

Fig. 2

Percentage of Patients Able to Achieve a 1% or Better Decrease in HgbA1c by Treatment Dose: Study 302

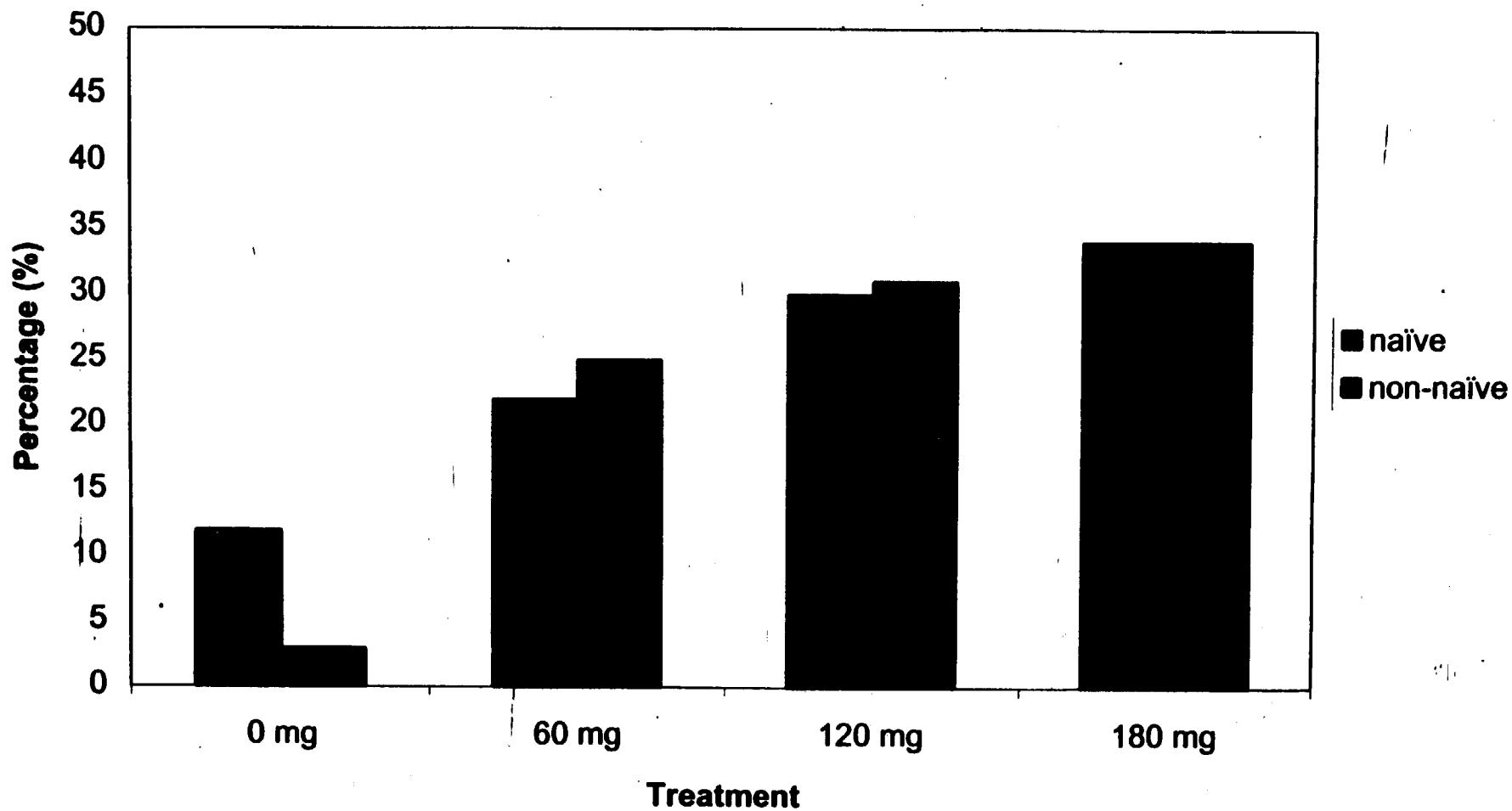


Fig. 3

**Percent of Patients with $\geq 1\%$ Decrease in HgbA1c:
By Body Mass Index, Prior Exposure to Anti-diabetic Drugs,
and DJN 608 Dose: Study 302**

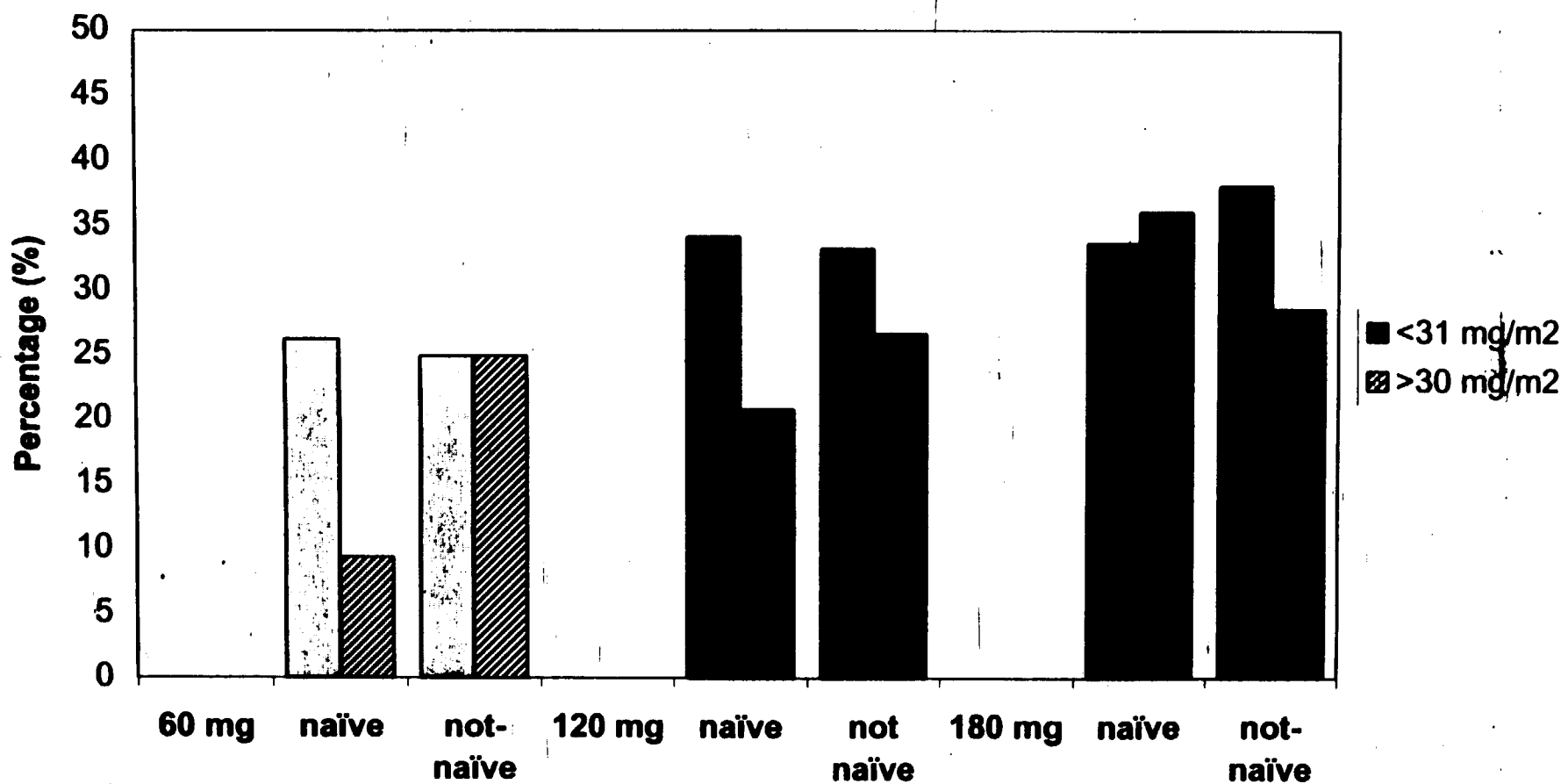


Table 7
Efficacy by Age: Study 302

	Aged $\geq$ 65 Years					Aged $<$ 65 Years					Endpoint P-value
	n	Mean Age	HgbA1c Endpoint	HgbA1c Delta	r*	n	Mean Age	HgbA1c Endpoint	HgbA1c Delta	r*	
Placebo											
All	50	70.0	8.16	0.24	-0.24	117	53.2	8.20	0.29	0.01	N.S.
Not-Naïve	16		8.72	0.49		19		9.51	1.14		
Naïve	34		7.92	0.14		98		7.95	0.12		
60 mg TID											
All	55	71.5	7.39	-0.37	-0.12	112	52.5	7.77	-0.23	-0.04	0.03
Not-Naïve	15		7.25	-0.61		25		8.46	-0.04		
Naïve	40		7.37	-0.28		87		7.57	-0.29		
120 mg TID											
All	44	70.2	7.68	-0.53	0.06	123	52.8	7.60	-0.47	0.06	N.S.
Not-Naïve	17		7.85	-0.58		19		7.95	-0.33		
Naïve	27		7.58	-0.51		104		7.53	-0.49		
180 mg TID											
All	53	69.6	7.39	-0.66	0.00	113	53.5	7.57	-0.63	0.24	N.S.
Not-Naïve	15		7.69	-0.47		21		8.23	-0.42		
Naïve	38		7.27	-0.74		92		7.42	-0.67		

*r=correlation coefficient

Table 8
Efficacy by Gender: Study 302

	Male			Female			Endpoint P-value	Delta P-value
	n=	HgbA1c Endpoint	HgbA1c Delta	n=	HgbA1c Endpoint	HgbA1c Delta		
Placebo								
All	98	8.17	0.15	86	8.22	0.34	N.S.	N.S.
Not-Naïve	21	9.00	0.67	13	9.46	0.56		
Naïve	77	7.94	0.00	55	7.93	0.29		
60 mg TID								
All	99	7.52	-0.40	86	7.79	-0.10	N.S.	0.06
Not-Naïve	22	7.71	-0.53	16	8.35	-0.10		
Naïve	77	7.46	-0.37	50	7.61	-0.16		
120 mg TID								
All	97	7.62	-0.51	86	7.62	-0.45	N.S.	N.S.
Not-Naïve	23	7.86	-0.52	13	7.98	-0.28		
Naïve	74	7.55	-1.00	55	7.53	-0.49		
180 mg TID								
All	94	7.97	-0.52	72.00	7.31	-0.79	0.06	0.10
Not-Naïve	20	7.97	-0.26	15.00	7.85	-0.83		
Naïve	74	7.59	-0.59	57.00	7.17	-0.78		

Fig. 4

Fasting Plasma Glucose Changes: During Washout and After Treatment: Study 355

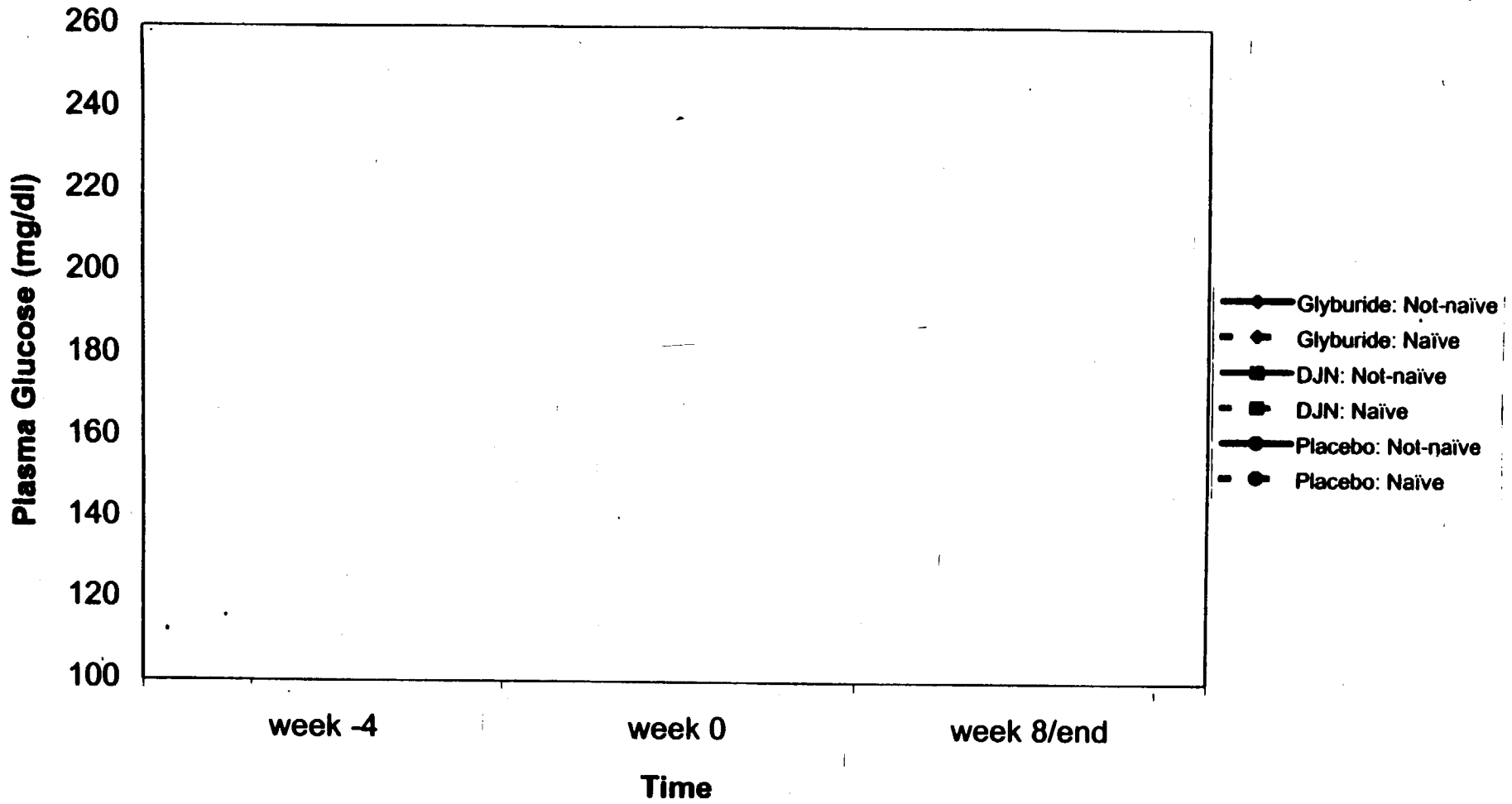


Fig. 5

HgbA1c over Controlled Trial 251 (12 weeks) and Extension: DJN 608 Add-on to Glyburide: Study 251

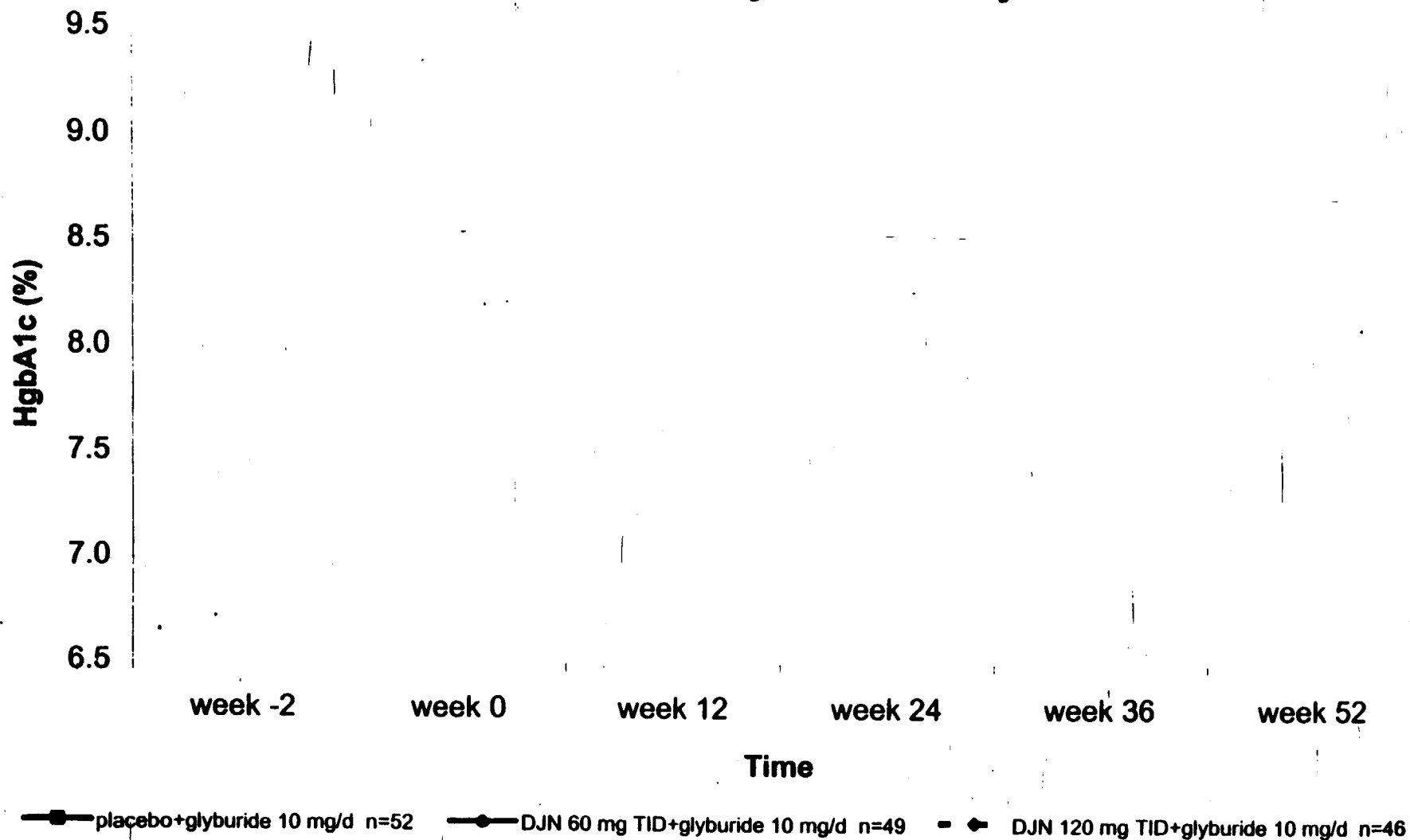


Fig. 6

Changes in HgbA1c over Time and by Prior Diabetic Drug Use: Study 351

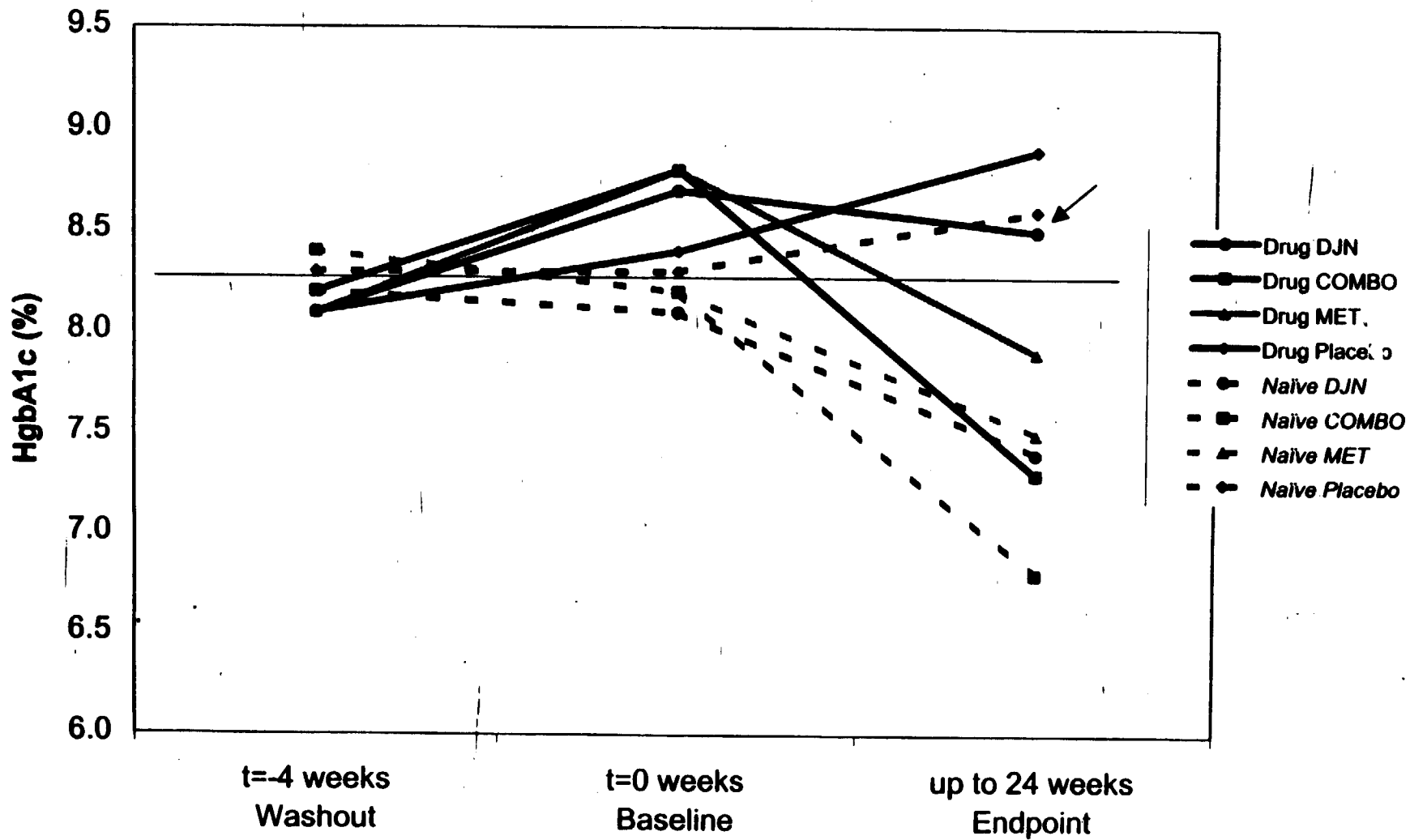


Fig. 7

HgbA1c Levels in Patients on Metformin +/-Nataglinide: Study 354 (Patients with HgbA1c Levels <7% at t=0 Included)

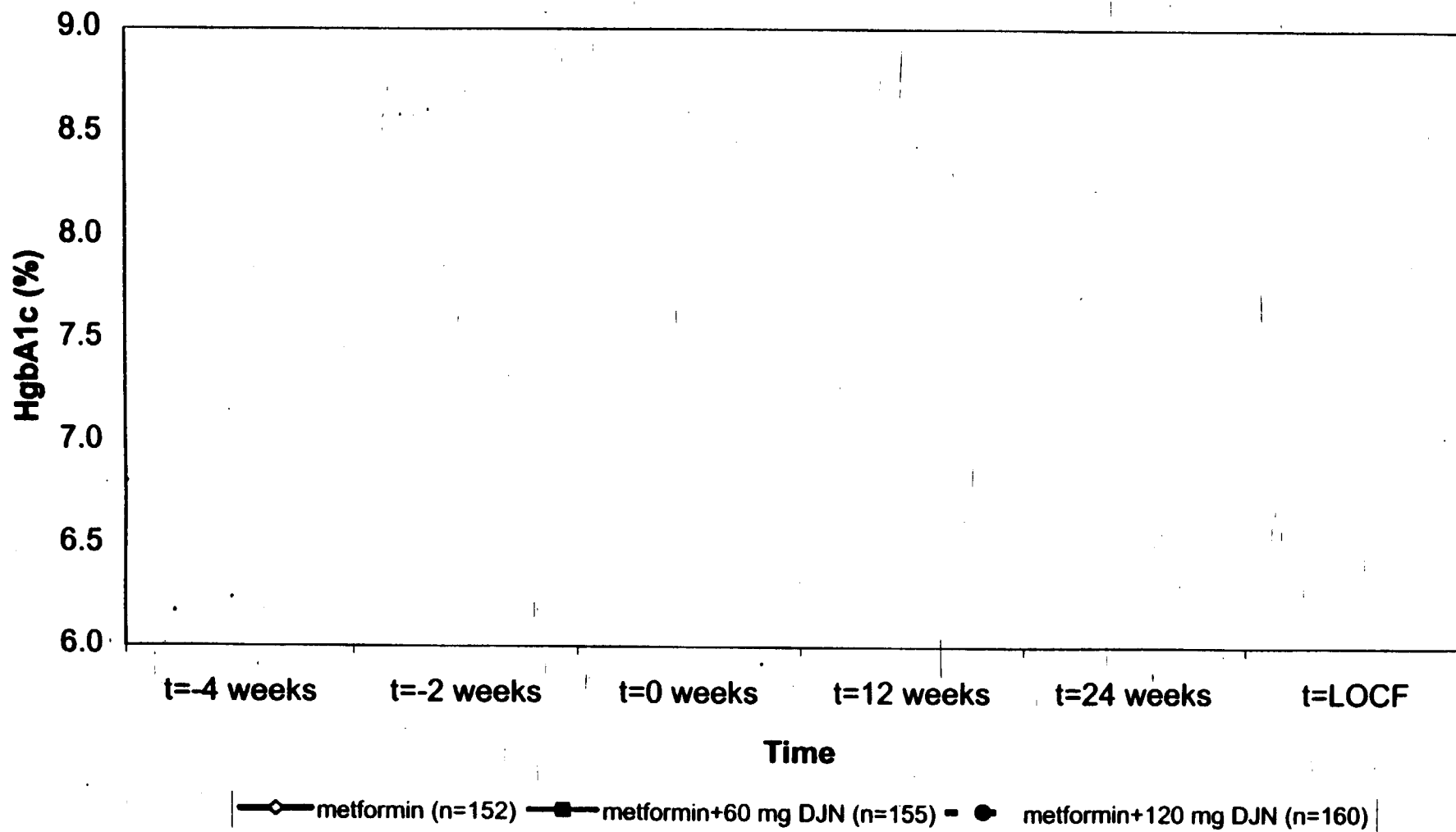


Fig. 8

HgbA1c Levels in Patients Who Failed Metformin: Study 354 (Patients with HgbA1c Levels <7% at t=0 Excluded)

