

requiring IV glucose or glucagon was listed as 26 (Vol. 67, p117), 25 (Vol. 67, p118), and 25 (SAS data set).

The number of hypoglycemic events for X-14 requiring intervention was listed as 314 (Vol. 82, p117), 312 (Vol. 67, p118), and 312 (SAS data set). The number of events for human regular requiring IV glucose or glucagon was listed as 42 (Vol. 67, p117), 40 (Vol. 67, p118), and 40 (SAS data set).

Study 036 The number of hypoglycemic events for human regular requiring intervention was listed as 157 (Vol. 82, p107), 155 (Vol. 82, p110), and 155 (SAS data set).

The number of hypoglycemic events for X-14 requiring intervention was listed as 266 (Vol. 82, p107), 265 (Vol. 82, p110), and 265 (SAS data set).

10.2.4. Ketosis

The sponsor did not rigorously collect data on ketoacidosis so it is difficult to assess relative risk. (And it was difficult to assess other patient characteristics of those who had experienced adverse events because the Sponsor did not always correctly record the investigator name on the narrative; patient data were grouped by investigator-not by patient number.) There were multiple patients with abdominal complaints in whom DKA must be considered despite the inadequacy of the adverse event narrative. Calculations were also complicated by the failure of the sponsor to distinguish between events that occurred during the run-in, during which all patients received human regular insulin, and the actual experimental treatment periods. This would tend to overestimate the amount of ketosis in the human regular group. There were three patients for whom this determination could not be made (See *) because there were no accompanying data listing the date of entry into the run-in and the date of entry into the treatment phase. Also a disproportionate of DKA cases in 035 occurred in a single patient, who had DKA during the run-in period. The patient was not excluded from the trial and, it appears that she did not receive a urologic work-up for the urinary tract infections that contributed to her DKA. Overall, the risk for ketoacidosis appears to be similar in the two treatment groups. Curiously, preliminary data from the European extension trial 050 suggest that there may be more ketosis in the X-14 arm: 3 ketotic events + 3 less well-defined events with no events in the human regular arm, X-14/HR ratio 3:1.

Table 16

Episodes of DKA and possible DKA by study

035 Human regular

*35/012-0291 DKA (mild), nausea, vomiting
35/012-0291 DKA (mild), urinary tract infection (multiple ?UTIs from screening onward)
35/012-0291 DKA (mild), ?urinary tract infection (multiple ?UTIs from screening onward)
92/131-1317 Abdominal pain, not appendicitis
45/022-0045 Gastric upset, dehydration
38/015-0166 Vomiting
*37/14-0277 Abdominal pain, ?diverticulitis

035 X-14

36/013-0243 DKA
86/119-1449 DKA, gastritis
35/018-0289 DKA, viral infection
44/021-0121 Abdominal pain, nausea, vomiting, hyperglycemia, ?urinary tract infection
73/520-5033 Abdominal pain, ?appendicitis
38/015-0162 ?Appendicitis
28/005-0172 Nausea, anxiety

036 Human regular

- 147:630-6455 DKA, viral symptoms, vomiting,
- 148:631-6107 Nausea, vomiting, RLQ pain, ?pyelonephritis
- *148:631-6459 Nausea, vomiting, dehydration, chest pain, hyperglycemia
- 119:602-6533 Nausea, headache, fever, hyperglycemia, ?meningitis

36 X-14

- 120:603-6497 DKA, upper respiratory infection
- 145:628-6289 DKA, nausea, vomiting, increased glucose, ? because of oral contraceptives
- 134:617-6797 Hyperglycemia
- 146:629-97909 Hyperglycemia, abdominal complaints
- 165:648-98534 Nausea, vomiting, abdominal pain, ?appendicitis
- 137:620-6241 Abdominal pain, (-) U.S. except for small amount of pelvic fluid
- 6712 Fever, chills, dizziness, ?influenza
- 122:605-6704 Pain, fever, ?pyelonephritis

10.2.5. Antibodies

The most significant changes in antibodies were seen with the cross-reacting species. The increases were seen in the patients treated with X-14. In the pivotal trials, increases were apparent by three months-with some decrease at six months. Such antibodies are important only if they result in allergic (local or systemic) reactions or are associated with significant changes in insulin doses requirements. Multiple patients had increases in their cross-reacting antibodies without having a systemic reaction. The data, however, do suggest that patients treated with X-14 used approximately one to three more insulin units of insulin per day. This increased dosage may reflect three phenomena:

- a) the HgbA1c was minimally lower in the X-14 treated patients,
- b) the shorter duration of action of X-14 may increase insulin needs, and/or
- c) the increase in the dose of basal insulin appears to be related, in a limited way, to the increase in cross-reacting antibodies. (See Statistical review.)

