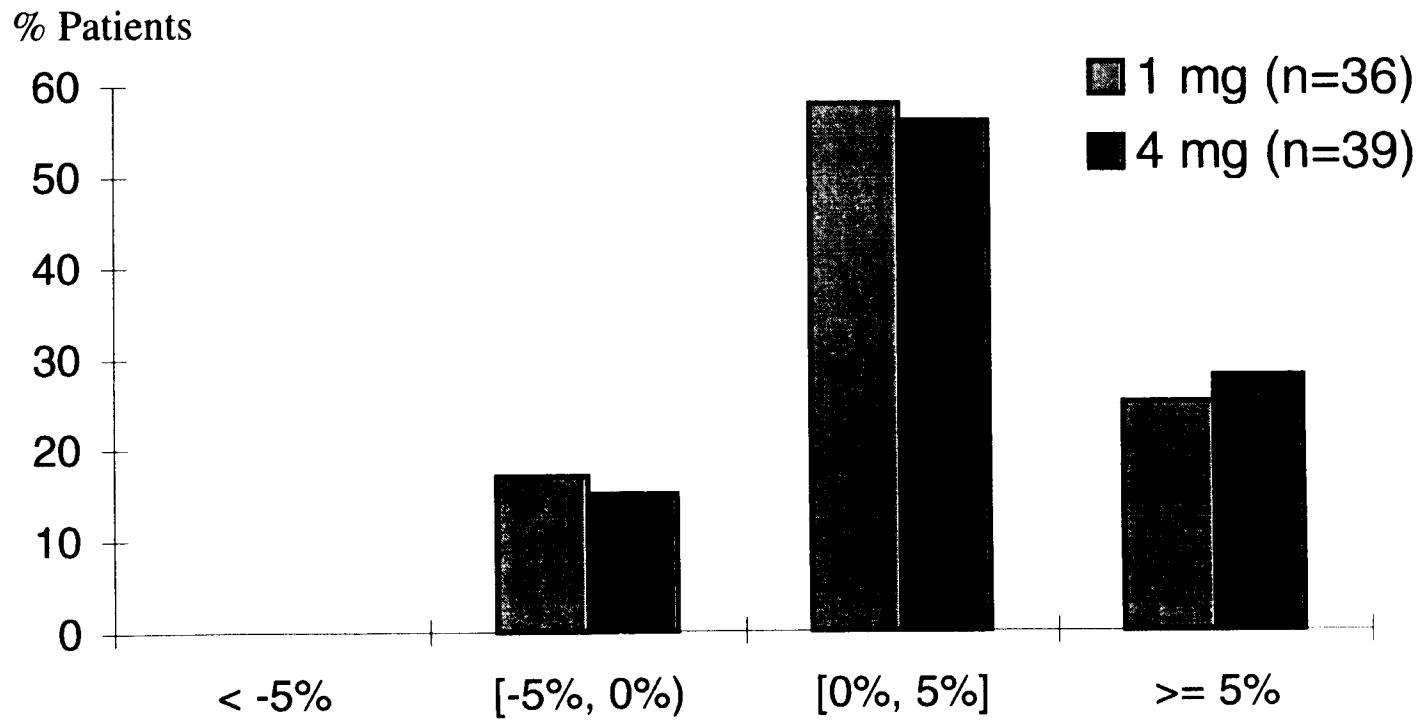
Weight Change 065, Naïve Patients



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Body Weight (kg) Change

Trial		N	Mean Change	Max Loss	Max Gain
033/USA	Rep	64	0.7	-7.7	9.5
	Plc	32	-2.0	-7.7	1.8
065/USA	1 mg	129	0.9	-10	15
	4 mg	132	1.1	-6.4	11.8
	Plc	66	-2.4	-8.6	3.6
049/USA	Rep	320	0.1	-22.9	19
	Glyb	166	0.2	-12.3	11.8
EU 1-year	Rep	832	0	-12	13.9
	Glyb	219	0.3	-9.1	9.7
	Glip	79	-0.7	-8	8.4
	Glic	96	0.1	-22	15

Body Weight (kg) Change

Trial	N	Mean Change	Max Loss	Max Gain
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065/USA				
1 mg	129	0.9	-10	15
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