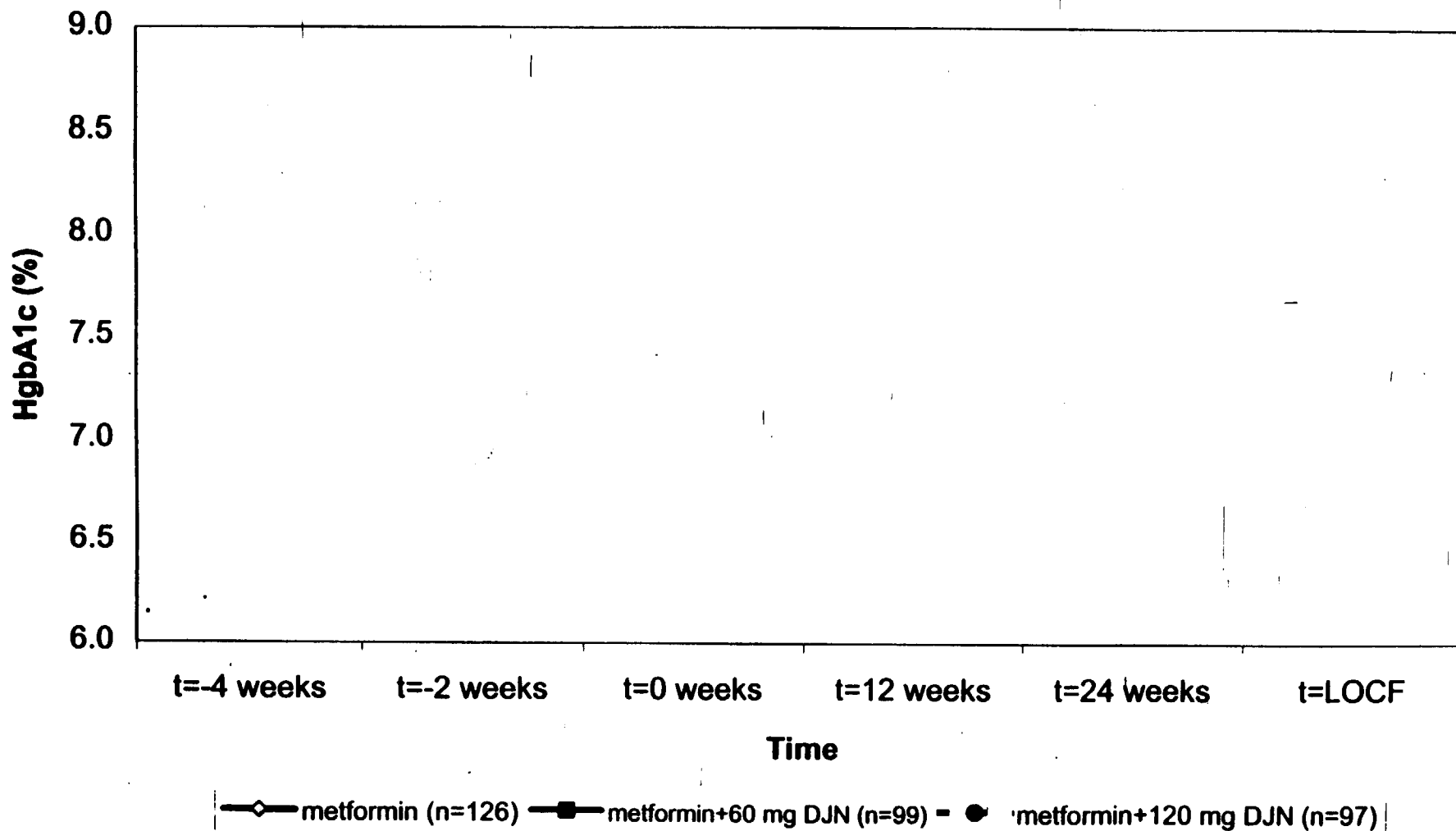


Table 9
Measures of Glycemic Control: Study 355

	Fructosamine			Delta			Fasting Serum Glucose			Delta			2 Hr PP		Glucose Excursion		AUC-2 Hr		AUC-4 Hr	
	t=0 Wks (umol/dl)	n	t=8 Wks (umol/dl)	n	t=0 Wks (mg/dl)	n	t=8 Wks (mg/dl)	n	t=0 Wks (mg/dl)	n	t=8 Wks (mg/dl)	n	t=8 Wks (mg/dl)	n	t=8 Wks mgxhridl	n	t=8 Wks mgxhridl	n		
Placebo																				
non-naive	245.3	15	254.1	17	5.3	15	211.2	17	221.2	17	10.0	17	282.7	16	62.2	16	547.0	15	1020.2	16
naive	235.4	28	236.9	29	1.8	28	195.7	29	203.1	30	8.2	29	240.5	30	37.4	30	506.7	30	936.4	30
DJN 608																				
non-naive	237.5	12	223.3	12	-14.2	12	216.2	12	207.1	12	-9.2	12	224.1	11	11.3	11	486.4	11	839.6	12
naive	226.5	34	211.5	34	-15.0	34	180.4	34	165.9	36	-14.3	34	166.7	35	-5.0	35	377.2	34	658.0	35
DJN vs Placebo (all) p=	N.S.		0.001		0.003		N.S.		0.002		0.009		<0.001		<0.001		<0.001		<0.001	
DJN vs Gly (all) p=	0.001		N.S.		<0.001		0.04		0.01		<0.001		N.S.		<0.001		N.S.		N.S.	
Glyburide																				
non-naive	255.8	19	218.4	19	-37.4	19	231.0	19	160.3	19	-70.7	19	213.5	19	53.3	19	423.1	18	782.6	19
naive	246.6	29	209.0	29	-37.6	29	203.1	29	146.8	29	-56.3	29	176.0	28	33.1	28	380.0	27	658.1	29
Gly vs Placebo (all) p=	0.15		<0.001		<0.001		N.S.		<0.001		<0.001		<0.001		N.S.		<0.001		<0.001	

Gly=glyburide
PP=postprandial
AUC=area-under-the curve
hr=hour
Excursion=2 hr PP-fasting glucose

Table 10
Measures of Glycemic Control: Study 351

	HgbA1c				Fasting Plasma Glucose					2 Hr PP		Glucose Excursion		AUC-2 Hr				
	t=0 Wks (%)	n	t=24 Wks (%)	n	Delta (%)	n	t=0 Wks (mg/dl)	n	t=24 Wks (mg/dl)	n	Delta (mg/dl)	n	t=24 Wks (mg/dl)	n	t=24 Wks (mgxhrid)	n		
Placebo																		
Not-naïve	8.17	38	8.89	39	0.70	38	188.5	38	197.0	38	8.5	38	239.9	38	43.4	37	493.6	37
Naïve	8.07	73	8.31	74	0.23	73	181.1	72	192.0	73	11.0	72	220.4	67	28.4	66	464.0	66
DJN 608																		
Not-naïve	8.53	57	8.26	57	-0.26	57	206.8	56	195.5	57	-12.0	56	215.4	56	20.0	56	461.1	55
Naïve	8.15	78	7.31	78	-0.83	78	182.4	82	166.9	82	-15.5	82	171.8	78	5.7	78	383.1	78
DJN vs Placebo (all) p=	0.13		<0.001		<0.001		0.12		0.02		<0.001		<0.001		<0.001		<0.001	
DJN vs Metformin (all) p=	N.S.		0.08		0.008		N.S.		0.01		0.008		N.S.		<0.001		N.S.	
DJN vs Combo (all) p=	0.05		<0.001		<0.001		0.14		<0.001		<0.001		<0.001		N.S.		<0.001	
Metformin																		
Not-naïve	8.73	54	7.68	54	-1.05	54	214.8	54	172.6	54	-42.2	54	197.6	48	29.3	48	421.4	48
Naïve	8.17	83	7.30	84	-0.86	83	178.6	83	157.9	84	-20.3	83	182.7	77	24.4	75	391.8	75
Metformin vs Placebo (all) p=	0.04		<0.001		<0.001		0.09		<0.001		<0.001		<0.001		0.10		<0.001	
Combo																		
Not-naïve	89.1	69	7.19	69	-1.72	69	213.7	68	158.4	69	-55.3	68	176.0	66	16.5	66	380.2	65
Naïve	8.24	68	6.62	68	-1.62	68	187.2	66	146.7	67	-40.7	66	149.8	68	3.8	68	346.8	67
Combo vs Placebo (all) p=	<0.001		<0.001		<0.001		0.002		<0.001		<0.001		<0.001		<0.001		<0.001	

PP=postprandial

AUC=area-under-the-curve

hr=hour

Excursion=2 hr PP-fasting glucose

Table 11
Correlation Coefficients for Parameters of Glycemic Control (LOCF): Study 302

	<u>HgbA1c vs Fasting Glucose</u>	<u>Delta HgbA1c vs Delta Fasting Glucose</u>	<u>HgbA1c vs Fructosamine</u>	<u>Delta HgbA1c vs Delta Fructosamine</u>
Placebo				
not-naïve	0.84	0.65	0.84	0.66
naïve	0.72	0.56	0.76	0.60
DJN 60 mg				
not-naïve	0.68	0.67	0.54	0.55
naïve	0.69	0.35	0.62	0.62
DJN 120 mg				
not-naïve	0.49	1.00	0.76	0.82
naïve	0.73	0.65	0.67	0.65
DJN 180 mg				
not-naïve	0.69	0.60	0.75	0.73
naïve	0.71	0.57	0.78	0.64

LOCF=last observation carried forward

Table 12
Correlation Coefficients for Parameters of Glycemic Control: Study 355*

<u>Fructosamine vs. Fasting Plasma Glucose</u>		$\bar{r}$	<u>Change in Fructosamine vs. Change in Fasting Plasma Glucose (over 8 weeks)</u>		$\bar{r}$
DJN 608		0.63	DJN 608		0.24
Glyburide		0.60	Glyburide		0.46
Placebo		0.82	Placebo		0.57
<u>Fructosamine vs. 2 Hour Glucose</u>			<u>Change in Fructosamine vs. 2 Hour Glucose</u>		
DJN 608		0.66	DJN 608		0.5
Glyburide		0.57	Glyburide		0.10
Placebo		0.82	Placebo		0.34
<u>Fructosamine vs. Glucose AUC-2 Hour</u>			<u>Change in Fructosamine vs. Glucose AUC-2 Hour</u>		
DJN 608		0.72	DJN 608		0.23
Glyburide		0.48	Glyburide		0.25
Placebo		0.85	Placebo		0.40
<u>Fructosamine vs. Glucose AUC-4 Hour</u>			<u>Change in Fructosamine vs. Glucose AUC-4 Hour</u>		
DJN 608		0.70	DJN 608		0.28
Glyburide		0.42	Glyburide		0.05
Placebo		0.72	Placebo		0.37
<u>Fructosamine vs. Glucose Excursion</u>			<u>Change in Fructosamine vs. Glucose Excursion</u>		
DJN 608		0.29	DJN 608		0.03
Glyburide		0.22	Glyburide		0.08
Placebo		0.30	Placebo		0.02
<u>Fructosamine at t=0 vs. HgbA1c at t=-2 Weeks</u>					
Naive patients		0.59			

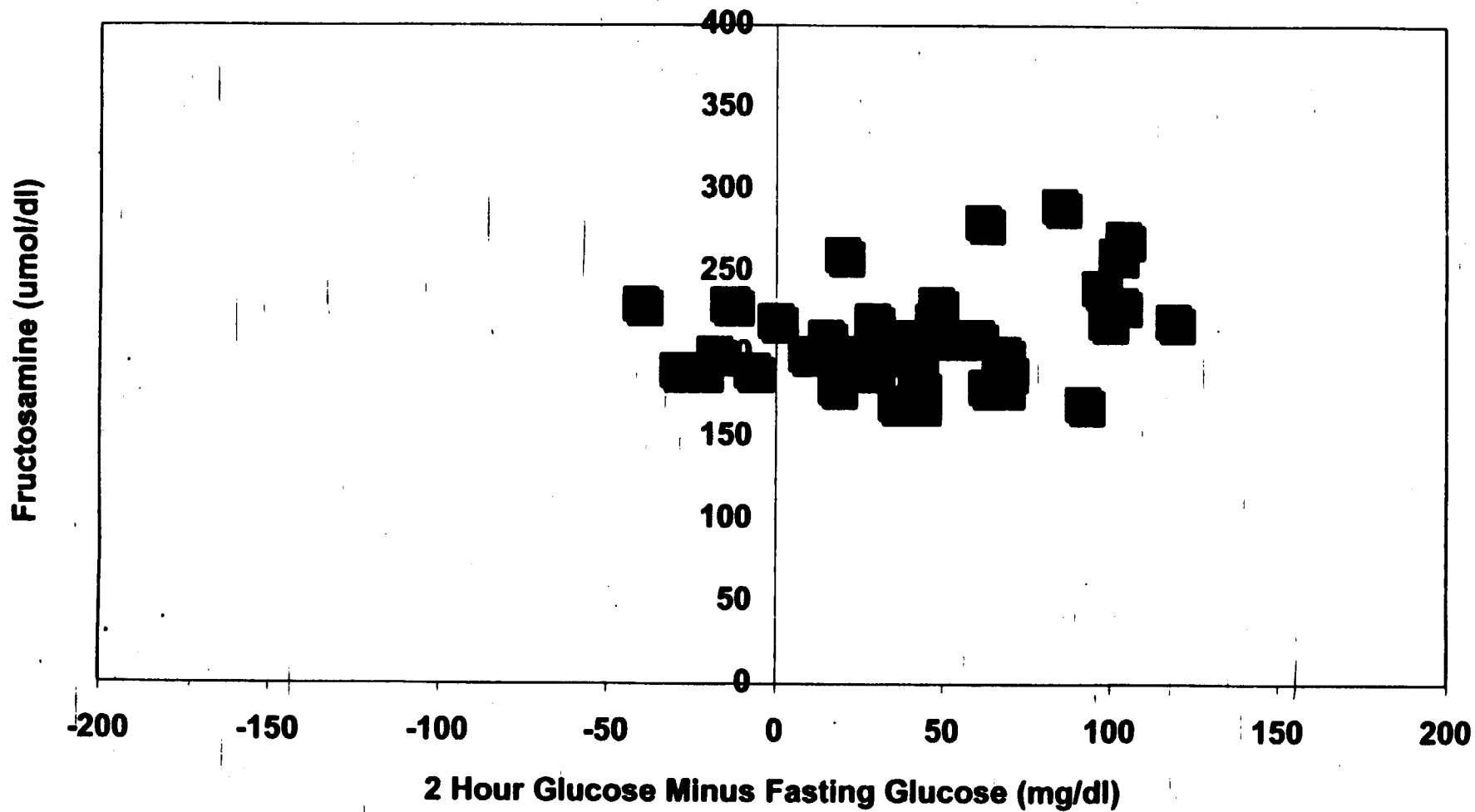
*Unless otherwise specified, values are those at t=0 and t=8 weeks.

Table 13
Correlation Coefficients for Parameters of Glycemic Control: Study 351

<u>HgbA1c vs. Fasting Plasma Glucose</u>	<u>r=</u>	<u>Change in HgbA1c vs. Change in Fasting Plasma Glucose (over 24 weeks)</u>	<u>r=</u>
Placebo	0.71	Placebo	0.67
DJN 608	0.80	DJN 608	0.63
Metformin	0.81	Metformin	0.68
DJN+Metformin	0.84	DJN+Metformin	0.62
<u>HgbA1c vs. 2 Hour Glucose</u>		<u>Change in HgbA1c vs. 2 Hour Glucose</u>	
Placebo	0.81	Placebo	0.56
DJN 608	0.76	DJN 608	0.39
Metformin	0.79	Metformin	0.33
DJN+Metformin	0.77	DJN+Metformin	0.22
<u>HgbA1c vs. Glucose AUC-2 Hour</u>		<u>Change in HgbA1c vs. Glucose AUC-2 Hour</u>	
Placebo	0.81	Placebo	0.60
DJN 608	0.78	DJN 608	0.43
Metformin	0.82	Metformin	0.40
DJN+Metformin	0.83	DJN+Metformin	0.31
<u>HgbA1c vs. Glucose Excursion</u>		<u>Change in HgbA1c vs. Glucose Excursion</u>	
Placebo	0.30	Placebo	0.08
DJN 608	0.25	DJN 608	0.10
Metformin	0.16	Metformin	-0.12
DJN+Metformin	0.11	DJN+Metformin	-0.19

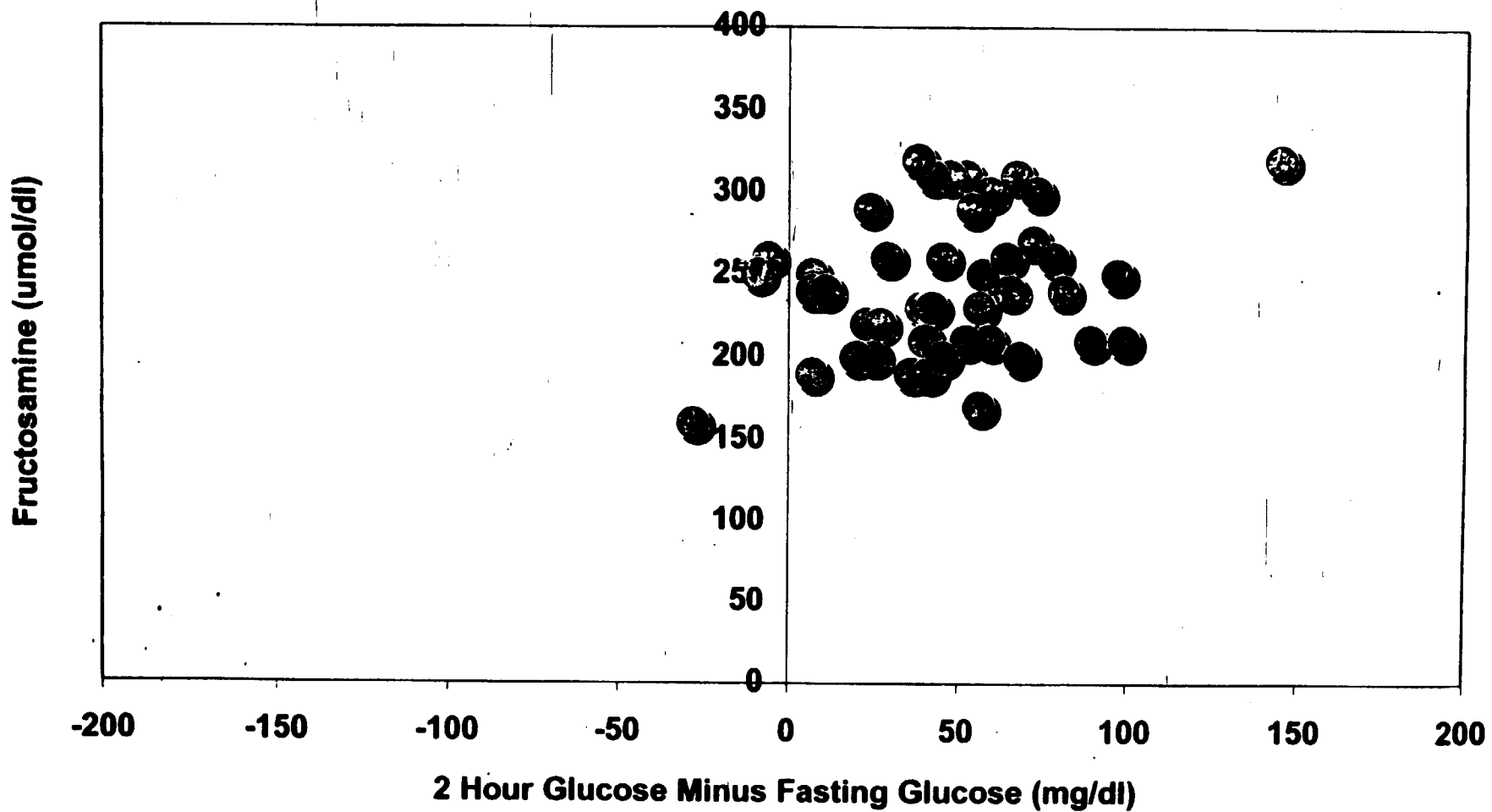
*Values are those at t=0 and t=24 weeks.

Fructosamine vs. Glucose Excursion: Glyburide (Study 355; 8 Weeks)