Table 17
Antibodies

Study	<i>Human regular</i>		<i>X-14</i>	
	<i>Baseline (n)</i>	<i>6 months (n)</i>	<i>Baseline (n)</i>	<i>6 months (n)</i>
035	11.0 (354)	11.0 (340)	11.2 (701)	16.9 (676)
036	16.7 (277)	15.9 (253)	16.6 (577)	19.6 (542)
037	9.7 (90)	8.1 (82)	11 (89)	14.1 (87)

N.B. No antibodies were obtained for one site in Study 036.

Long-term follow-up of the patients and changes in antibodies is important to exclude any tachyphylaxis associated with use of the drug product. For proper evaluation, one must have an integrated assessment of the levels of the cross-reacting antibodies over time, the changes in cross-reacting antibodies over time, changes in glycemic control over time, and changes in the insulin dose required to maintain comparable glycemic control over time. Patients who drop-out because of tachyphylaxis must be included in the analysis. The sponsor has presented some preliminary data in the safety up-date that suggests that the cross-reacting antibodies continue to decrease between 6 and 12 months for patients using X-14, but they provided only graphic data from the North American extension study and not the IDDM patients and not the European extension study (050).

They also do not include the numbers of patients with and without values at each time-point and the numbers of drop-outs.

10.2.6. Allergic reactions

Insulin is known to cause allergic reactions, both local and systemic. Some of these reactions may be more of an irritant reaction, e.g. as seen with cresol and phenol. Others may be frank allergic reactions. Although these reactions were more common with animal insulin (with differences at one or two amino acids sites), they have been known to occur even with human regular insulin. Because of the amino acid substitution in X-14, it would not be surprising for the insulin to act as a foreign protein and to trigger an allergic reaction. The codification of the adverse events into tabulations make it difficult to determine whether there were more local allergic reactions with X-14. Case reports of potential allergic reactions were not provided. Some symptoms suggest that there were small differences between the two treatments. Pruritus was listed three times and five times for patients using X-14 respectively in studies 035 and 036. It was not listed for patients using human regular insulin in either study. (There was no comparable data table for study 037.) There were two cases of facial edema and one case of angioedema among the IDDM patients treated with X-14. There were no such cases among the users of human regular insulin. Under the headings: rash, rash--erythematous, and rash--maculopapular, there were 32 listings for IDDM patients who used X-14 and ten listing for IDDM patients who used human regular insulin. There were at least two patients who were discontinued from the trials for allergic-type reactions. Patient 1083 was withdrawn from the trial (035) after approximately 50 days of treatment because of urticaria (There is some discrepancy in the records regarding exposure time.) Patient 6043 was withdrawn from the extension trial (day 98) because of pruritus. It was not indicated whether either patient had been rechallenged with X-14.

10.2.7. Clinical laboratory values

There were small, but statistically significant increases in the mean alkaline phosphatase for X-14 compared to human regular in both of the IDDM studies. These changes were not present in the NIDDM study. These increased levels persisted during the 036 extension trial. It is not known if they persisted in study 050, the extension trial for study 035. It is not known whether the source of the increase hepatic or bone because fractions were not obtained. Evaluation of the outliers did not provide further insight into the underlying etiology for these small and not clearly pathologic changes.

11. Special populations

11.1. Obesity-subcutaneous skin thickness

No specific PK-PD studies were performed to assess these variables. Nonetheless, despite their limitations, the blood glucose profiles from the Type 2 patients, who were approximately 10 kg heavier than their Type 1 counterparts, suggested that X-14 insulin did not have the same, more rapid onset of action. Exploratory post hoc analyses with HgbA1c and blood glucose 90 minutes post breakfast versus weight (Study 035) suggest that there are differences in the glucose parameters by weight, but that gender contributes

independently to the differences in glucose parameters. (See figures 1-6.) (See Pharmacokinetic issues-Weight/skin thickness and Special populations-Gender.)

11.2. Smoking

No specific PK-PD studies were performed to assess this variable. (Refer to Variables influencing absorption-smoking.)