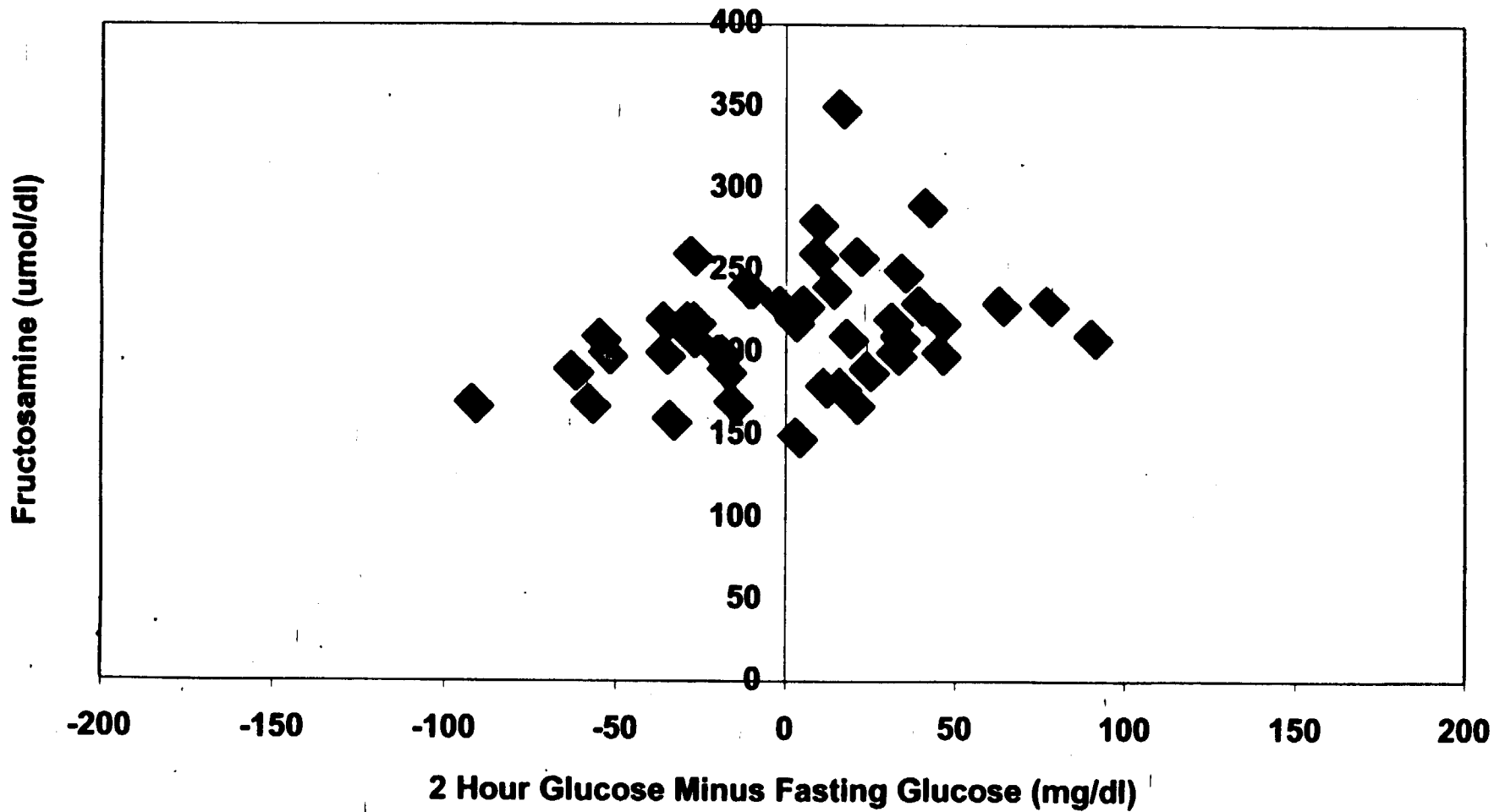


Appendix 1
Panel A-1

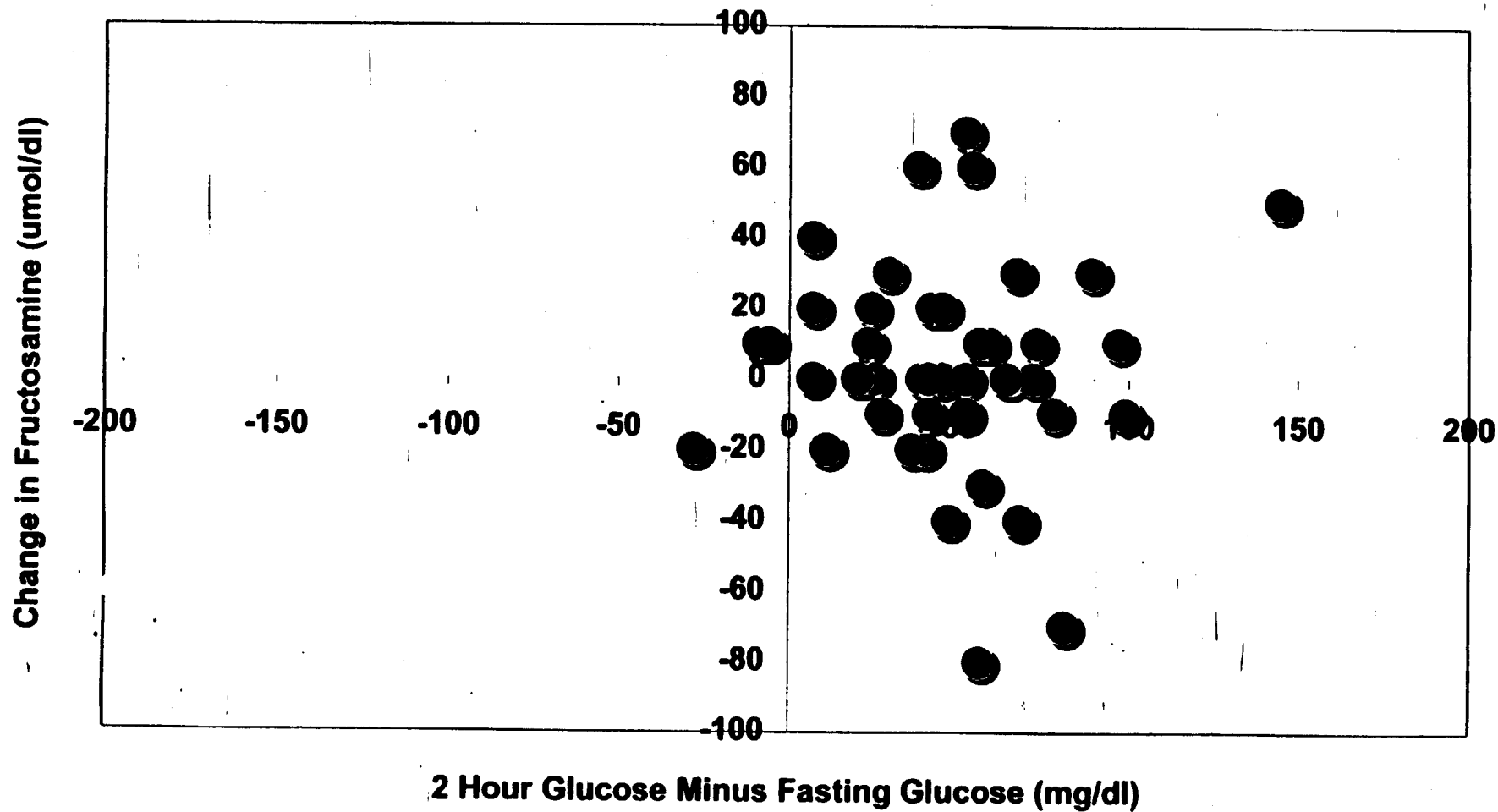
Fructosamine vs. Glucose Excursion: Placebo (Study 355; 8 Weeks)



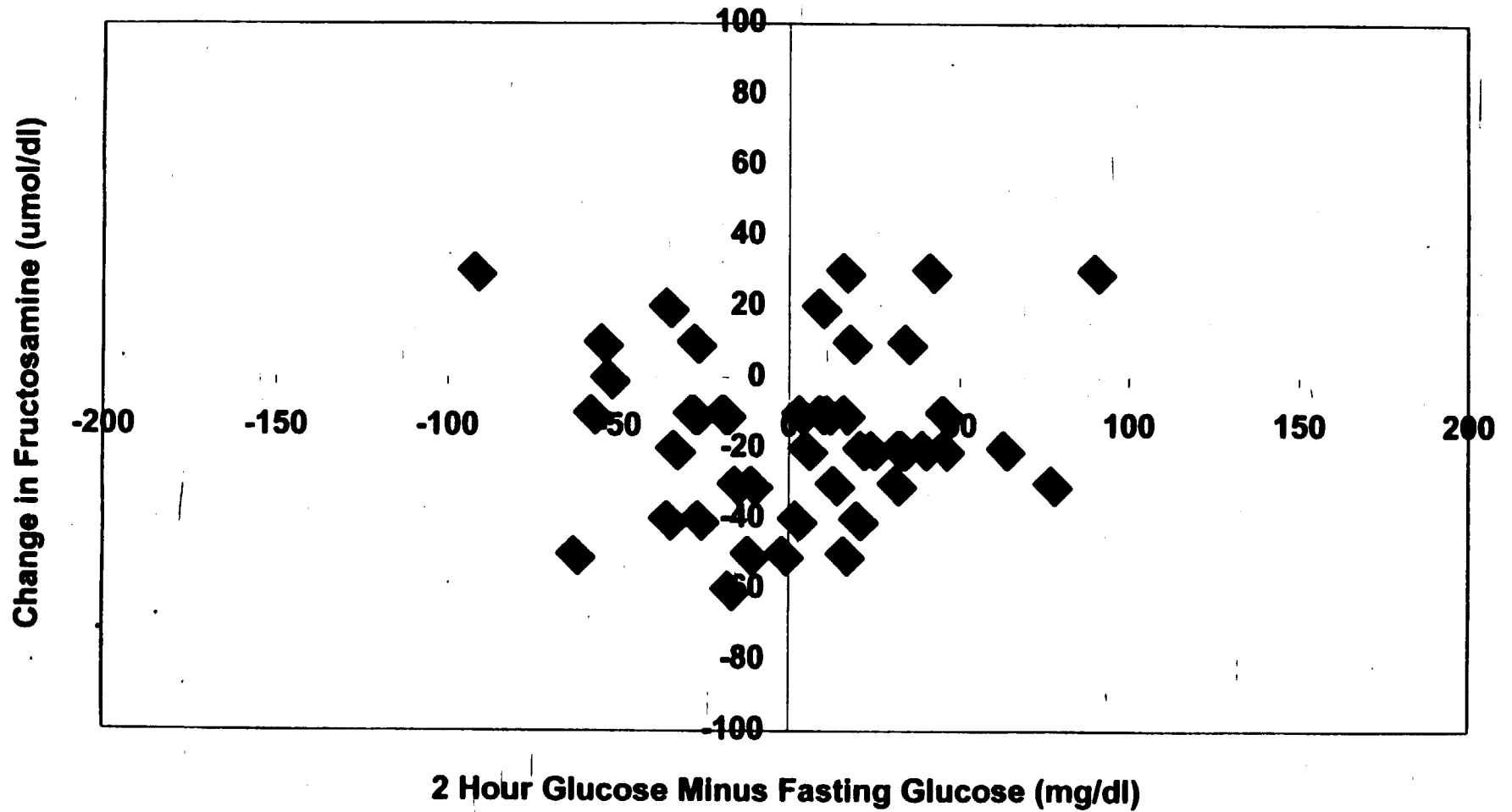
Fructosamine vs. Glucose Excursion: DJN 608 (Study 355; 8 Weeks)



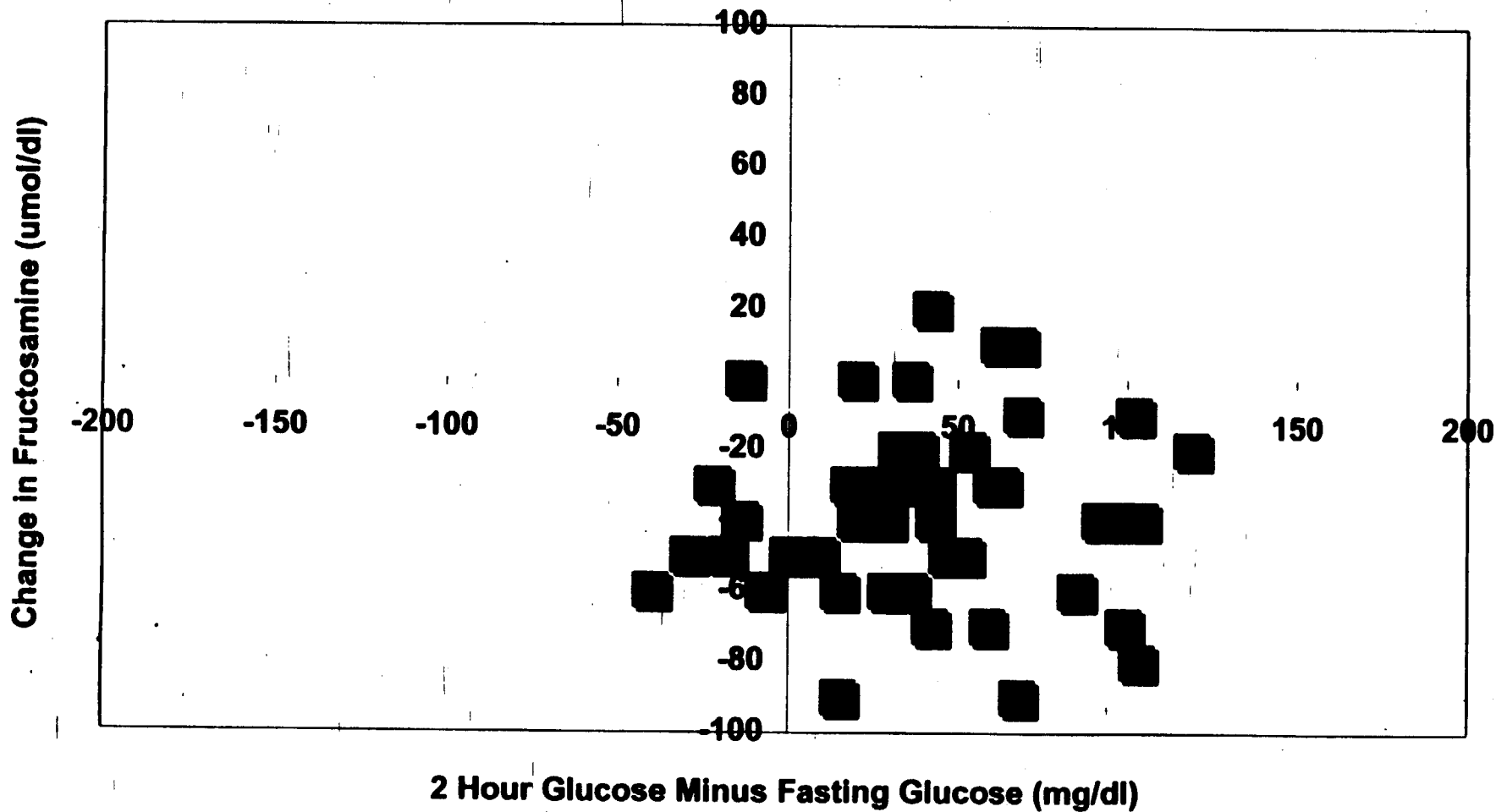
Change in Fructosamine vs. Glucose Excursion: Placebo (Study 355; 8 Weeks)



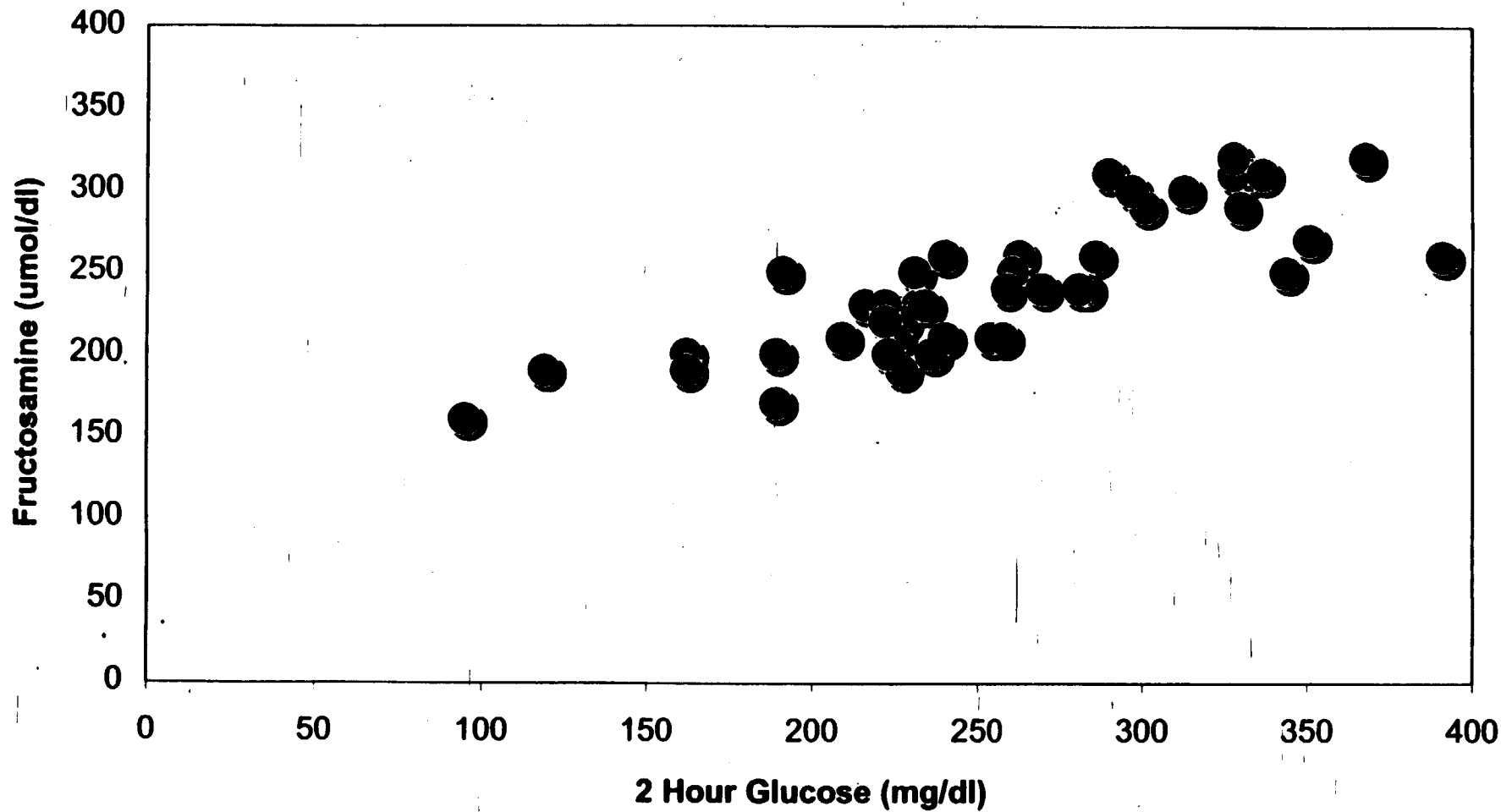
Change in Fructosamine vs. Glucose Excursion: DJN 608 (Study 355; 8 Weeks)



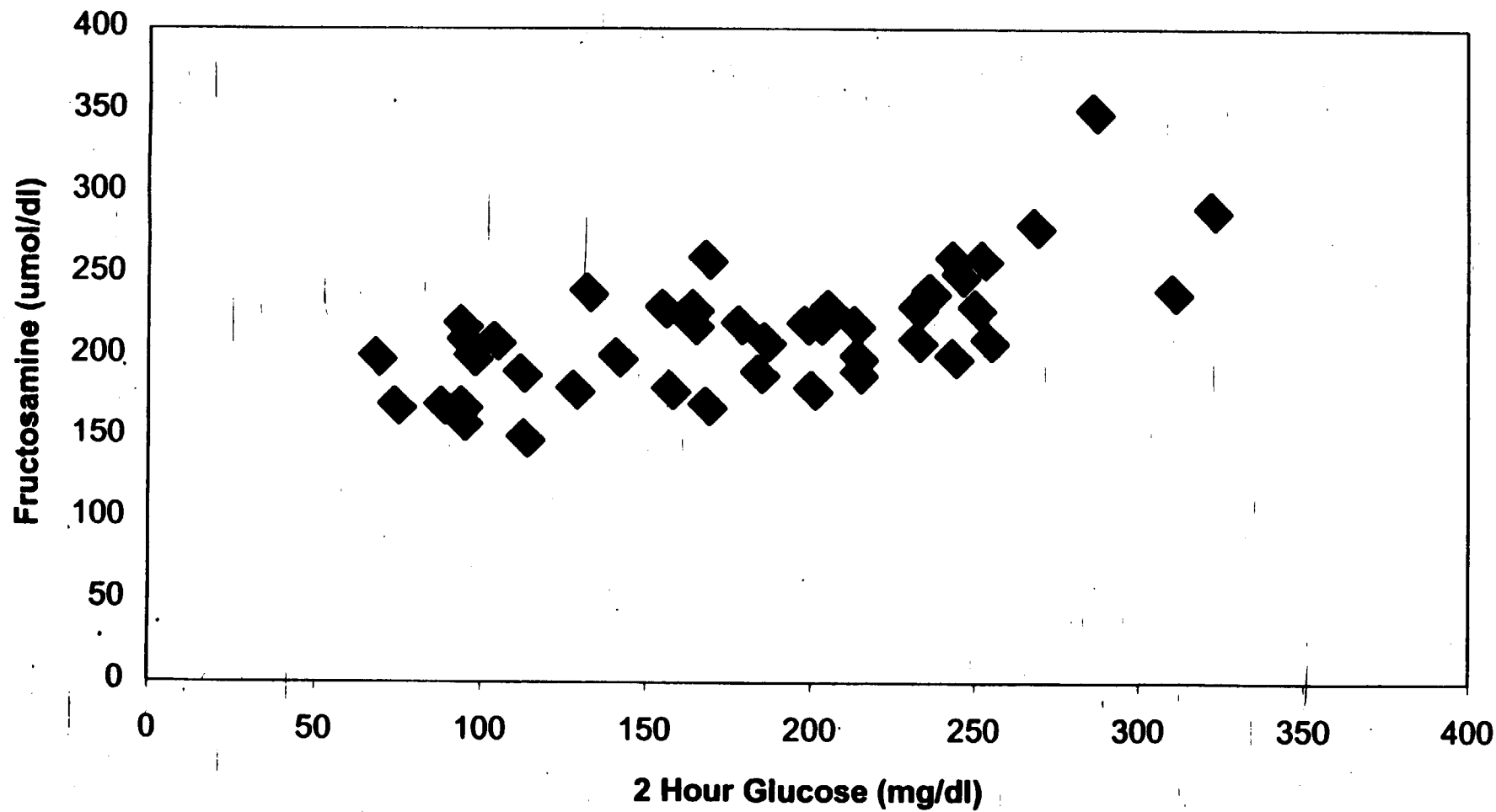
Change in Fructosamine vs. Glucose Excursion: Glyburide (Study 355; 8 Weeks)



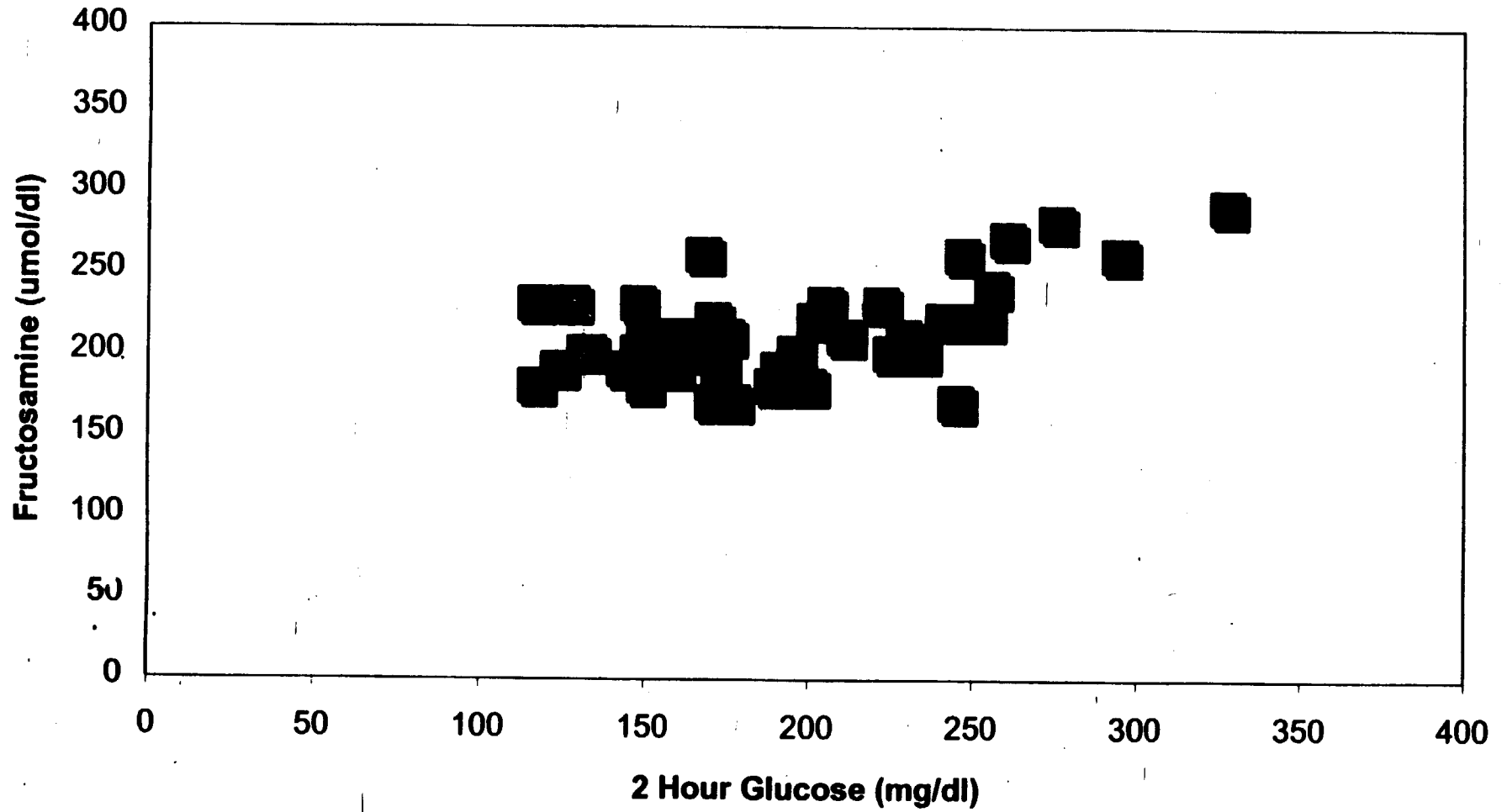
Fructosamine vs. 2 Hour Post-prandial Glucose: Placebo (Study 355; 8 Weeks)



Fructosamine vs. 2 Hour Post-prandial Glucose: DJN 608 (Study 355; 8 Weeks)

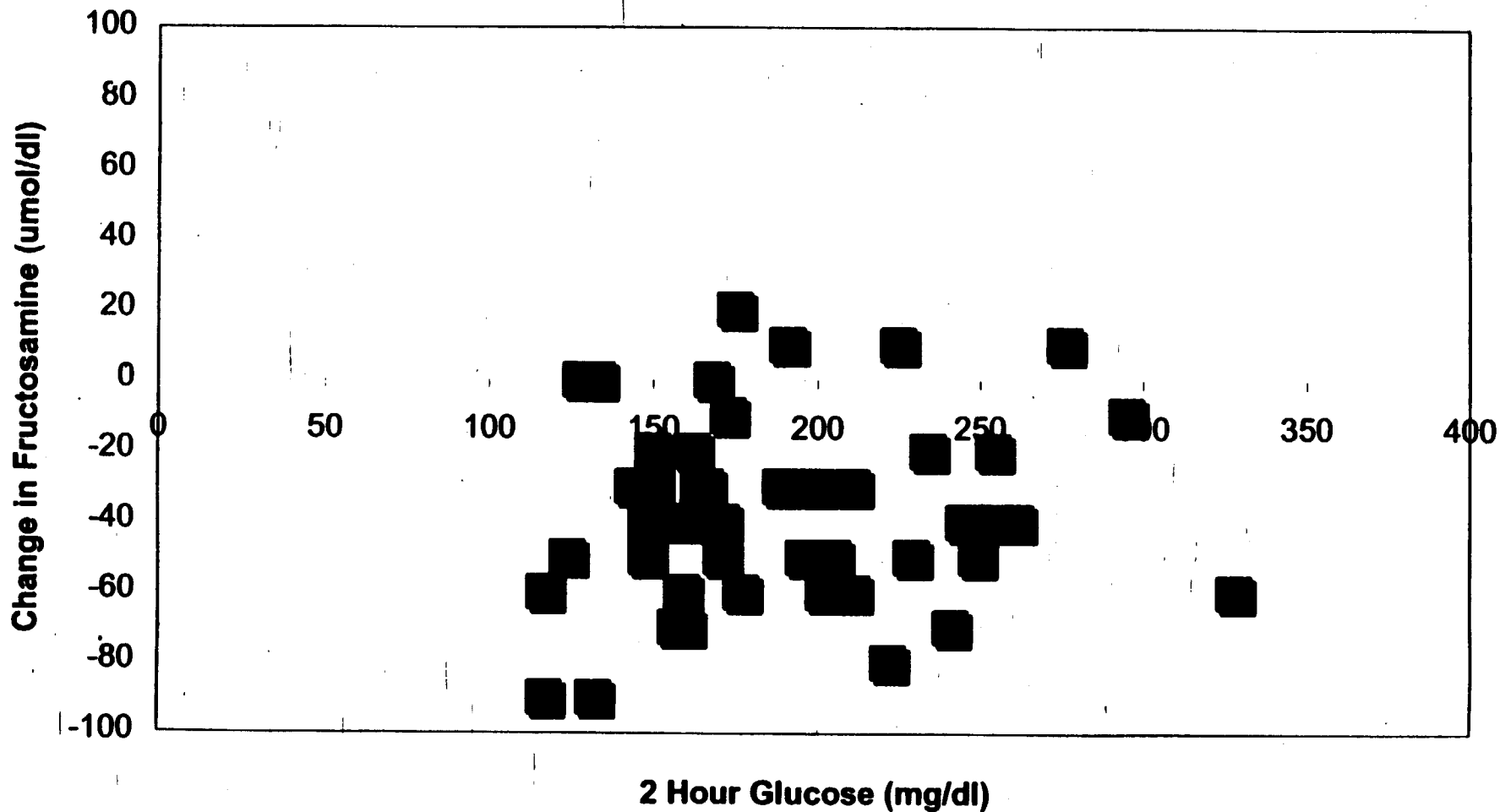


Fructosamine vs. 2 Hour Post-prandial Glucose: Glyburide (Study 355; 8 Weeks)

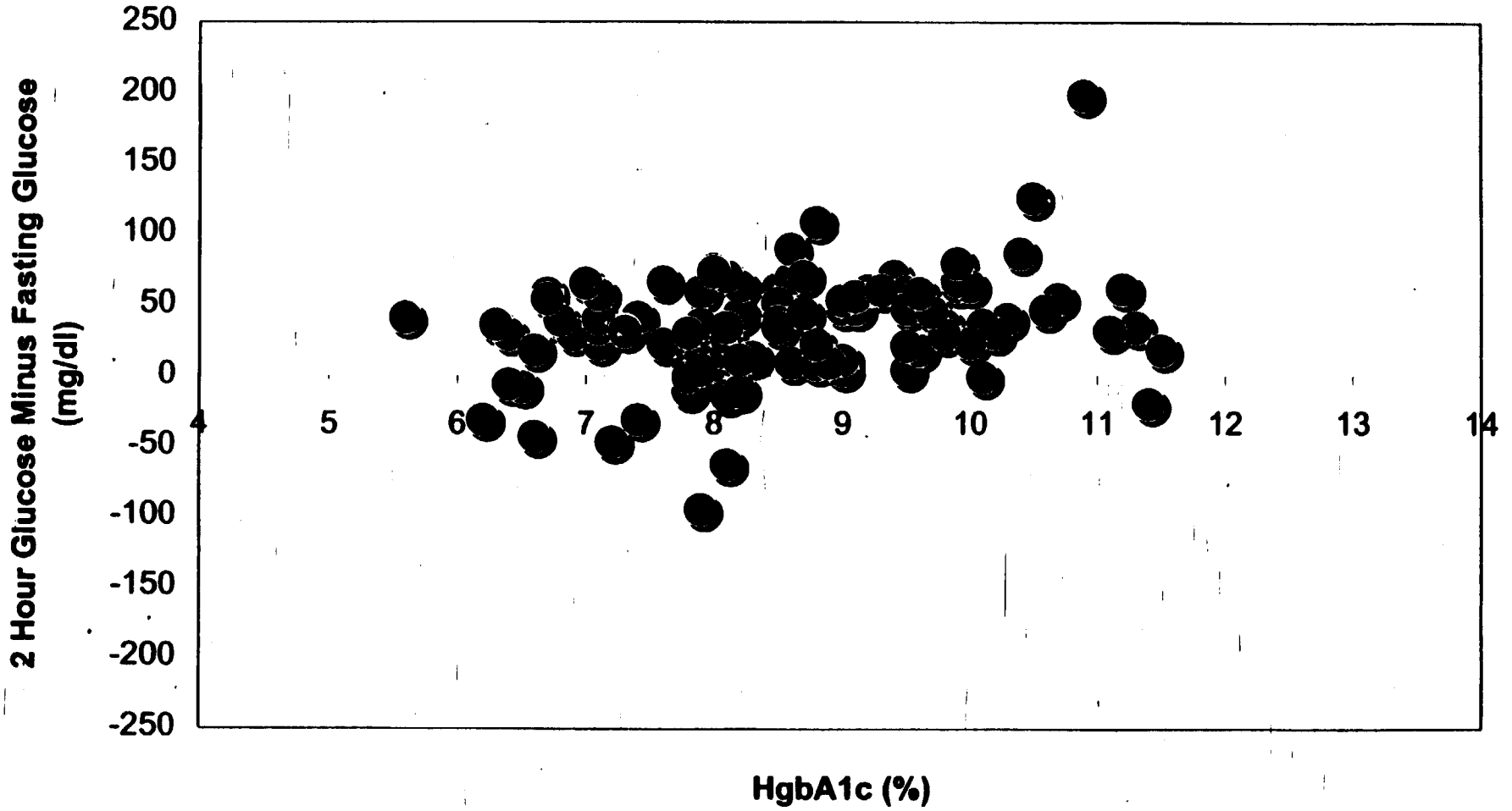


Appendix 1
Panel D-3

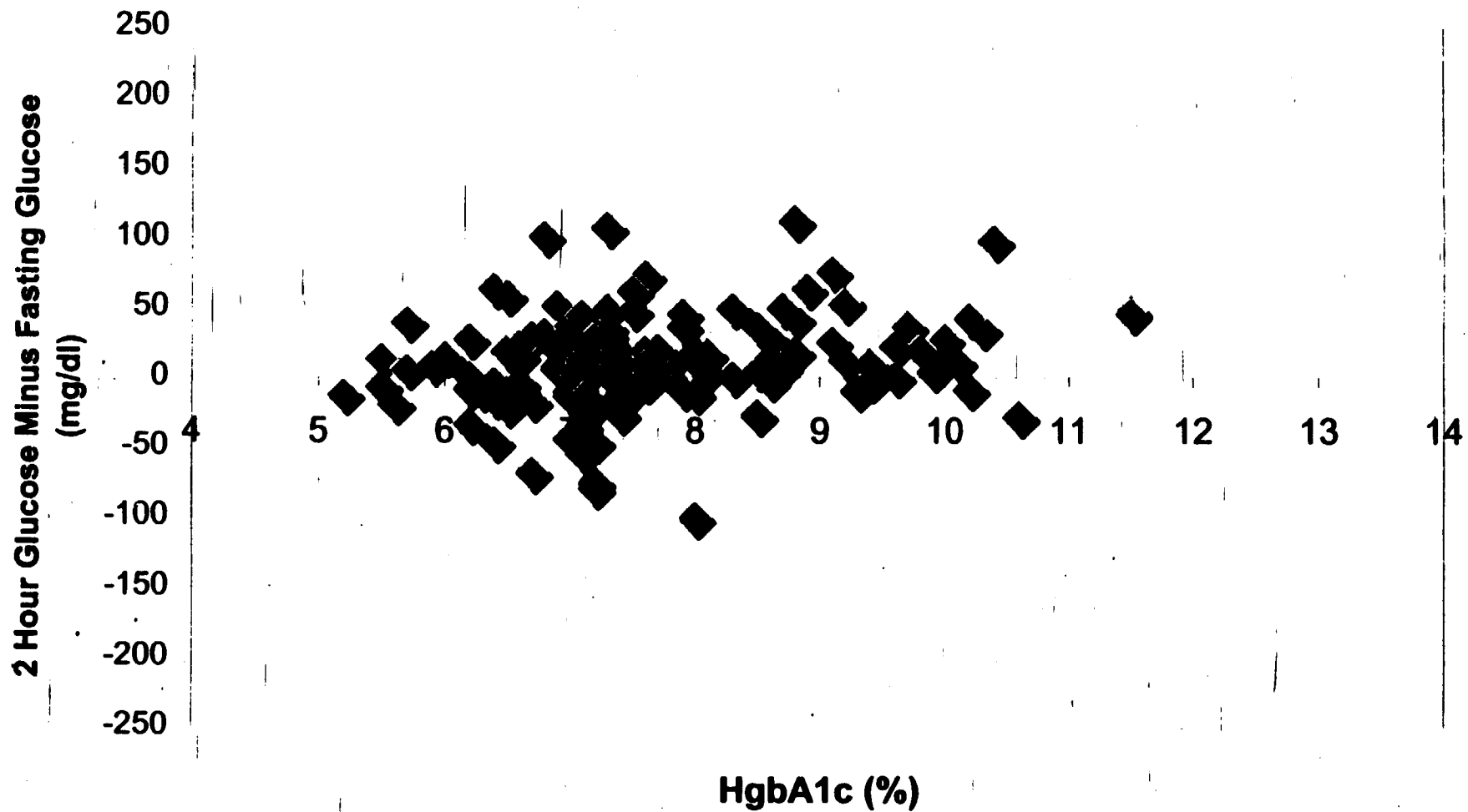
Changes in Fructosamine vs. 2 Hour Post-prandial Glucose: Glyburide (Study 355; 8 Weeks)



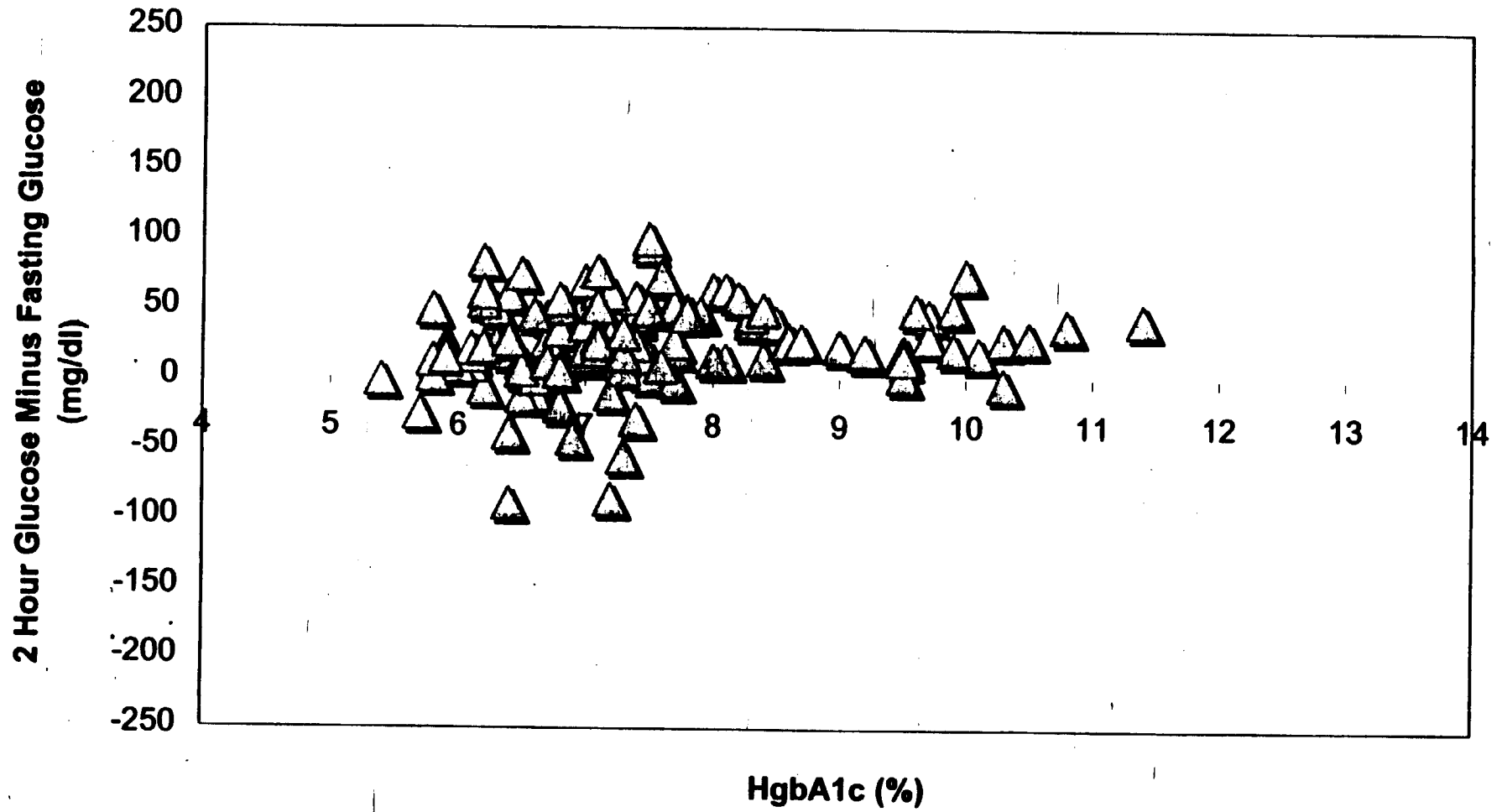
Endpoint HgbA1c vs. Glucose Excursion: Placebo (Study 351; 24 Weeks)



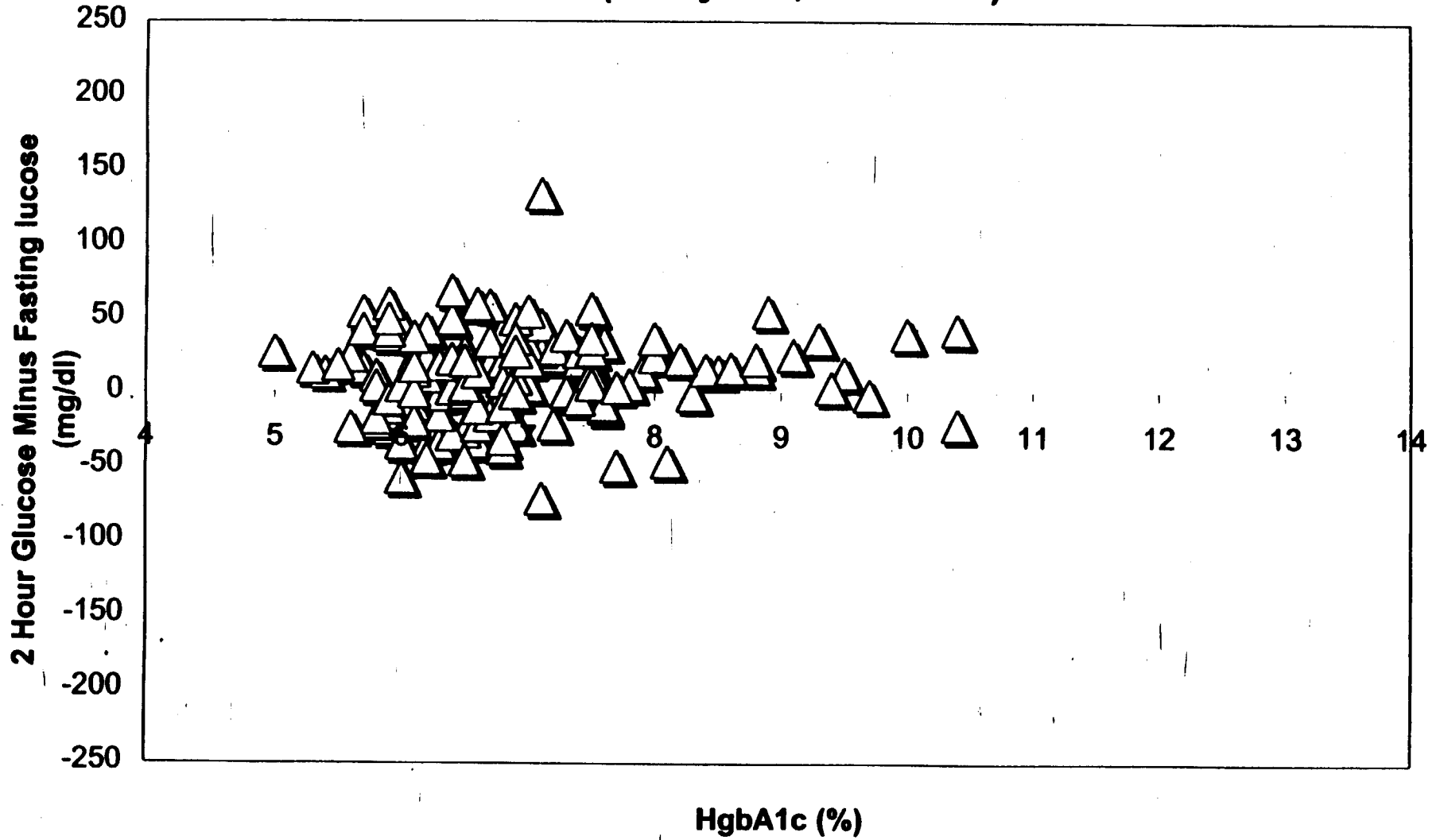
Endpoint HgbA1c vs. Glucose Excursion: DJN 608 (Study 351; 24 Weeks)



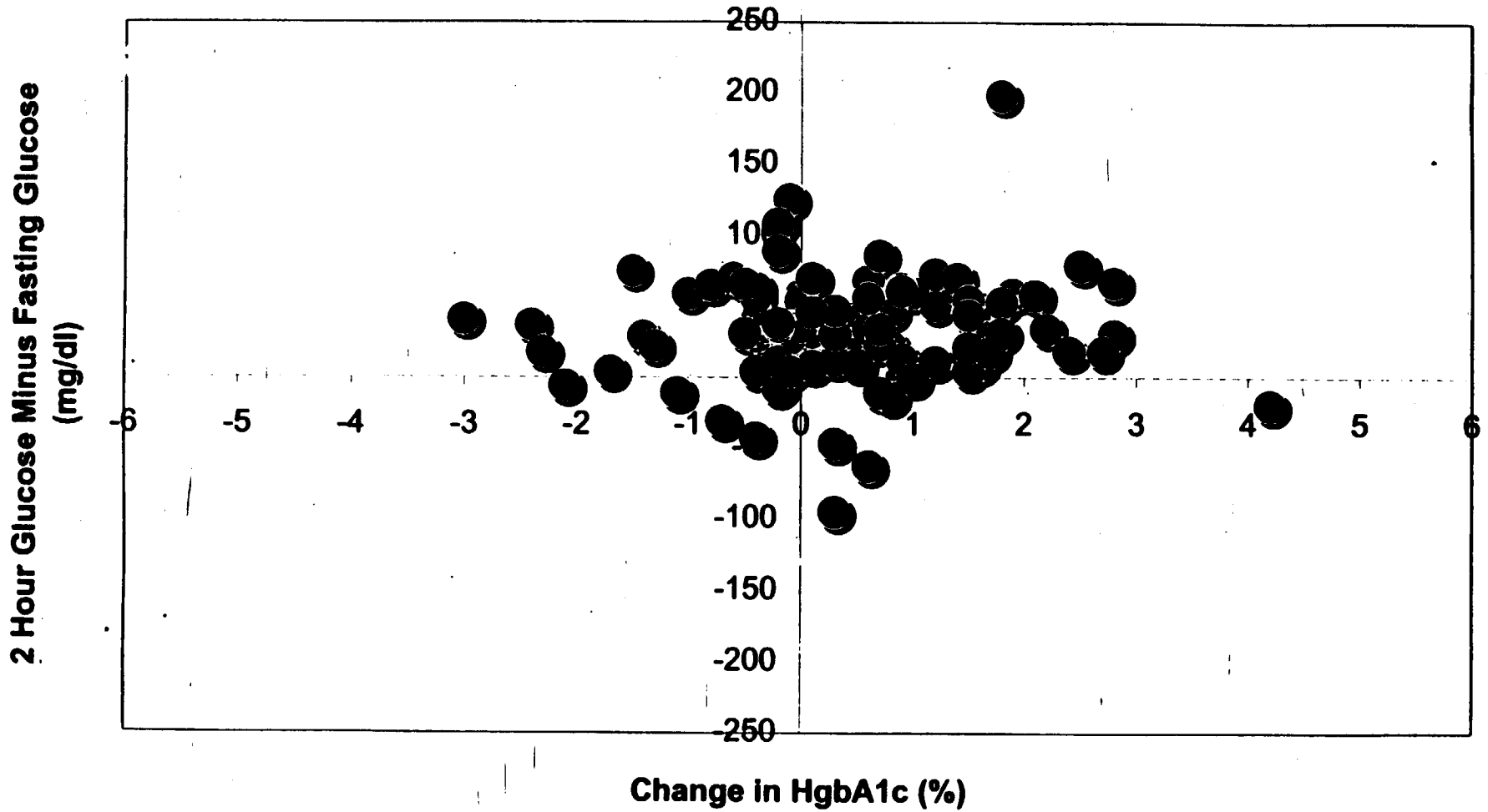
Endpoint HgbA1c vs. Glucose Excursion: Metformin (Study 351; 24 Weeks)



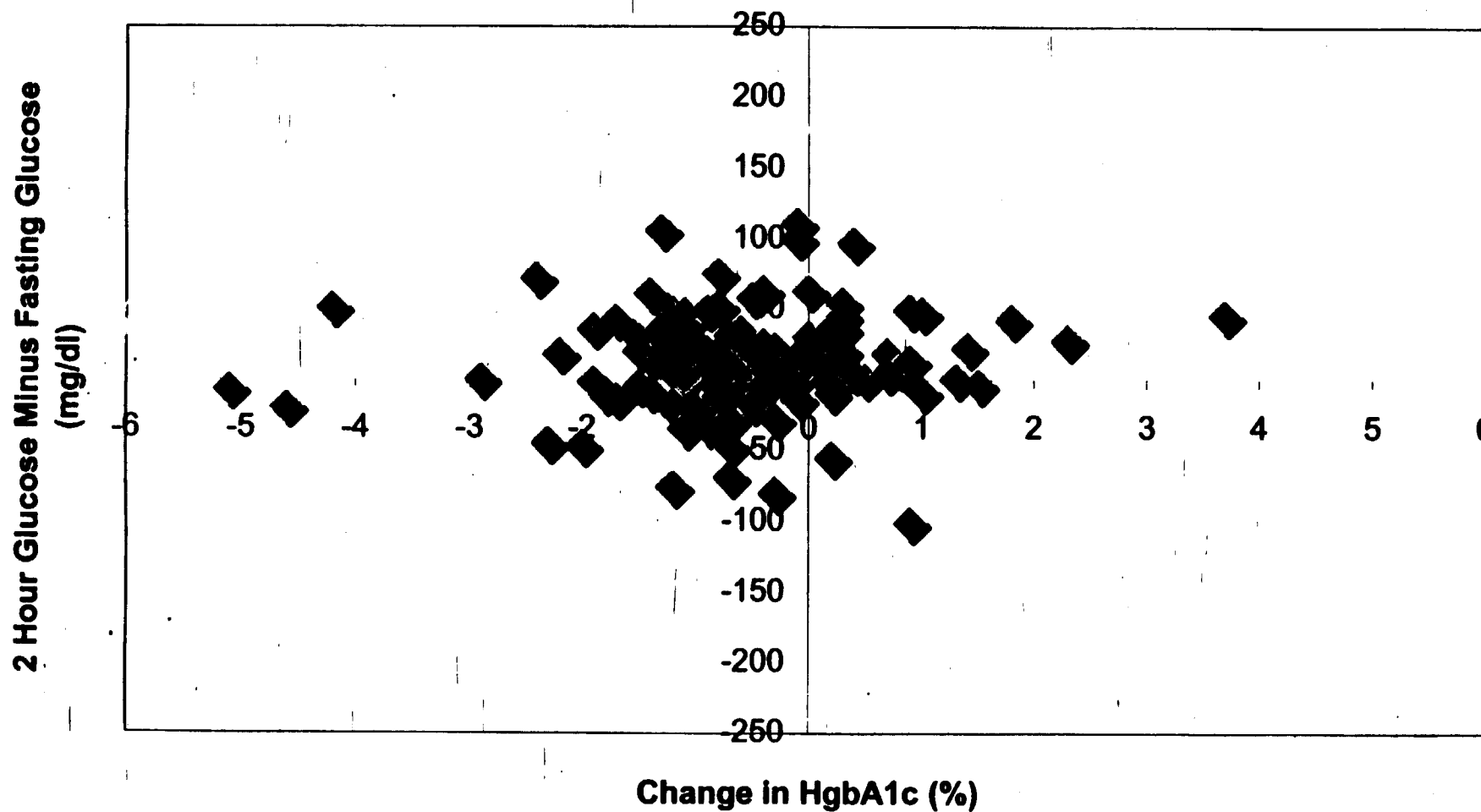
Endpoint HgbA1c vs. Glucose Excursion: Combo (Study 351; 24 Weeks)