11.3. Pregnancy

There have been no clinical trials conducted with women who are pregnant or who desire pregnancy. This product is likely to be used in women with IDDM or gestation diabetes. Altered gastric emptying can occur during pregnancy and could effect blood glucose levels and the timing of hypoglycemia. The different PK-PD profile will need to be carefully considered before dosing in the various stages of pregnancy.

The sponsor reported that there were 19 pregnancies in the clinical trials: 10 in X-14 treated patients and 9 in human insulin treated patients, however we have received at least 1 additional adverse event report under the and 1 additional report in the safety-update (8/5/99). The outcomes are listed below:*

	<i>X-14</i>	<i>Human regular insulin</i>
Healthy baby	7	4**
Elective abortion	2	1
Spontaneous abortion	0	1 (at 20 weeks)
Transient problem	asphyxia x3 days	hypoglycemia in 3 babies (1 with the heart murmur)
Congenital abnormality	renal dysgenesis	hypospadias heart murmur, thickened ventricular wall, high PCV

*Based on the 1/14/99 safety update, 6/8/99 submission in response to a request for more information on pregnancy outcomes, and a 7/27/99 adverse event report (and 8/11/99 follow-up).

**2 of these pregnancies were identified during the screening period so patients never entered the trial.

Attribution of adverse outcomes in the offspring of diabetic patients using insulin analogues will be complicated. Maternal hyperglycemia and, to a lesser extent, hypoglycemia have been associated with adverse outcomes. Spontaneous abortion, congenital malformation, and stillbirth in the third trimester are more common in diabetic patients. The most common congenital malformations in diabetic women are in the genito-urinary tract (agenesis, cystic kidney, duplex kidney), the cardiac system (situs inversus, transposition of the great vessels, ASD, VSD), the CNS (anencephalus, hydrocephalus, spina bifida), and caudal regression-rectal atresia. Although minimal amounts of insulin are thought to cross the placenta, the potential for direct effects from X-14 and indirect effects from hypoglycemia from the rapid onset of insulin action (particularly during the first trimester when organogenesis occurs and when insulin sensitivity increases) cannot be excluded.

Maternal health during the pregnancy is also a consideration. The potential growth promotion effects of insulin analogues on the retinal vessels must be considered. The literature is mixed on pregnancy itself as a risk factor for diabetic retinopathy. Kitzmiller et al. recently reported accelerated retinopathy in pregnant patients with a long history of diabetes (Diabetes Care. 1999;22:874). In response to this publication, the sponsor was asked to present information on the progression of retinopathy during pregnancy in the patients who became pregnant during clinical development of X-14. It appears that three patients treated X-14 and one patient treated with regular insulin had pre-existent retinopathy. The sponsor reports that "no patient reported worsening of retinopathy after delivery". This response, however, does not indicate whether there was progression of retinopathy during pregnancy. (Indeed some regression of retinopathy post-partum can be expected.) The response also suggests that the patients and their physicians may not have been actively queried about the course of retinopathy during pregnancy-only that there were no available comments in the record.

11.4. Nursing mothers

No clinical trials have been conducted with women who are nursing. Although it is known that insulin is secreted in breast milk, it is unknown whether the levels are sufficient to induce any biological response. It is known that gut barriers to foreign proteins are incomplete in infants.

11.5. Children-Adolescents

A single dose PK-PD study was conducted in children (ages 7-12 years, n=9) and teenagers (ages 13-17; n=9). No adjustments for pubertal staging were made. The median for t-max was 40 minutes for X-14 and 70-75 minutes for regular human insulin. The glucose data could not be interpreted because the meals were not standardized.

11.6. Geriatric patients

There are no PK-PD data on geriatric patients. There were only 35 patients (primarily with NIDDM) greater than age 65 years who were treated with X-14 for up to six months. The small number of patients limits the conclusions that can be drawn.

11.7. Gender

In a PK-PD study with both men and women (healthy volunteers), there was no difference in the median half-life and t-max. The C-max was somewhat higher for men, but this reflects the higher doses of insulin given for greater body weight.

In the clinical trials, enrollment was not appreciably different by gender. There were somewhat fewer women in the trials. In a post hoc analysis, there was no apparent difference in HgbA1c by gender for a given treatment group. (See figure 12.) Weight and gender may have some independent effects on post-prandial glucose parameters. (See Pharmacokinetic issues-Weight/skin thickness.) The sponsor did not have adequate data from the clinical trials to definitively assess differences in post-prandial glucose parameters by gender.