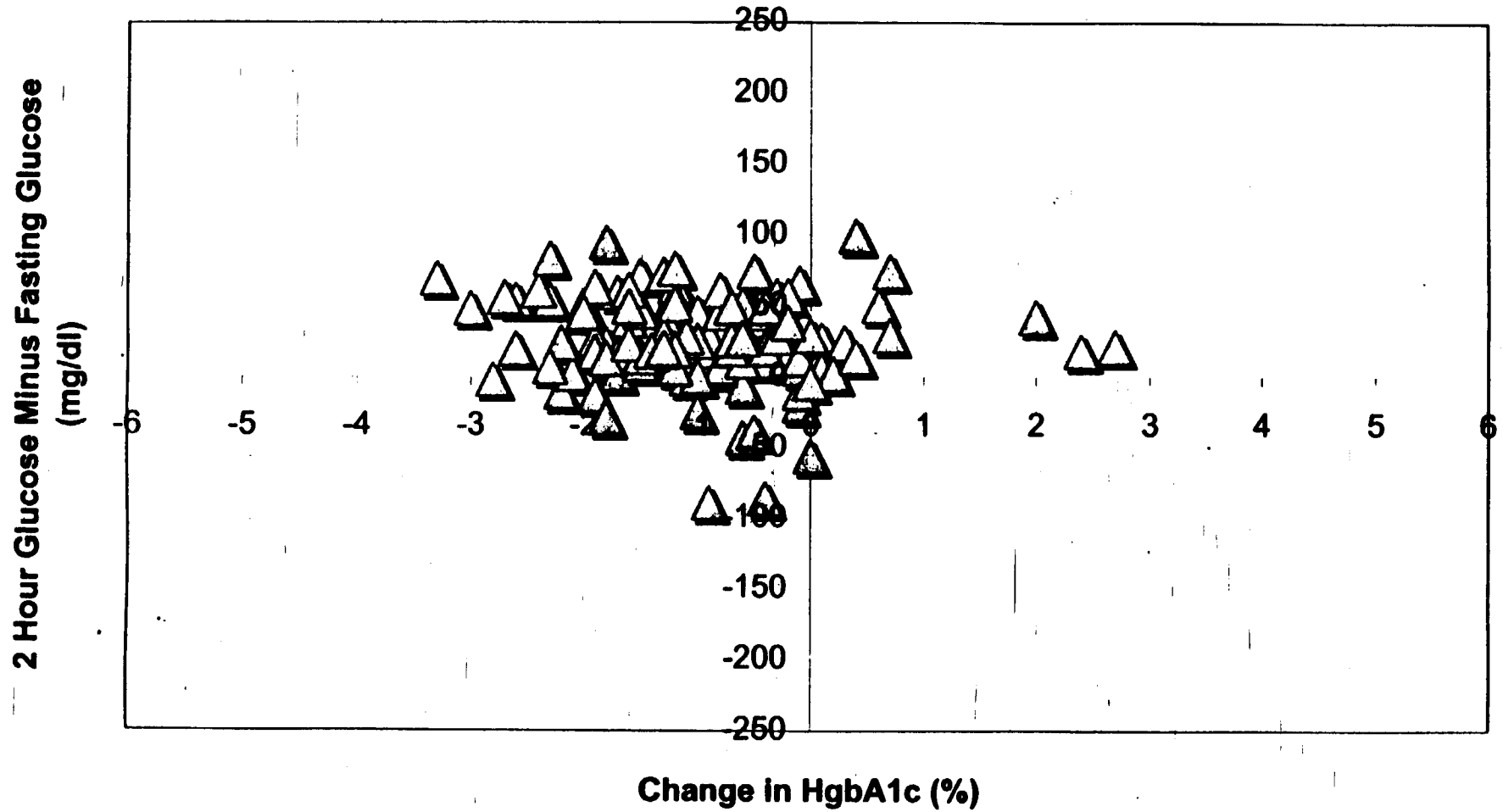
Change in HgbA1c vs. Glucose Excursion: Placebo (Study 351; 24 Weeks)



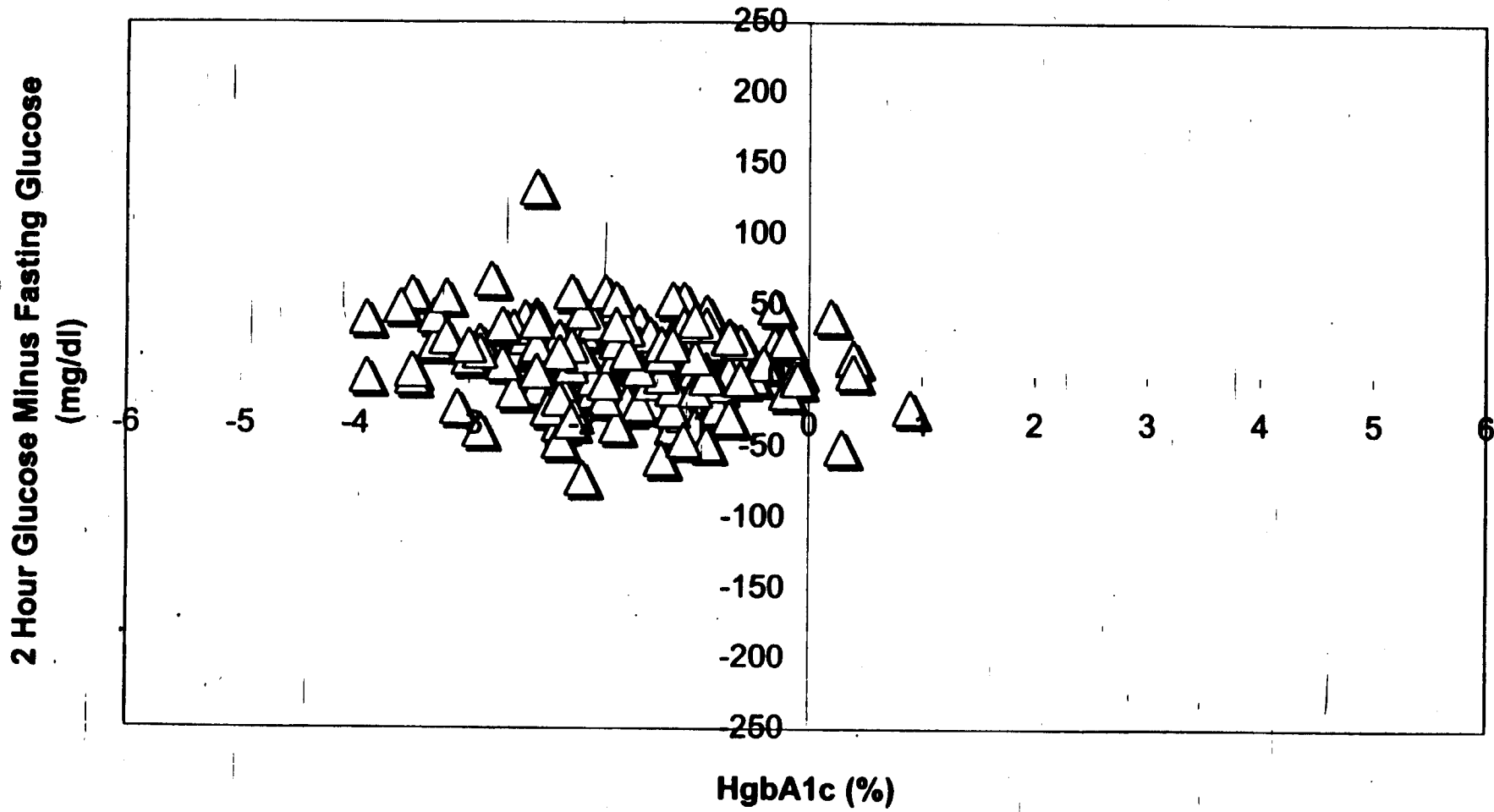
Change in HgbA1c vs. Glucose Excursion: DJN 608 (Study 351; 24 Weeks)



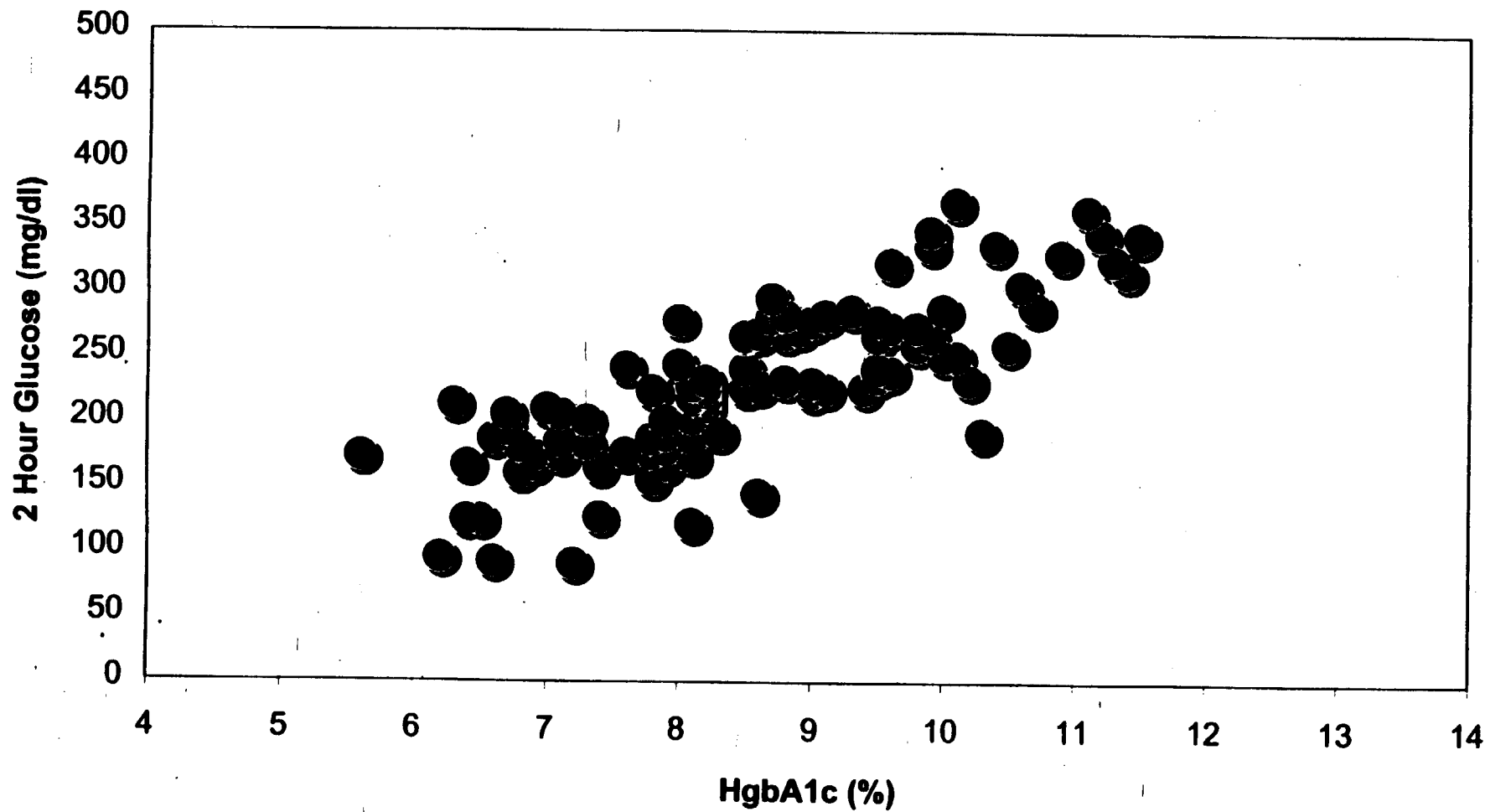
Change in HgbA1c vs. Glucose Excursion: Metformin (Study 351; 24 Weeks)



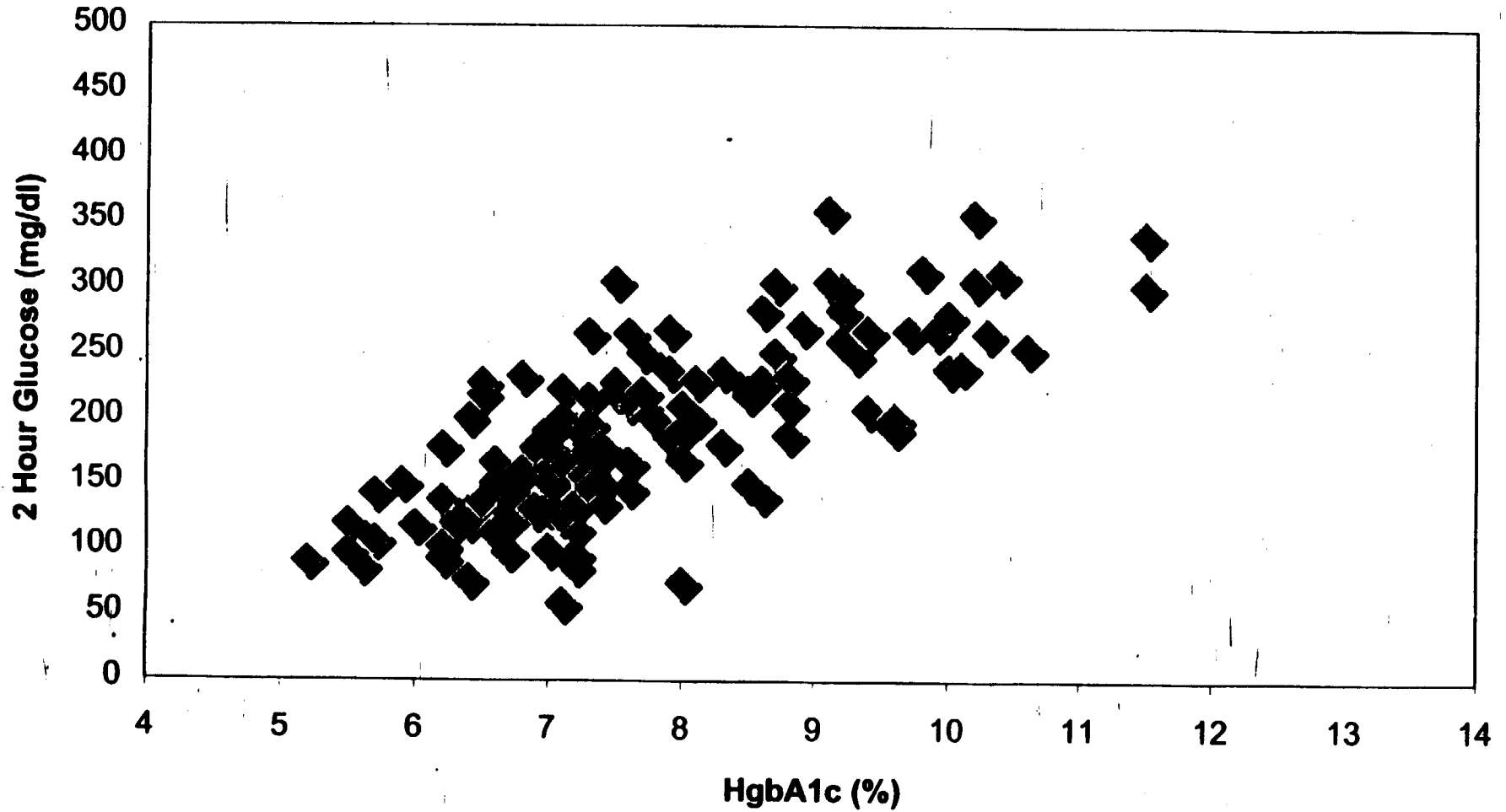
Change in HgbA1c vs. Glucose Excursion: Combo (Study 351; 24 Weeks)



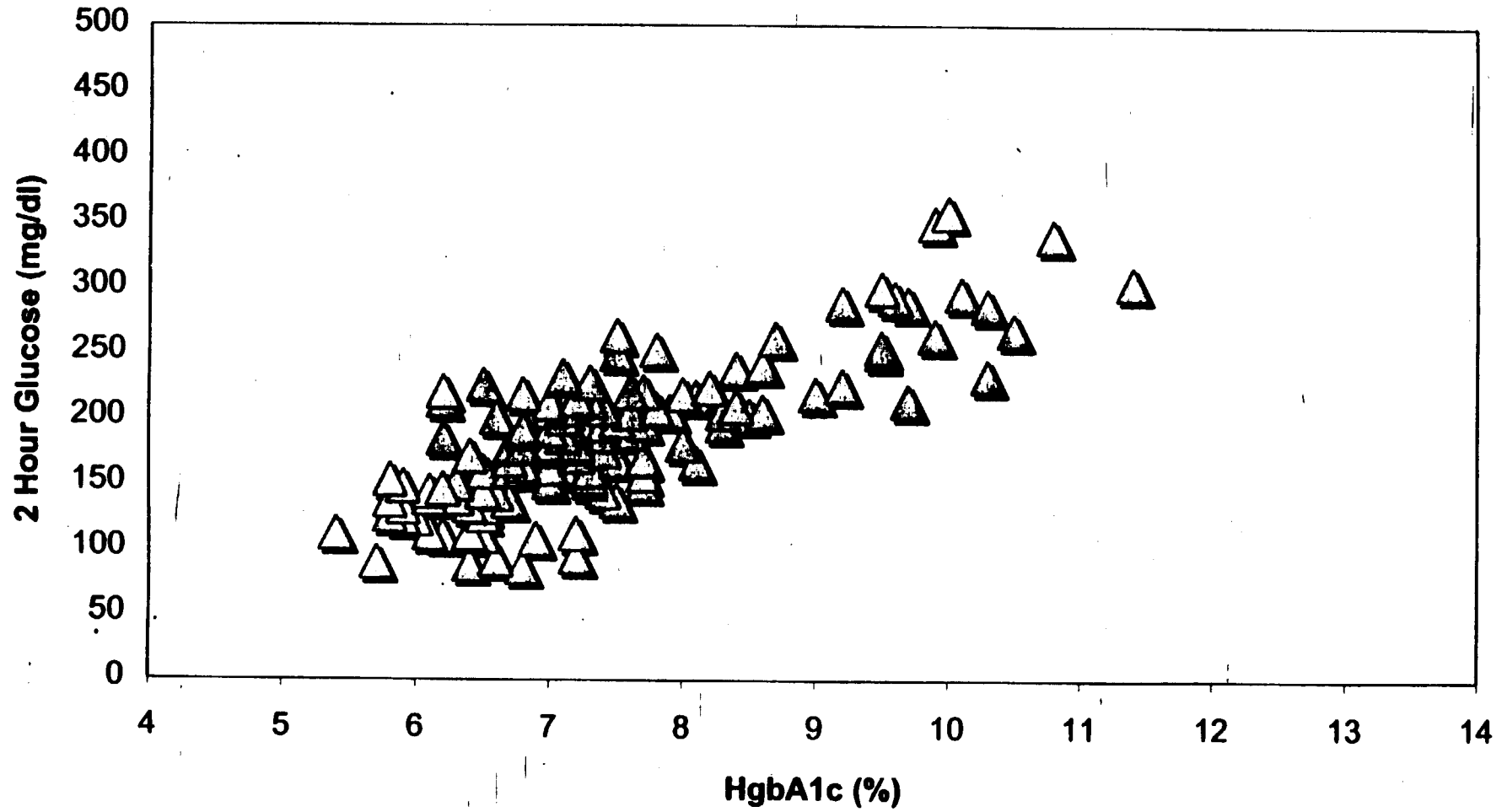
Endpoint HgbA1c vs 2 Hour Post-prandial Glucose: Placebo (Study 351; 24 Weeks)



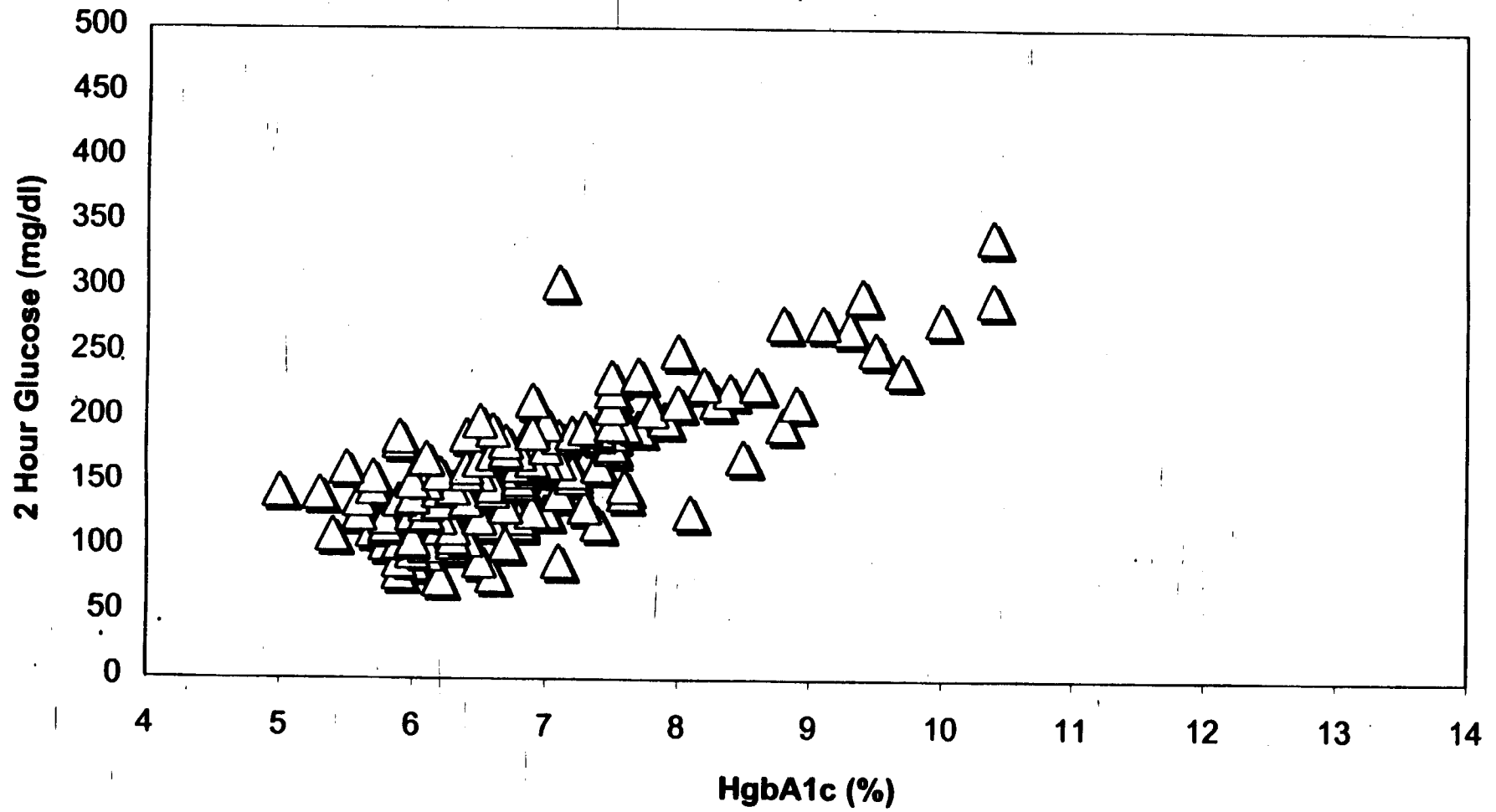
Endpoint HgbA1c vs. 2 Hour Post-prandial Glucose: DJN 608 (Study 351; 24 Weeks)



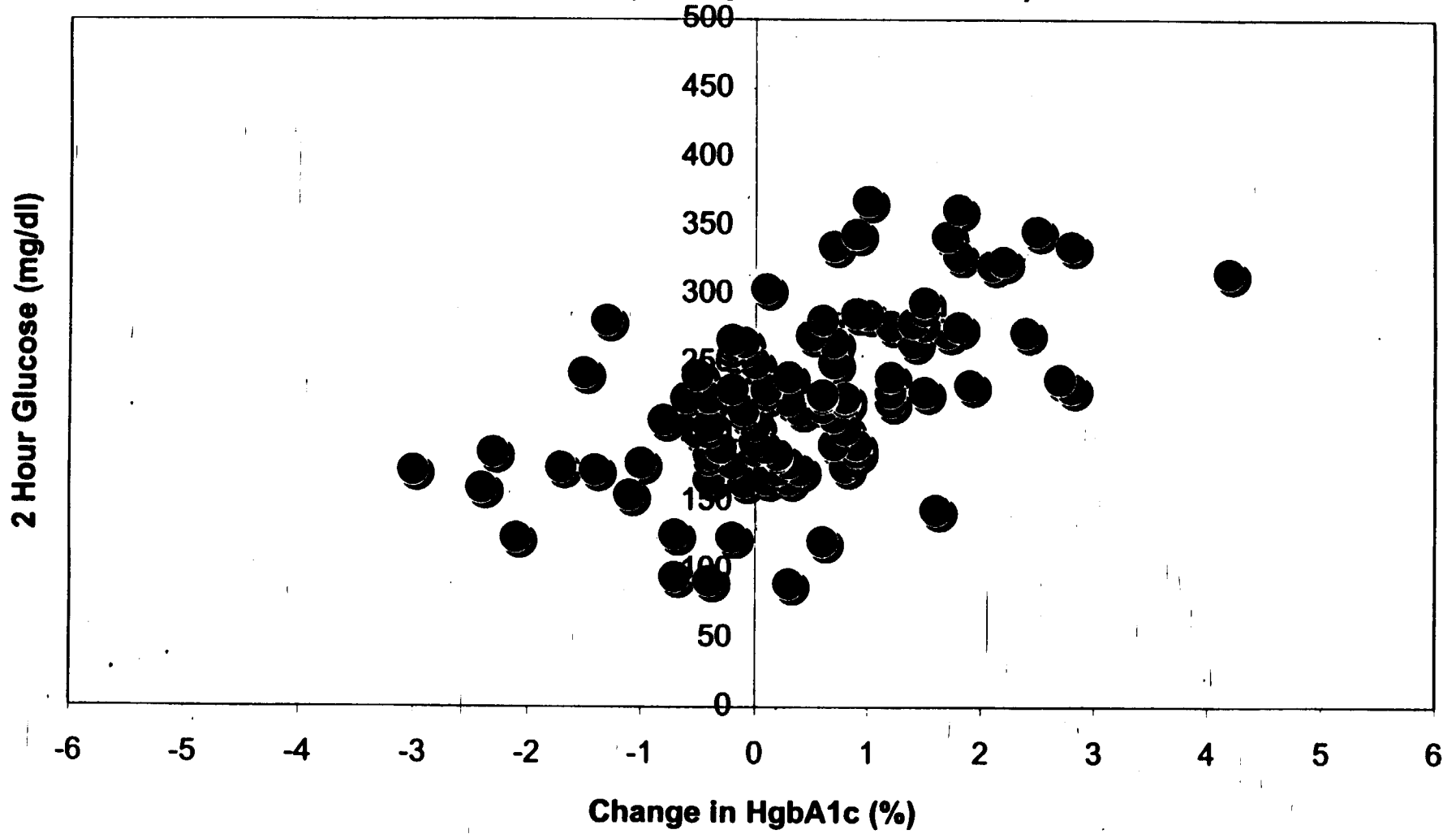
Endpoint HgbA1c vs. 2 Hour Post-prandial Glucose: Metformin (Study 351; 24 Weeks)



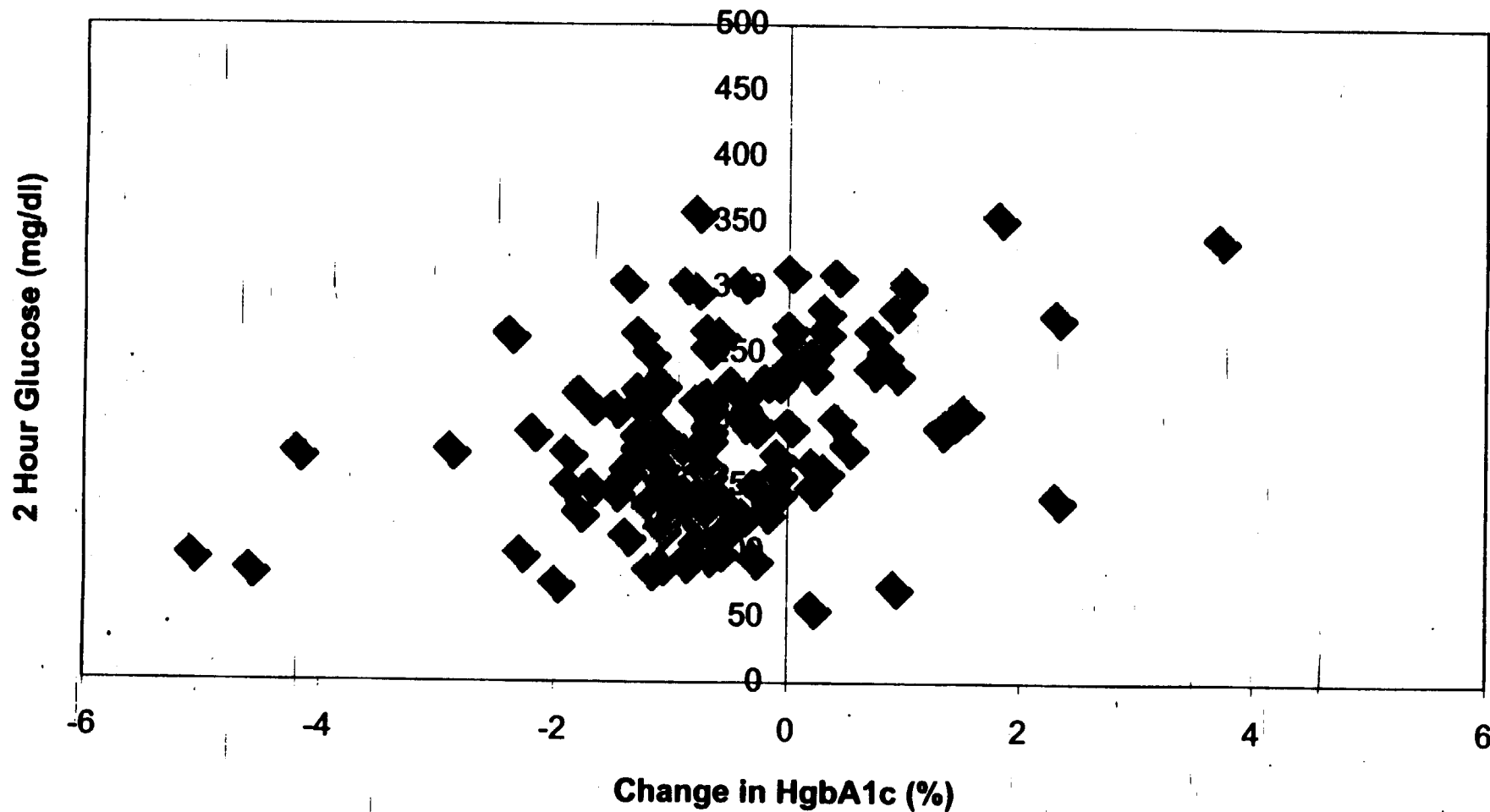
HgbA1c at Endpoint vs. 2 Hour Post-prandial Glucose: Combo (Study 351; 24 Weeks)



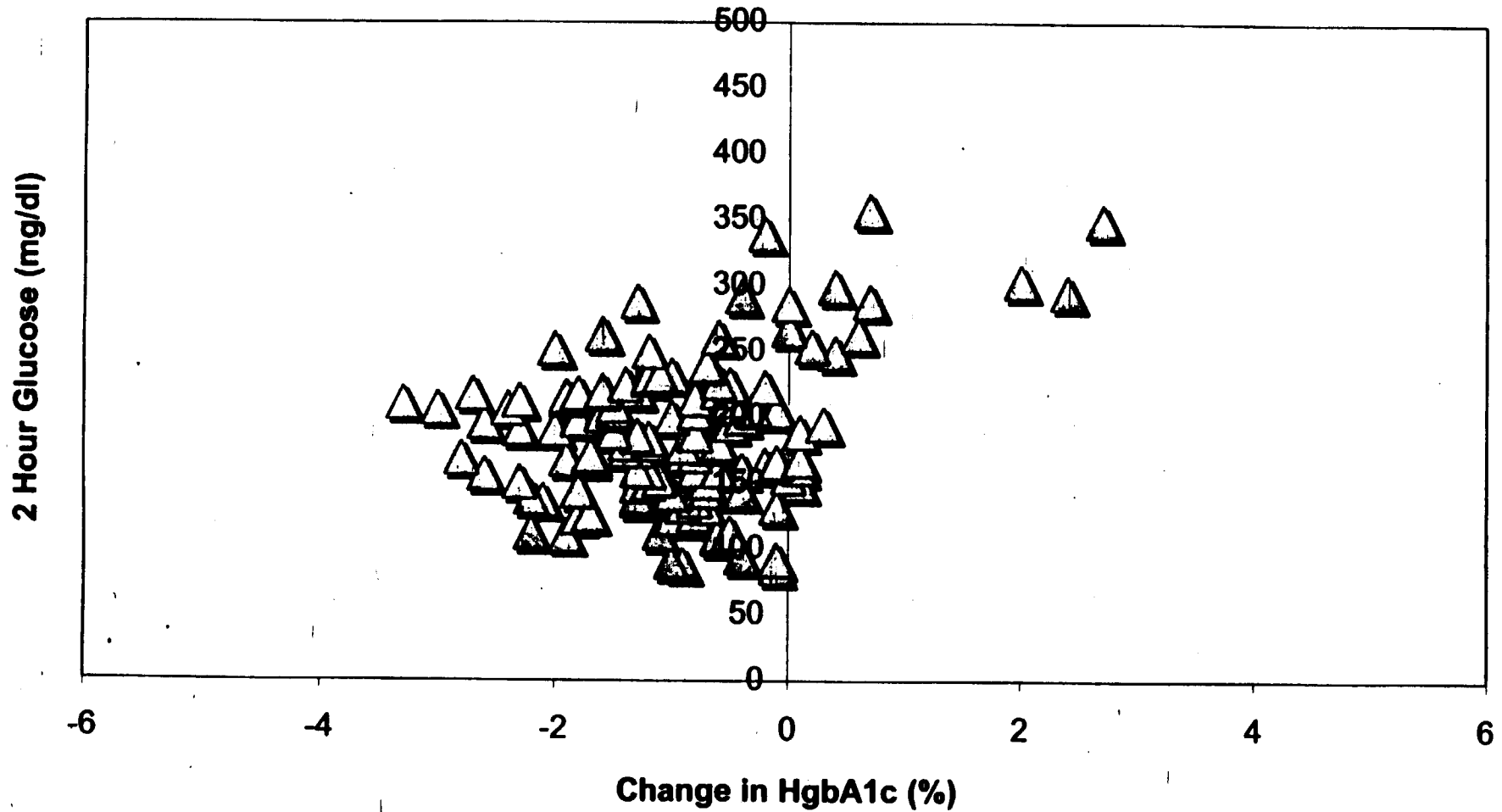
Change in HgbA1c vs 2 Hour Post-prandial Glucose: Placebo (Study 351; 24 Weeks)



Change in HgbA1c vs 2 Hour Glucose: DJN 608 (Study 351; 24 Weeks)



Change in HgbA1c vs. 2 Hour Post-prandial Glucose: Metformin (Study 351; 24 Weeks)



Change in HgbA1c vs. 2 Hour Post-prandial Glucose: Combo (Study 351; 24 Weeks)

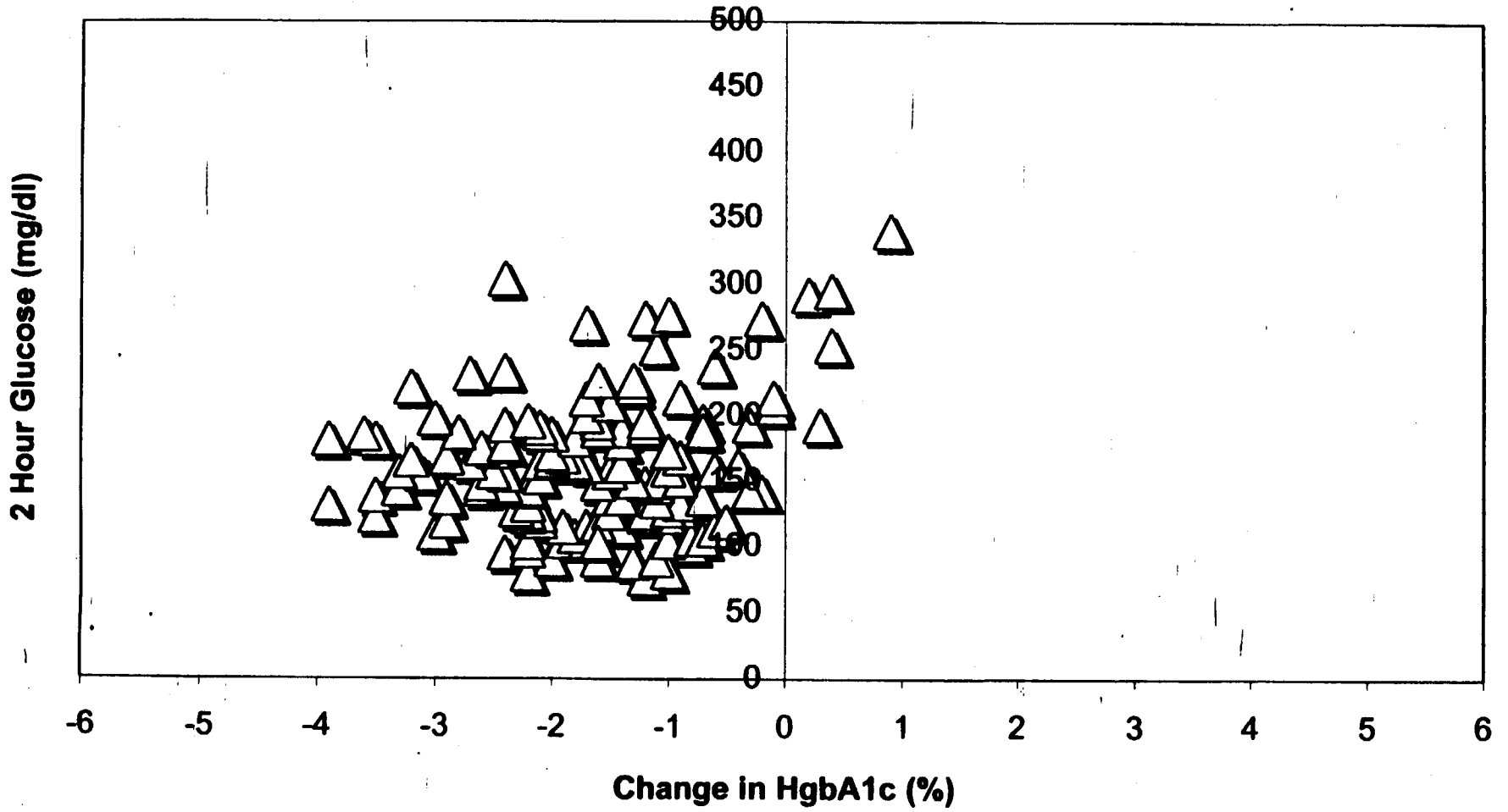


Fig. 9

Fructosamine and Fasting Glucose Changes by Treatment Group and by Prior Anti-diabetic Drug Exposure: Study 355

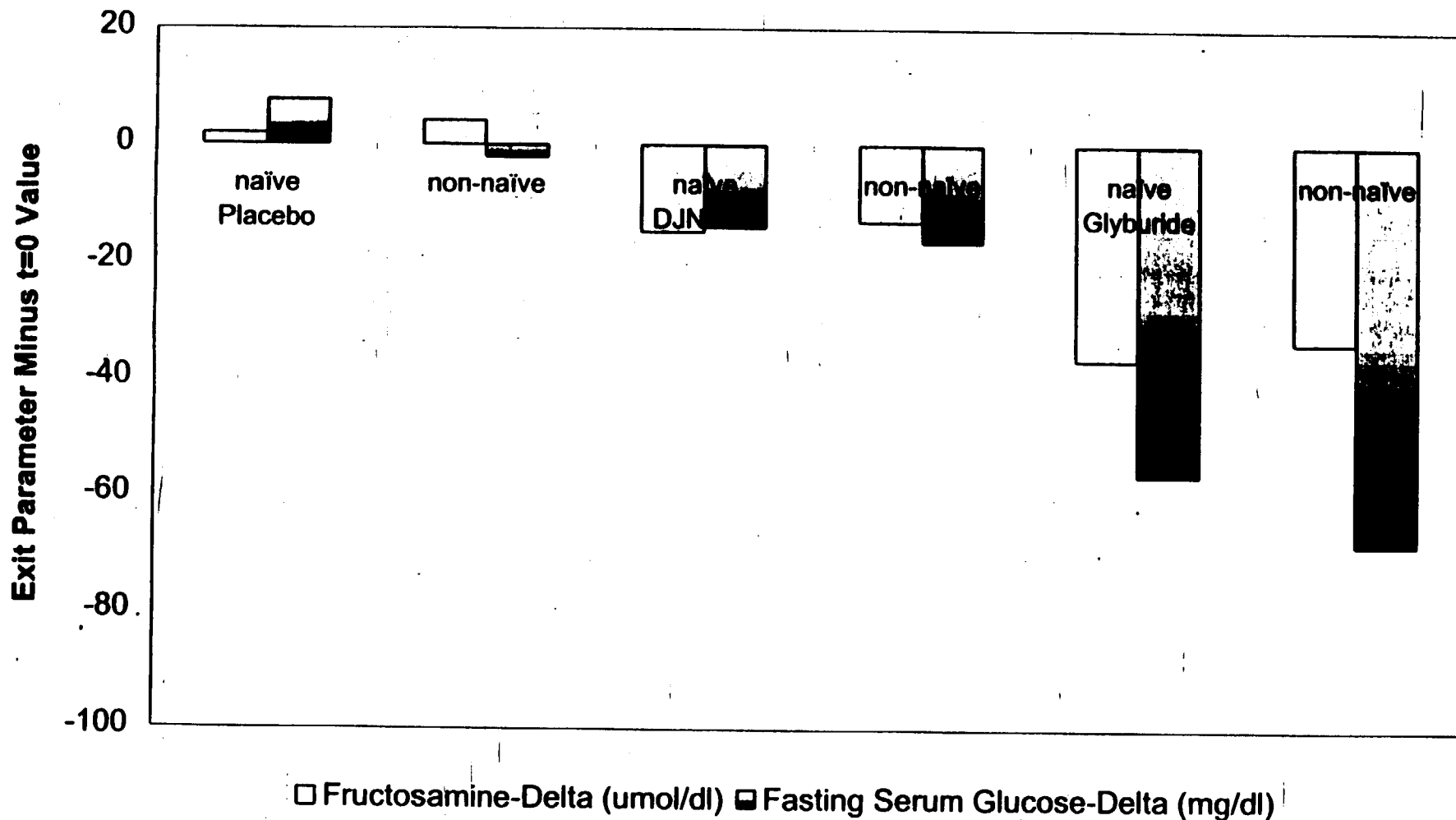


Fig. 10

Glucose Excursion vs. Fructosamine Level vs. Fructosamine Change over 8 Weeks by Patient Subgroup (Naïve vs. Non-naïve to Use of Diabetic Medications): Study 355

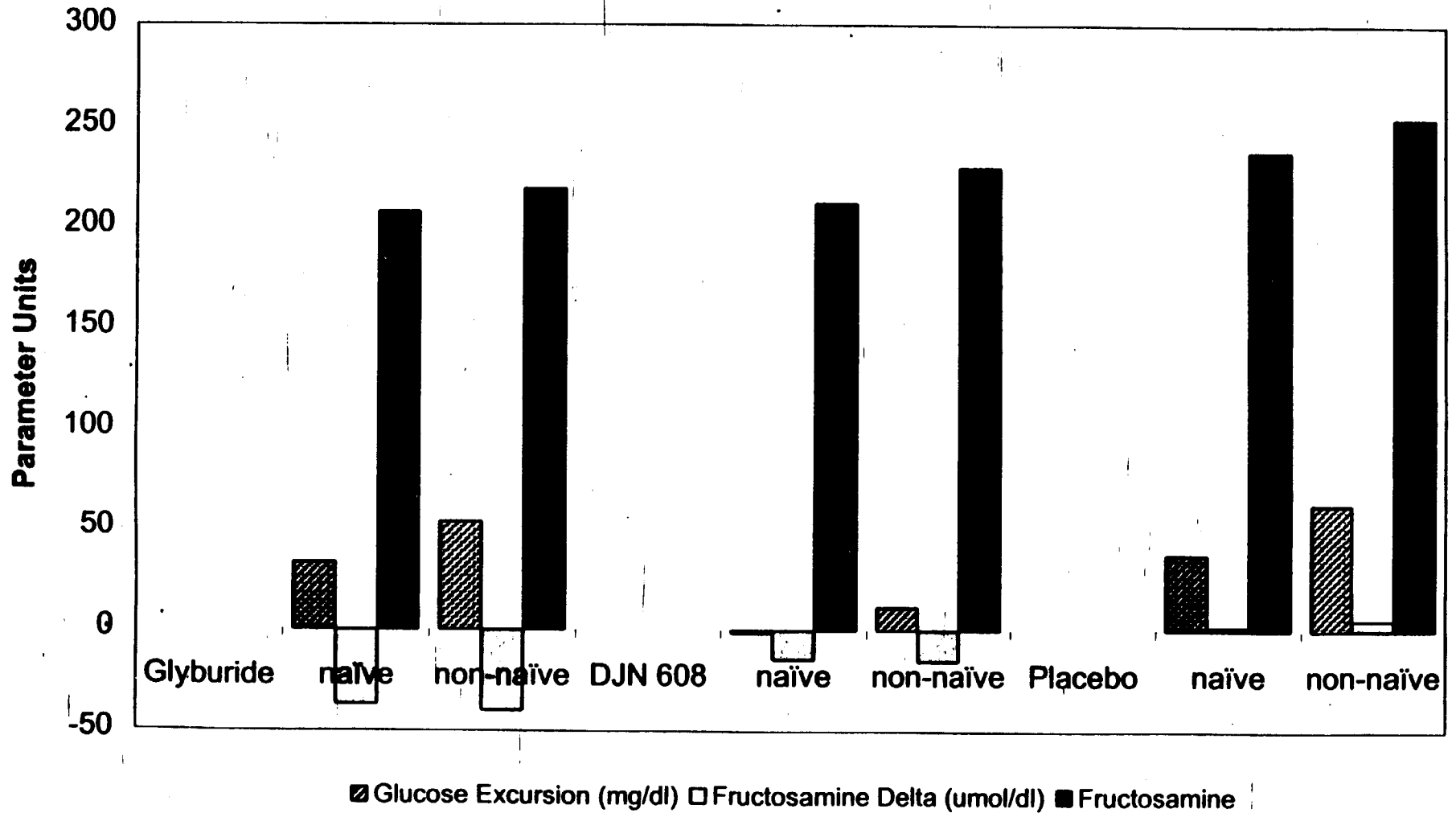


Fig. 11

Glucose Parameters in Naive and Non-Naive Patients by Treatment Group: Study 351

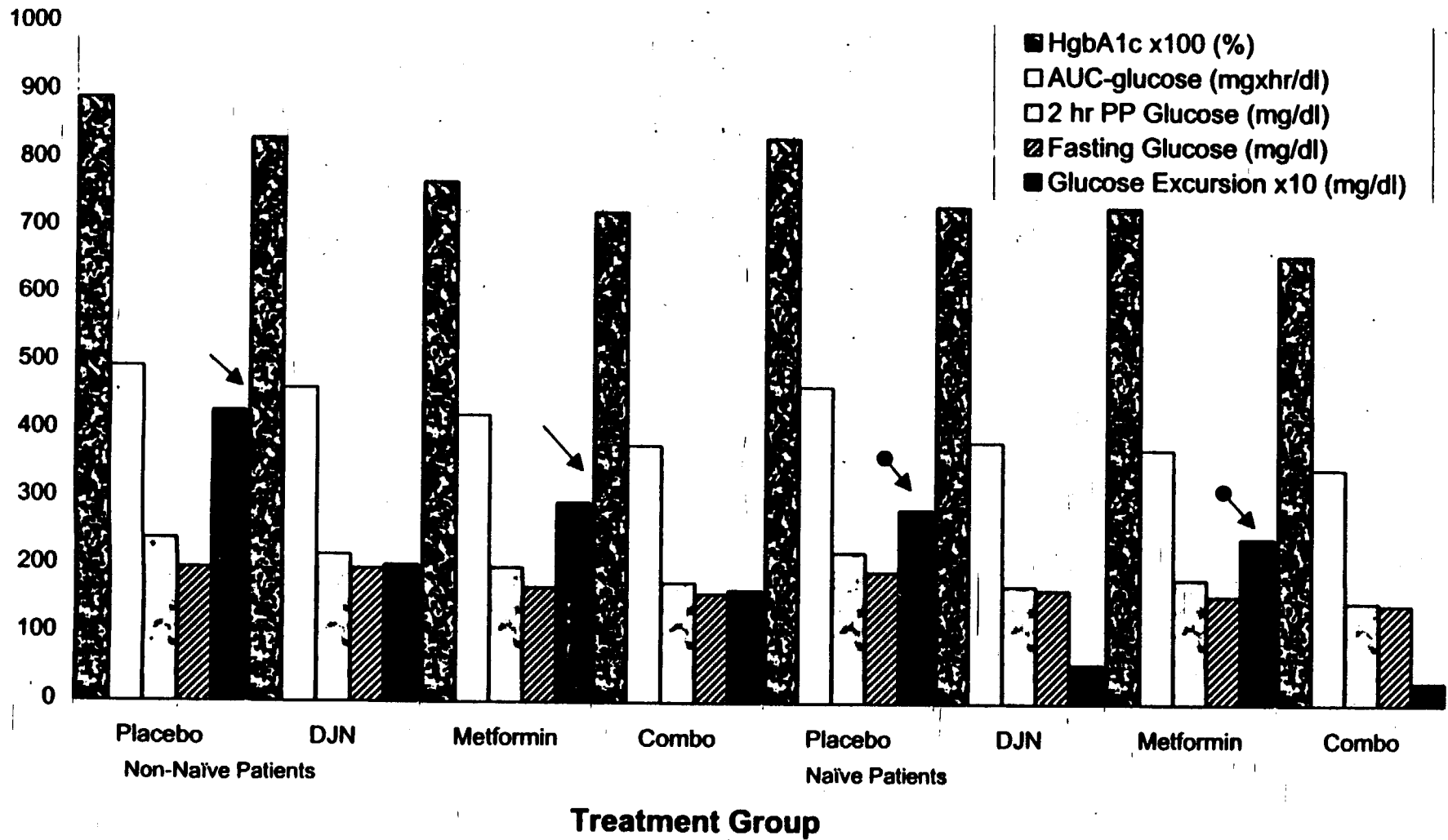


Fig. 12

Glucose AUC after Sustacal Challenge vs. Change in Fructosamine over 8 Weeks by Drug Treatment: Study 355