11.8. Autonomic neuropathy

Abnormal gastric emptying can occur secondary to autonomic neuropathy or may be iatrogenic. Patients with delayed or erratic gastric emptying may be less tolerant of a more rapid acting insulin. For example, patient 159/642-6267, with a history of diabetic neuropathy and s/p partial gastrectomy, had hypoglycemia with seizures after X-14 despite ingestion of a meal. Furthermore, the increased intra-patient variability with the C-max of X-14 (versus human regular) could potentially accentuate this.

Patients with autonomic neuropathy are also more likely to experience abnormal vasodilatory responses after the administration of insulin are more likely to be interpreted as hypoglycemia. Concomitant atherosclerosis may further limit blood flow to the brain and/or other organs. These phenomena may explain the "episodes requiring intervention" experienced by patients 32-343, 39-191, and 49-113 during which the respective measured glucose values were 10.8, 10.5, and 12 mmol/L. Whether these responses would be aggravated by an insulin with a higher C-max, X-14, is unknown.

The sponsor did not delineate patients with autonomic neuropathy to assess these potential problems.

11.9. Renal disease

Some of the published literature suggests that insulin doses may need to be reduced in renal failure. No adequate PK-PD studies in non-diabetic patients with renal disease have been conducted. No adequate PK-PD or clinical studies in diabetic patients with renal complications have been conducted. Diabetic patients with elevated serum creatinine levels (>150 mmol/L [1.7 mg/dl]) were excluded from the clinical trials.

11.10. Cardiac disease

There were no gross differences in deaths from cardiac disease. It must be noted, however, that there were significant exclusion criteria to screen out patients with significant cardiac disease or autonomic neuropathy (that might cause abnormal vasodilatory responses). Moreover, the mean age of the patients in the larger Type 1 studies was less than 40 years. Cardiac events would be expected to occur at a low rate even if the patients were diabetics-particularly if those with more long-standing disease and diabetic complications were excluded. The rate of cardiac events would be expected to be greater in the Type 2 patients who were, on average, at least 16 years older than their Type 1 counterparts. This was true, but the study size was small (<200 patients) and the study duration relatively short (six months). These factors limit the conclusions that can be reached about the safety of the drug in cardiac patients.

11.11. Hepatic disease

No adequate PK-PD studies in non-diabetic or diabetic patients with hepatic disease have been conducted. Patients with ALT or alkaline phosphatase levels greater than twice the upper limit of normal were excluded from the clinical trials. Some patients did develop persistent elevations of alkaline phosphatase while on X-14. These increases were

insignificant for most of these patients. The clinical course of the few outliers did not appear to be different than that of the non-outliers.

12. Discussion

The sponsor has demonstrated in normal volunteers and IDDM patients that the modified insulin can be absorbed more quickly from subcutaneous tissue than regular human insulin-U 100. This more rapid absorption tends to be followed by a more rapid time to glucose nadir. Mixing can attenuate this absorption, but the blunting appears to be modest if the injection is given immediately after mixing. This PK-PD profile could offer some convenience with respect to meal-planning.

The efficacy assessment in the pivotal trials, however, was limited by the absence of any validated glucose values so that the sponsor was not able to demonstrate in the pivotal trials that X-14 had a more rapid glucose lowering effect. In addition, there was a disconnect between the mean glucose levels proved by the patients and the concomitant mean HgbA1c level. NIDDM patients had the lowest HgbA1c values and the highest glucose profile means. Even if one could assume that the glucometer values were valid, the glucose values obtained via glucometer for the NIDDM patients would tend to support the conclusion that X-14 may not have a more rapid glucose lowering effect than human regular in Type 2 diabetics. This conundrum is compounded by the fact that the pharmacokinetic studies for NIDDM patients were uninterpretable.)

Even the efficacy assessment by HgbA1c was limited. Patients using X-14 may have been treated for longer periods of time (even within protocol), used more injections, and had more optimization of the time of the injections. The sponsor has not provided data to exclude these potential causes for imbalance. The open-label nature of the trial contributes to the potential for such problems.