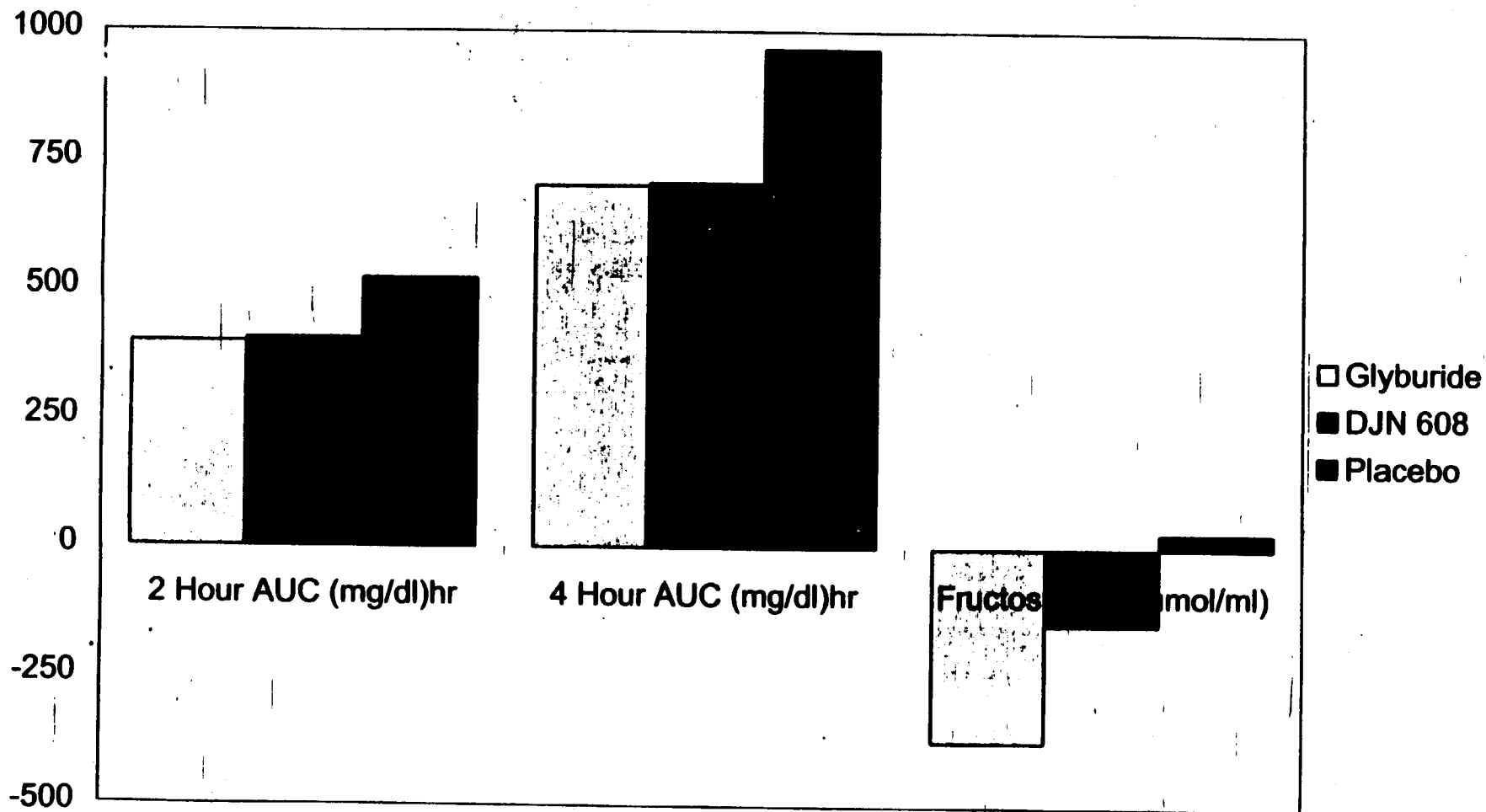


Fig. 13

Glucose AUC after Sustacal Challenge vs. Change in HgbA1c over 24 Weeks by Drug Treatment: Study 351

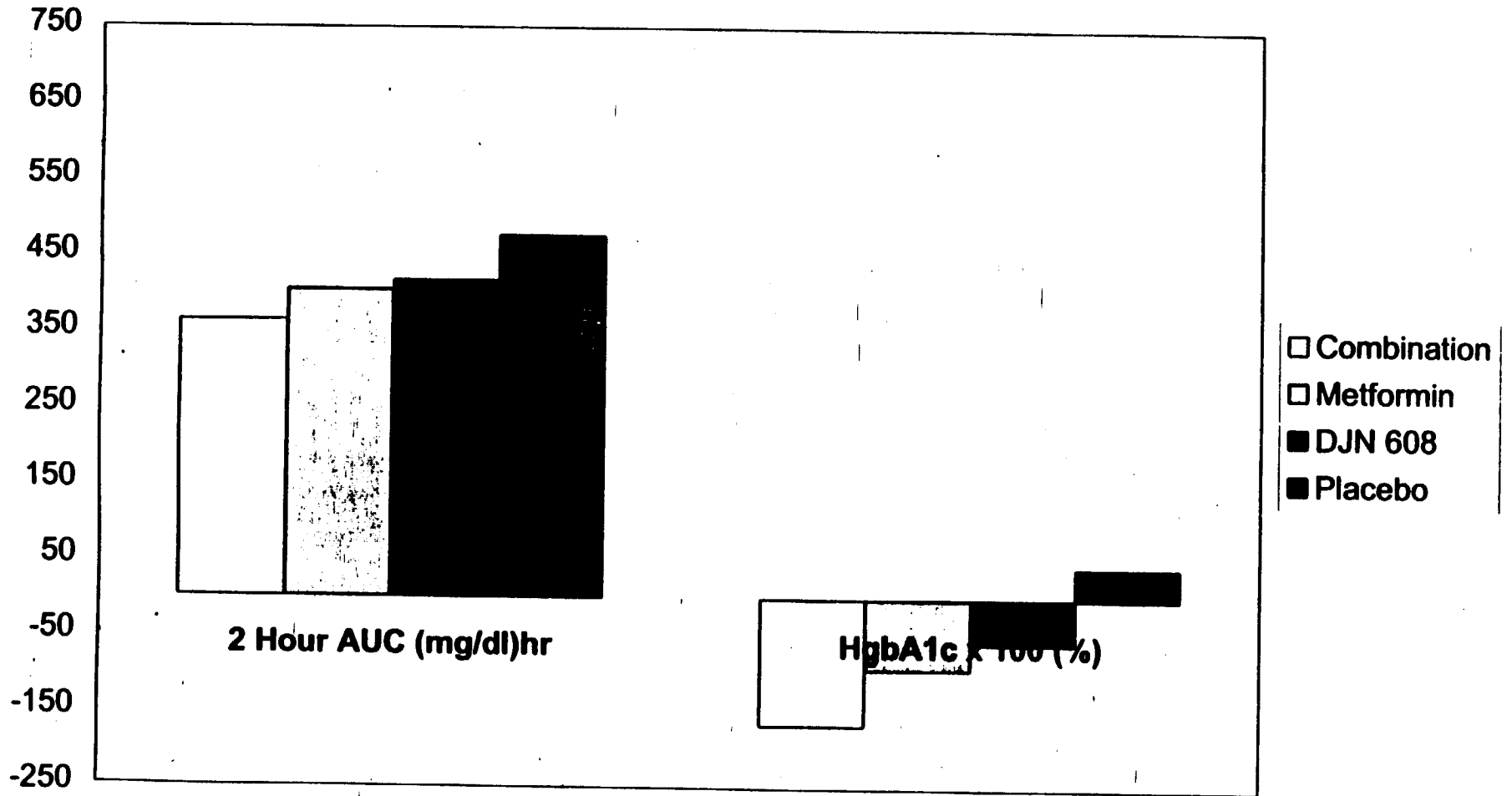


Fig. 14

**Serial HgbA1c Values for Individual Patients in 12 Week Study 251
+40 Week Extension: Cohort Treated with DJN 120 mg+Glyburide 10 mg**

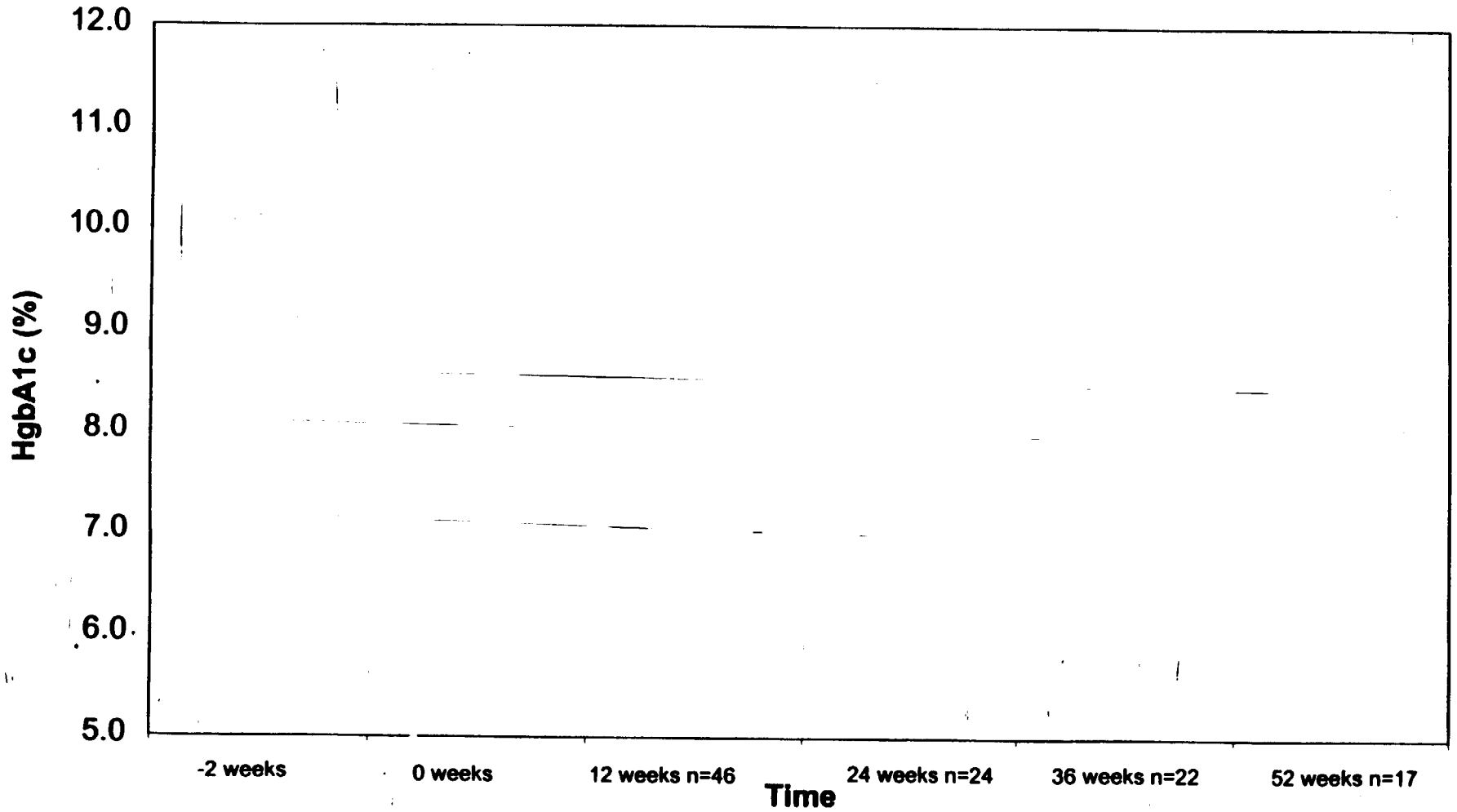


Fig. 15

HgbA1c over Controlled Trial 251 and Extension:
D/JN 608 (120 mg)+Glyburide (10 mg) Treatment Arm:
Cohort Designated by Time of Drop-out

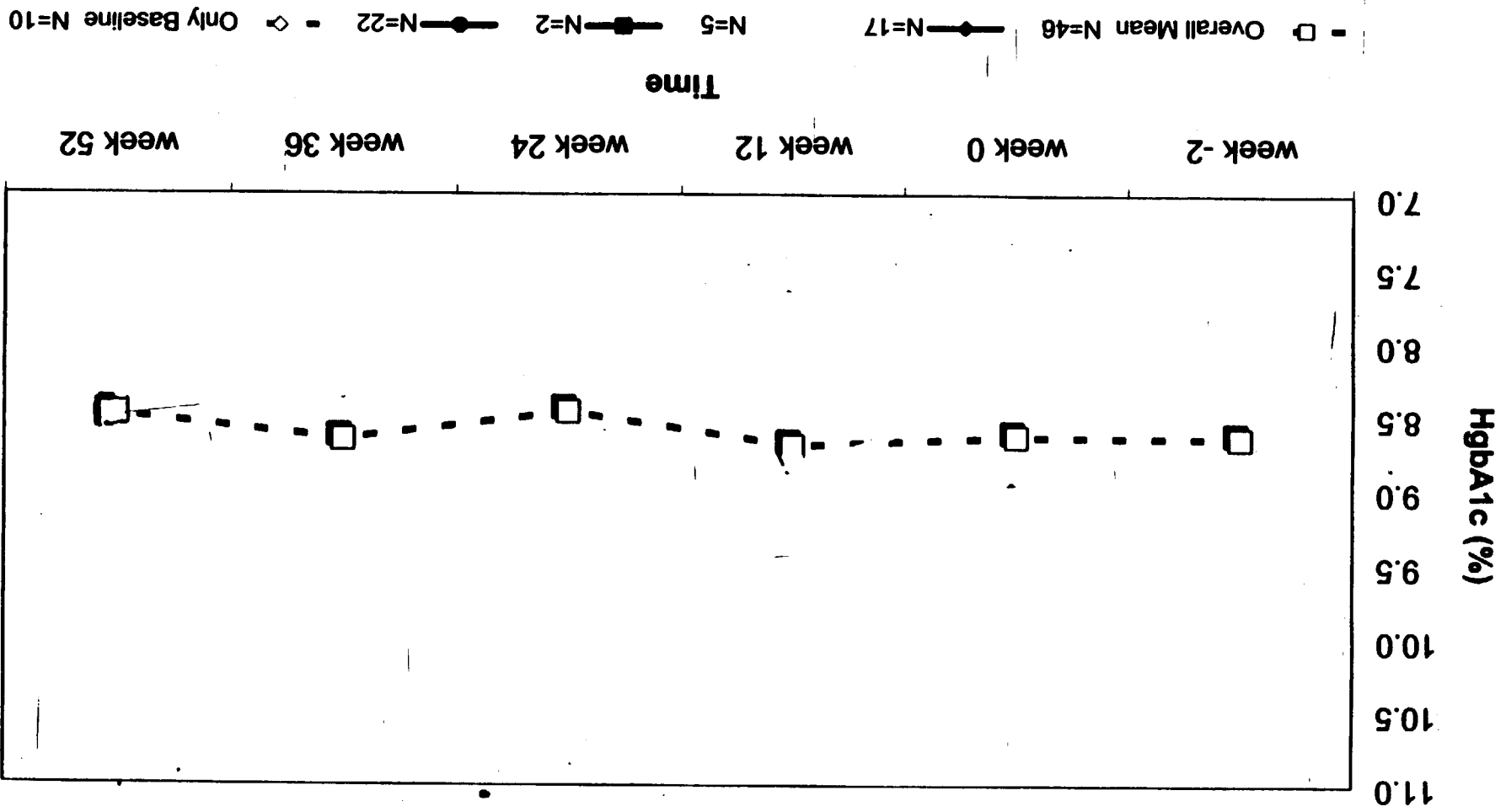


Table 14

Mean of HgbA1c Values at Each Timepoint and by Cohort (designated by time of patient drop-out): Study 251

	<u>Week -2</u>	<u>Week 0</u>	<u>Week 12</u>	<u>Week 24</u>	<u>Week 36</u>	<u>Week 52</u>	<u>Number of Patients in Cohort</u>
Placebo+Glyburide (10 mg/d)	8.72	8.69	8.96	8.7	8.81	8.77	n=52 of enrolled patients that had values at 12 weeks
	8.33	8.32	8.26	8.43	8.56	8.77	n=17 at 52 weeks
	8.43	8.27	8.83	9.32	9.52		n=6 stopped between 36 & 52 weeks
	8.40	8.30	8.55	8.90			n=2 stopped between 24 & 36 weeks
	9.05	9.06	9.46				n=27 stopped between 12 & 24 weeks
	8.48	8.43					n=6 stopped before 12 weeks
	8.69	8.67					n=58 of enrolled patients had values at baseline
DJN (60 mg TID)+glyburide (10 mg/d)	8.70	8.67	9.09	8.86	9.06	8.75	n=49 of enrolled patients that had values at 12 weeks
	8.21	8.15	8.41	8.23	8.54	8.75	n=14 at 52 weeks
	8.70	8.78	8.78	10.38	10.88		n=4 stopped between 36 & 52 weeks
	8.40	8.50	9.13	9.77			n=3 stopped between 24 & 36 weeks
	8.97	8.94	9.48				n=28 stopped between 12 & 24 weeks
	8.84	8.98					n=9 stopped before 12 weeks
	8.72	8.72					n=58 of enrolled patients had values at baseline
DJN (120 mg TID)+glyburide (10 mg/d)	8.65	8.64	8.70	8.47	8.66	8.49	n=46 of enrolled patients that had values at 12 weeks
	8.09	7.96	7.75	8.04	8.31	8.49	n=17 at 52 weeks
	8.38	8.38	8.84	9.18	9.86		n=5 stopped between 36 & 52 weeks
	9.35	9.45	9.55	10.35			n=2 stopped between 24 & 36 weeks
	9.05	9.15	9.31				n=22 stopped between 12 & 24 weeks
	9.03	9.05					n=10 stopped before 12 weeks
	8.72	8.71					n=56 of enrolled patients had values at baseline

Fig. 16

HgbA1c over Controlled Trial (24 weeks) and Extension: Study 351 (DJN 608 Added to Placebo at 24 Weeks)

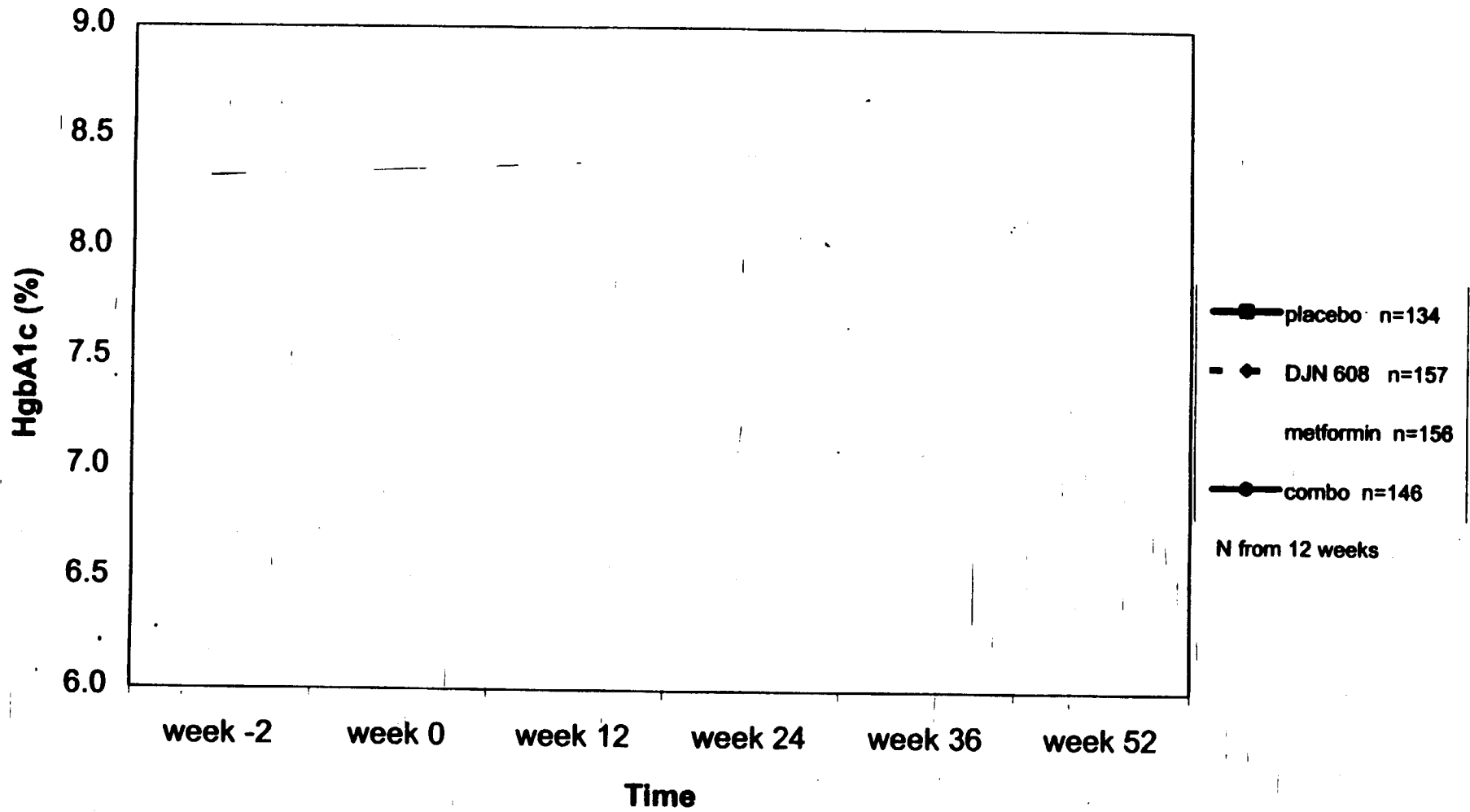


Fig. 17

Serial HgbA1c Values for Individual Patients in 24 Week Study 351 + 40 Week Extension: Cohort Treated with DJN 120 mg