Safety assessment was limited by a number factors. The sponsor did not assess major portions of the diabetic population because of their exclusion criteria. Patients with autonomic neuropathy and cardiac disease were under-represented. The tendency towards more bradycardia in patients with X-14 may not have been clinically significant in a healthier population of diabetics. The Sponsor did not systematically try to identify patients with autonomic neuropathy to identify whether this group might be less tolerant of the drug. The maneuvers required to identify such patients are non-invasive and part of routine diabetic care. The Sponsor did not exclude potential growth promotion effects of X-14 on the eye. Although they obtained retinal photos, the photos were collected in such a way as to be non-interpretable. There was no systemic assessment of ketosis. The documentation for hypoglycemic-like events was poor. Some events may well have represented the vasodilatory events that patients with neuropathy may experience post insulin. The open-label nature of the study could have biased attribution when the event was so poorly defined. Lastly the drug-interaction assessment was poor. There was an absence of beta-blockers in the drug interaction assessment, and the assessment was limited to hypoglycemia. Potential interactions with potassium-altering or potassium-sensitive drugs were not assessed.

13. Conclusions

The drug is approvable for subcutaneous use _____ in adults with reservations and stipulations. _____

The sponsor has shown that the modified insulin does lower glucose. Glycemic control and the associated hypoglycemia rates appear to be comparable. To achieve the stated HgbA1c values, which were still less than optimal, patients using X-14 had to take more insulin than patients using human regular insulin (1-3 U/d). Most of this insulin was basal insulin, specifically NPH. Presumably this basal insulin provided coverage in the late post-prandial period when X-14 is no longer active-unlike human regular. To achieve the stated levels of HgbA1c, many of the patients using X-14 had to take more than 4 shots per day. Patients may mix X-14 with NPH with limited attenuation of the rapid onset, but they must inject immediately after mixing. There are no data on mixing with other insulins-including human regular, velosulin, lente, or ultralente. The insulin does induce cross-reacting antibodies-which contributes in a small degree to the increased insulin requirements. Some preliminary data suggest that the antibodies decrease after 6 months.

The advantage of X-14 is essentially confined to convenience. Patients can take insulin immediately before eating rather than injecting human regular insulin 30-45 minutes before meals. This more rapid onset, however, may be a double-edged sword. Patients must eat after injection with X-14. There have been multiple reports of severe hypoglycemia if the patient forgets or is otherwise distracted and does not eat immediately. There is more grace time before the onset of hypoglycemia with human regular insulin. The severity of the subsequent hypoglycemia also could be less predictable because the variability of $C\text{-max}_{(X-14 \text{ insulin})}$ is greater than that of $C\text{-max}_{(\text{human regular insulin})}$. This variability may also make it more difficult to establish a reliable insulin regimen. This is a potential area for future study. It should also be noted that the advantages of rapid onset may not be present for all groups of diabetics. The blood glucose profiles for NIDDM patients suggest that the more rapid glucose lowering effect was present only after breakfast and the means of the 8-point profiles were equivalent. If this observation, albeit imperfect, were to be confirmed it would raise questions as to causality: weight, skin-SQ injection site thickness, skin-SQ injection site composition, or yet some other variable. In addition rapid onset of action may not be tolerated by many groups of diabetics who were not evaluated because of the exclusion criteria. Convenience may also be limited by the need to undergo periodic phlebotomy to assess alkaline phosphatase levels. Lastly, although this insulin analogue may offer convenience, the altered PK-PD profile does not appear to offer true physiologic benefit. The correlation between HgbA1c and the 90 minute post-prandial glucose level was negligible.

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14. Label review

14.1 General comments

The sponsor has overstated that which is known about their particular insulin. Claims will be severely limited by the absence of adequate glucose (fasting and post-prandial) samples from the pivotal trials. The sponsor has attempted to obscure the limited amount of data by including information on other insulins. The label should be directed at providing physicians with information about what makes this insulin product unique. General information about diabetes care should be minimized.

The sponsor has not included information that would help the patient understand the differences between X-14 and other insulins. The sponsor has not included information on the importance of a basal insulin and how mixing should be done.