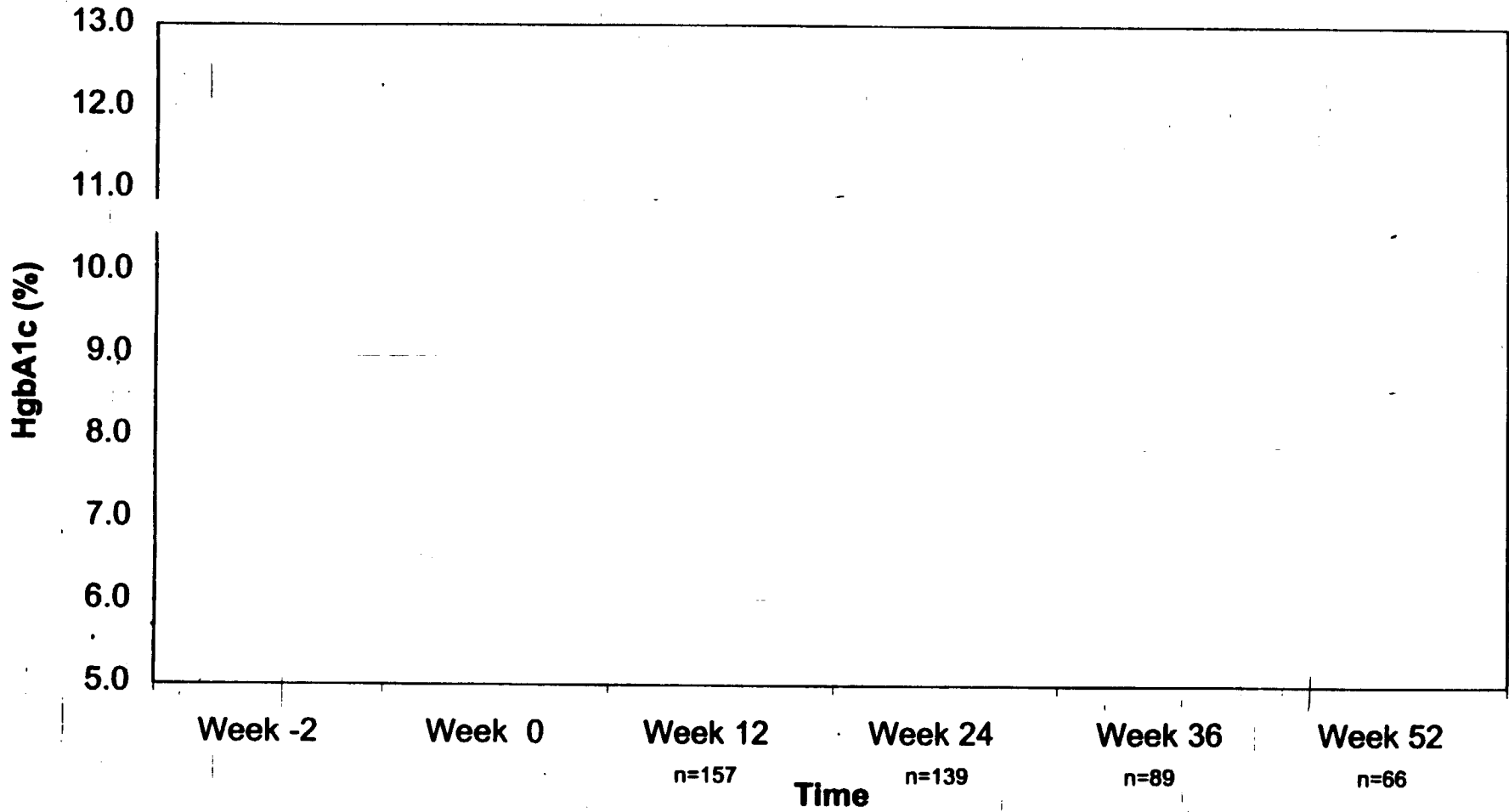


Fig. 18

HgbA1c over Controlled Trial 351 and Extension: DJN 608 (120 mg TID) Treatment Arm: Cohort Designated by Time of Drop-out

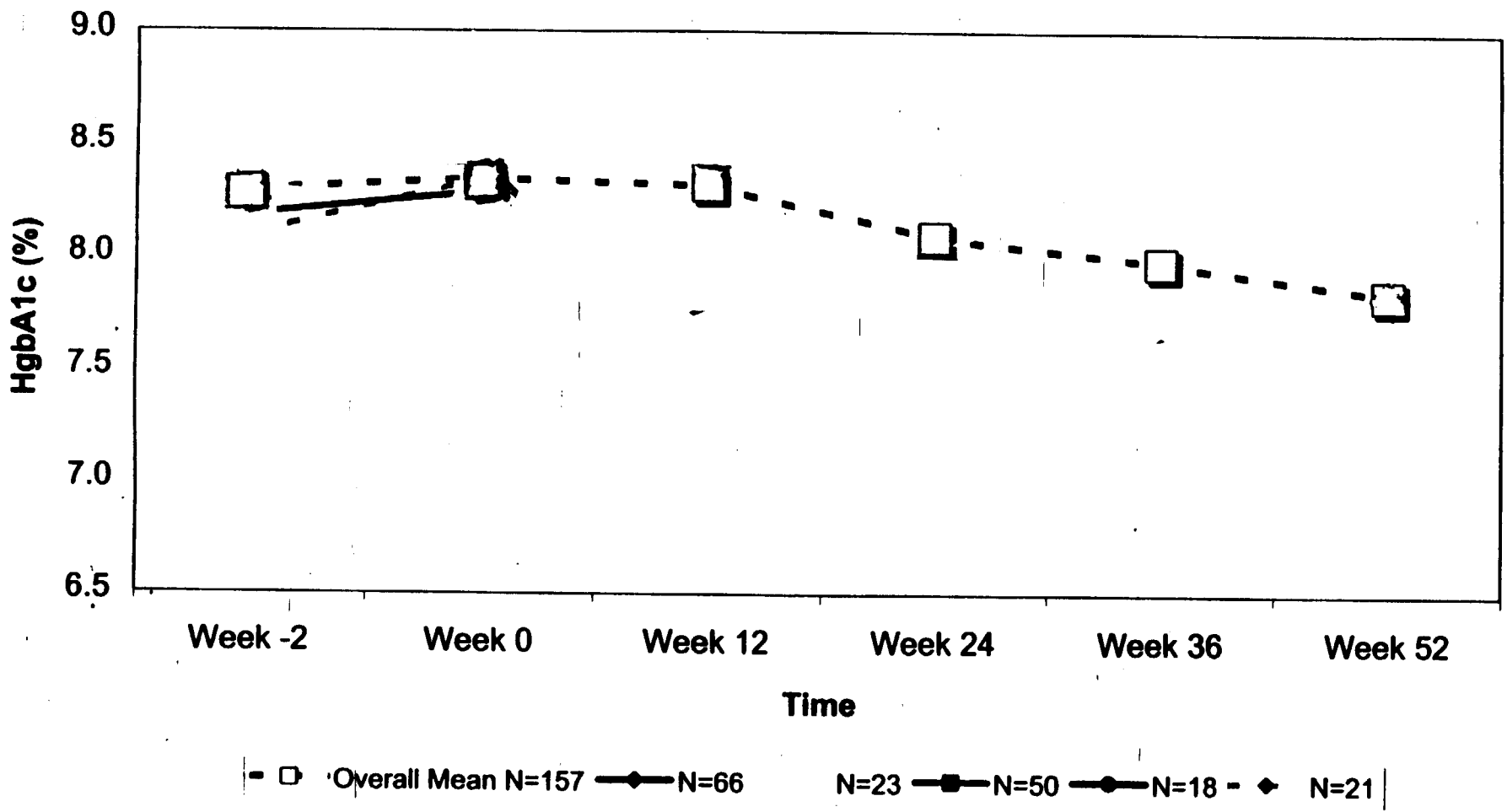


Table 15
 Mean of HgbA1c Values at each Timepoint and by Cohort (designated by time of patient drop-out): Study 351

	<u>Week -2</u>	<u>Week 0</u>	<u>Week 12</u>	<u>Week 24</u>	<u>Week 36</u>	<u>Week 52</u>	<u>Number of Patients in Cohort</u>
Placebo	8.16	8.19	8.49	8.51	7.75	7.85	n=134 of enrolled patients had values at 12 weeks n=60 at 52 weeks n=18 stopped between 36 & 52 weeks n=41 stopped between 24 & 36 weeks n=14 stopped between 12 & 24 weeks n=38 stopped before 12 weeks n=172 of enrolled patients had values at baseline
	8.21	8.27	8.54	8.48	7.68	7.85	
	8.12	8.17	8.21	8.62	7.98		
	7.96	7.90	8.15	8.50			
	8.61	8.72	9.54				
	8.54	8.73					
	8.25	8.81					
DJN 608 120 mg TID	8.29	8.34	8.31	8.08	7.97	7.83	n=157 of enrolled patients had values at 12 weeks n=66 at 52 weeks n=23 stopped between 36 & 52 weeks n=50 stopped between 24 & 36 weeks n=18 stopped between 12 & 24 weeks n=21 stopped before 12 weeks n=178 of enrolled patients had values at baseline
	8.36	8.42	7.41	7.42	7.57	7.83	
	8.30	8.25	8.05	8.03	8.34		
	8.18	8.28	7.68	7.94			
	8.30	8.86	8.40				
	8.09	8.34					
	8.26	8.34					
Metformin 500 mg TID	8.42	8.49	7.71	7.44	7.40	7.44	n=156 of enrolled patients had values at 12 weeks n=78 at 52 weeks n=18 stopped between 36 & 52 weeks n=44 stopped between 24 & 36 weeks n=15 stopped between 12 & 24 weeks n=22 stopped before 12 weeks n=177 of enrolled patients had values at baseline
	8.40	8.45	7.54	7.23	7.38	7.44	
	8.26	8.23	7.43	7.24	7.49		
	8.24	8.38	7.88	7.88			
	9.23	9.29	8.49				
	8.21	8.34					
	8.39	8.47					
Combination	8.44	8.54	6.95	6.91	7.00	7.14	n=146 of enrolled patients had values at 12 weeks n=82 at 52 weeks n=15 stopped between 36 & 52 weeks n=40 stopped between 24 & 36 weeks n=9 stopped between 12 & 24 weeks n=26 stopped before 12 weeks n=172 of enrolled patients had values at baseline
	8.43	8.56	6.87	6.80	6.98	7.14	
	8.30	8.37	6.93	6.93	7.11		
	8.62	8.69	7.14	7.12			
	7.93	7.99	6.79				
	8.06	8.25					
	8.38	8.48					

Fig. 19

Changes in Glycemic Control and Weight in Patients Not Previously Treated with Diabetes Drugs: Study 302

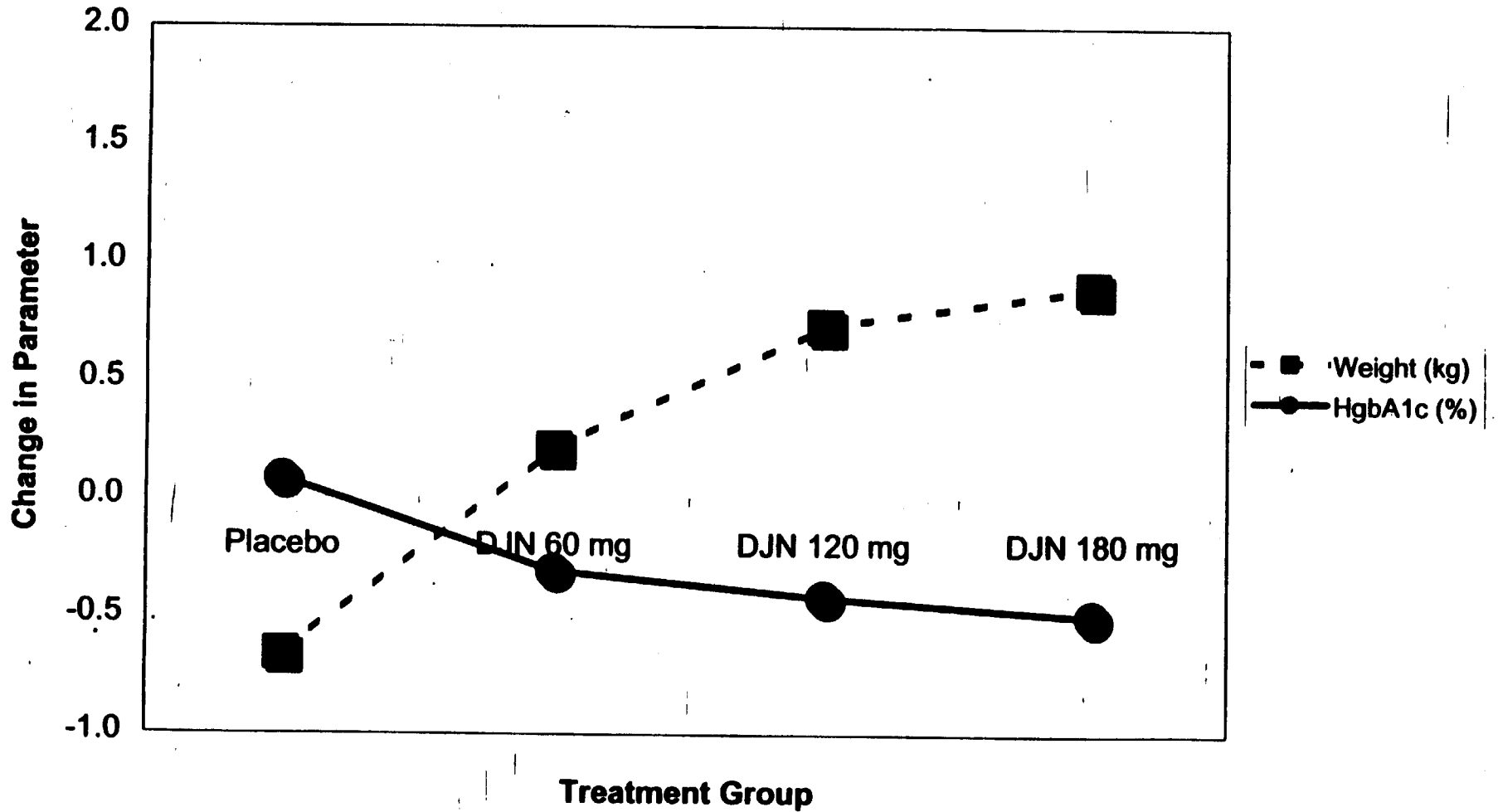


Fig. 20

Changes in Glycemic Control and Weight in Patients Previously Treated with Diabetes Drugs: Study 302

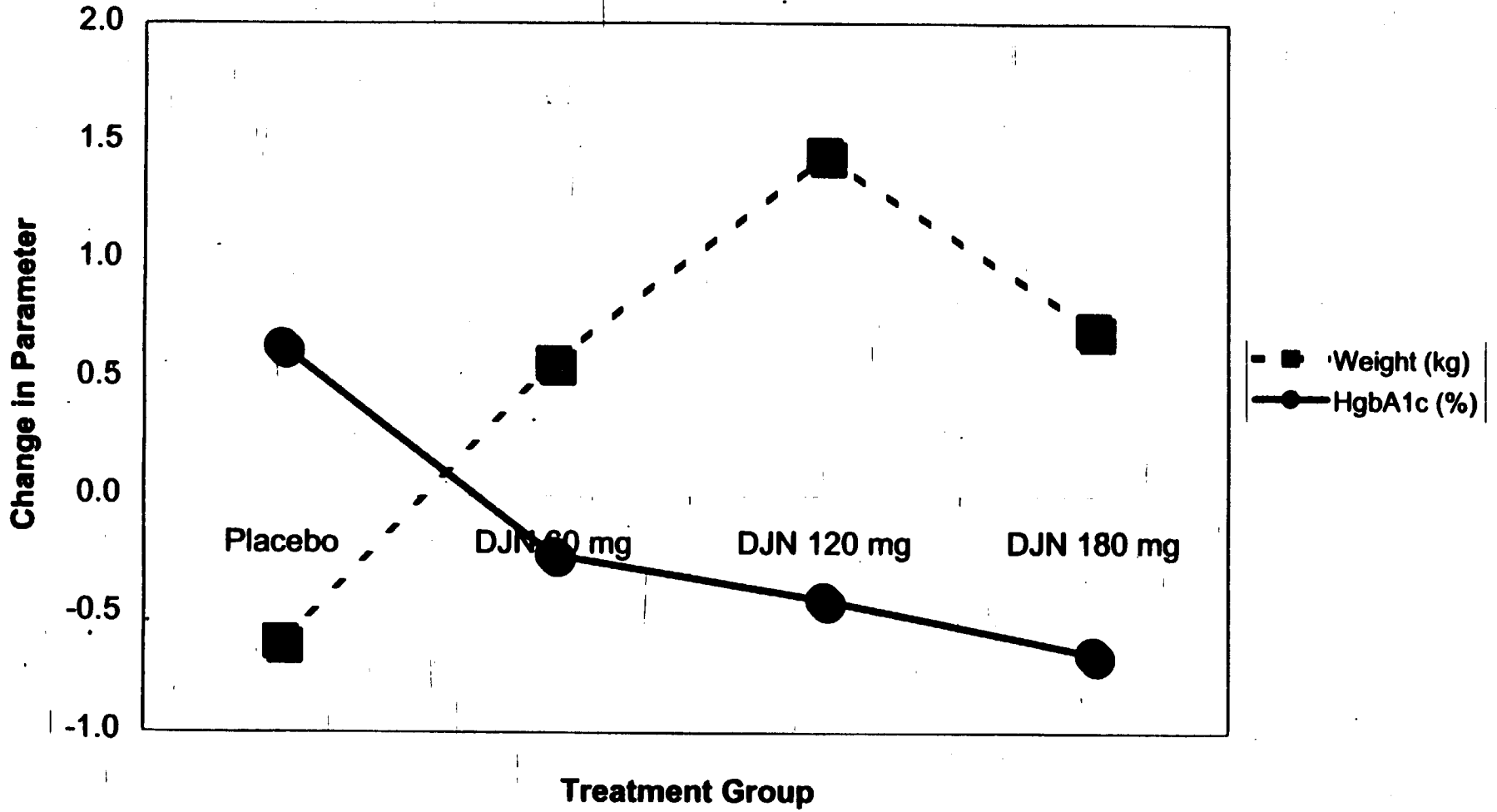


Fig. 21

Change in Glycemic Control and Weight by Treatment Group: Study 355 (8 Weeks)

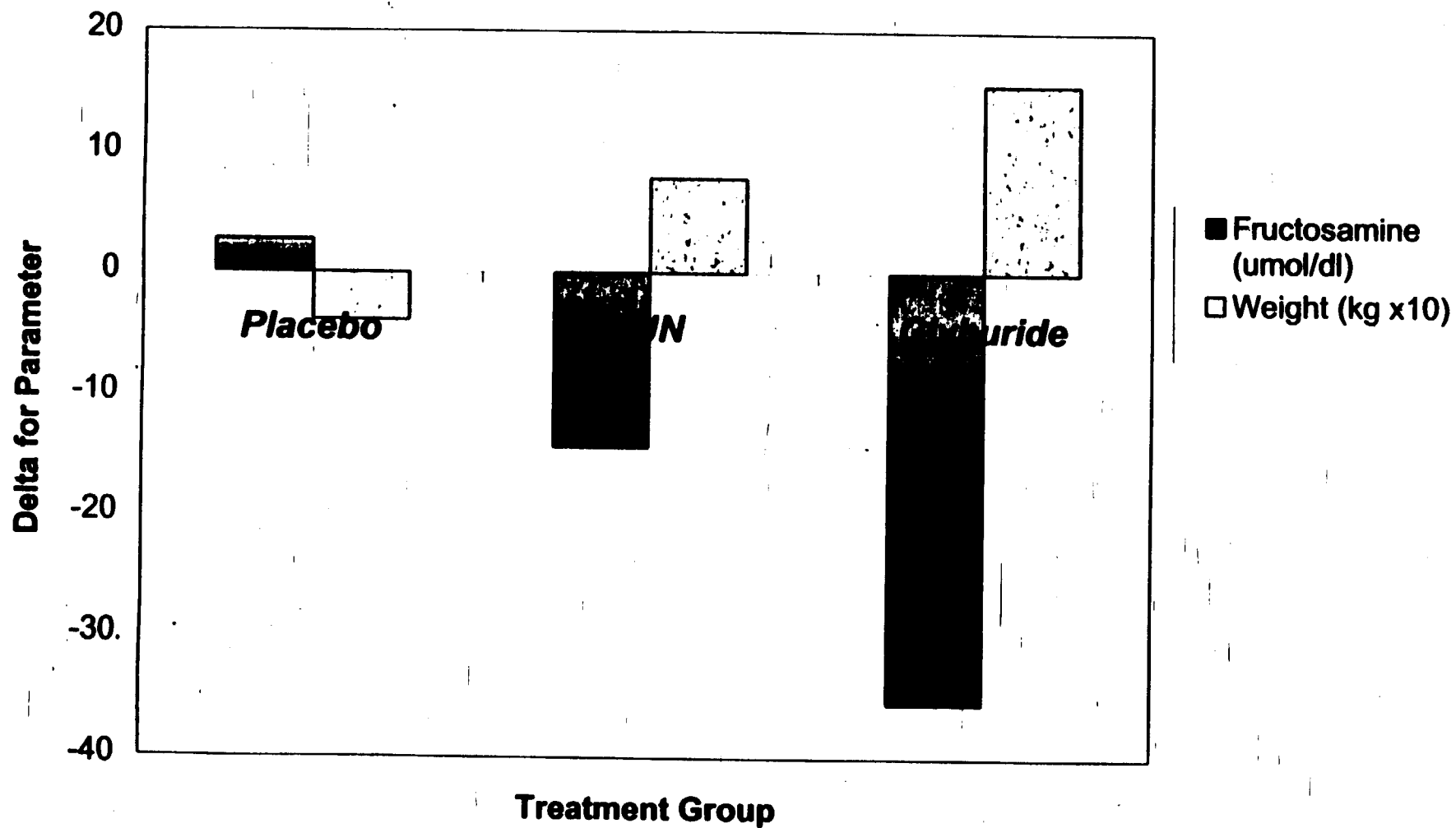


Fig. 22

Changes in Glycemic Control and Weight by Treatment Group: Study 351 (24 Weeks)

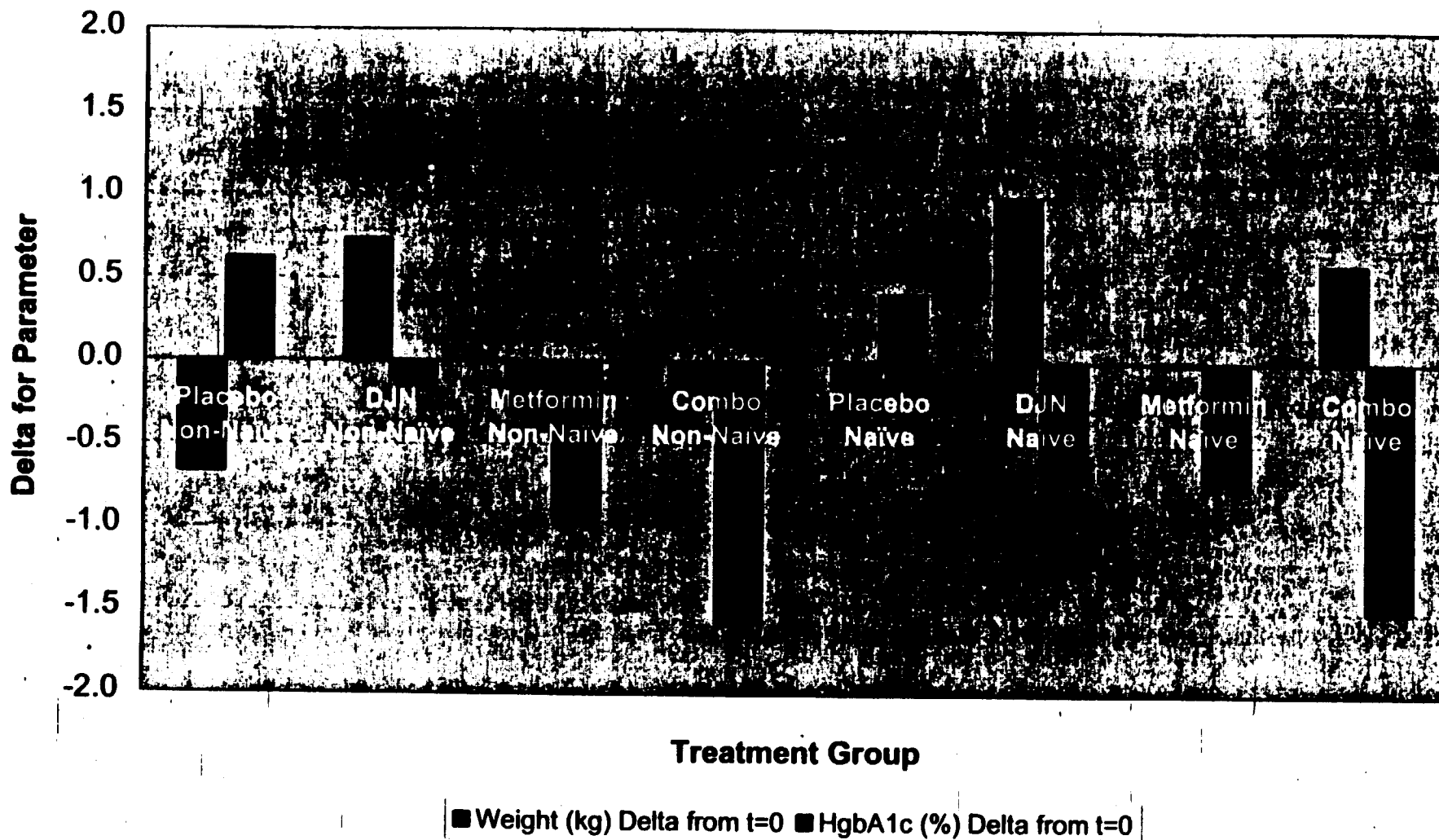


Table 16

Serious Adverse Events and Adverse Events That Resulted in Discontinuation vs. Treatment Cohort

Treatment	DJN	DJN+Metformin	DJN+Glyburide	Metformin	Glyburide	Placebo
N randomized	1448	640	114	406	293	459
AE→DC*	78 (5.4%)	46 (7.2%)	9 (7.9%)	29 (7.1%)	11 (3.8%)	28 (6.1%)
Serious AE	56 (3.9%)	30 (4.7%)	2 (6.1%)	18 (4.4%)	20 (6.8%)	20 (4.4%)

AE=adverse events DC=resulted in discontinuation %=percentage of that treatment group

APPEARS THIS WAY
ON ORIGINAL

4/1