14.2. Specific comments

14.2.1. Physician label



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Labeling

15. Appendices

Figure legends

Figure 1. HgbA1c vs Weight-Males Study 035

Figure 2. HgbA1c vs Weight-Females Study 035

Figure 3. 90 minute post-breakfast blood glucose vs Weight-Males Study 035

Figure 4. 90 minute post-breakfast blood glucose vs Weight-Females Study 035

Figure 5. Glucose excursion vs Weight-Males Study 035

Figure 6. Glucose excursion vs Weight-Females Study 035

Figure 7. HgbA1c vs 90 minute post-breakfast blood glucose by treatment group

Figure 8. HgbA1c vs Glucose excursion Studies 035, 036, and 037

Figure 9. Delta HgbA1c vs Glucose excursion Studies 035, 036, and 037

Figure 10. Hypoglycemic-like events (normalized) vs Time of day Study 035

Figure 11. Hypoglycemic-like events (normalized) vs Time of day Study 036

Figure 12. HgbA1c vs Gender Studies 035, 036, and 037

Recalculation of the HgbA1c data after the deletion of site —

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Figure Legends

Figure 1. The mean HgbA1c (%) at endpoint was determined for male IDDM patients in Study 035 with weights 10 kg above and below the mean of the group. The rectangles delineate the 25th and 75th percentiles.

Figure 2. The mean HgbA1c (%) at endpoint was determined for female IDDM patients in Study 035 with weights 10 kg above and below the mean of the group. The rectangles delineate the 25th and 75th percentiles.

Figure 3. The mean blood glucose (in mmol/l; by glucometer) at 90 minutes after breakfast (BG B90) at endpoint was determined for male IDDM patients in Study 035 with weights 10 kg above and below the mean of the group. The rectangles delineate the 25th and 75th percentiles.

Figure 4. The mean blood glucose (in mmol/l; by glucometer) at 90 minutes after breakfast (BG B90) at endpoint was determined for female IDDM patients in Study 035 with weights 10 kg above and below the mean of the group. The rectangles delineate the 25th and 75th percentiles.

Figure 5. The glucose excursion (in mmol/l; by glucometer) was defined as the blood glucose value at 90 minutes after breakfast (BG B90) minus the fasting blood glucose at endpoint. The glucose excursion was determined for male IDDM patients in Study 035 with weights 10 kg above and below the mean of the group. The rectangles delineate the 25th and 75th percentiles.

Figure 6. The glucose excursion (in mmol/l; by glucometer) was defined as the blood glucose value at 90 minutes after breakfast (BG B90) minus the fasting blood glucose at endpoint. The glucose excursion was determined for female IDDM patients in Study 035 with weights 10 kg above and below the mean of the group. The rectangles delineate the 25th and 75th percentiles.

Figure 7. HgbA1c has been shown to correlate with diabetic complications. The HgbA1c value (%) at endpoint was plotted against the 90 minute post-breakfast blood glucose at endpoint for both insulin treatment groups in Studies 035, 036, and 037. HI=human insulin; Iasp=X-14.

Figure 8. HgbA1c has been shown to correlate with diabetic complications. The HgbA1c value (%) at endpoint was plotted against the glucose excursion (90 minute post-breakfast blood glucose [BG B90] minus the fasting blood glucose) at endpoint for both insulin treatment groups in Studies 035, 036, and 037. HI=human insulin; Iasp=X-14.

Figure 9. HgbA1c has been shown to correlate with diabetic complications. The change in the HgbA1c value (%) over the course of the study was plotted against the change in the glucose excursion over the course of the study for both insulin treatment groups in

Studies 035, 036, and 037. The glucose excursion was defined as the 90 minute post-breakfast blood glucose [BG B90] minus the fasting blood glucose. HI=human insulin; Iasp=X-14.

Figure 10. Because of the 2:1 randomization, the numbers of hypoglycemic-like events requiring intervention (months 4-6) in each treatment group of Study 35 were normalized using a denominator of 100. The events were plotted against the time of day (hours). There were equivalent numbers of hypoglycemic-like events in the two treatment arms of this IDDM study.

Figure 11. Because of the 2:1 randomization, the numbers of hypoglycemic-like events requiring intervention (months 4-6) in each treatment group of Study 36 were normalized using a denominator of 100. The events were plotted against the time of day (hours). There were relatively more hypoglycemic-like events in the X-14 treatment arm of this IDDM study.

Figure 12. HgbA1c values (%) over the course of the studies were plotted by gender and treatment arm. HI=human insulin; Iasp=X-14.

CC: Orig NDA 20-986
HFD-510/DIU File
HFD-510/Koller/Malozowski
HFD-715/Pian/Sahlroot
HFD-870/Fossier/Ahn

AS per my [unclear] and [unclear]
ISI/
8/17/99

ISI

Elizabeth Koller, M.D.
HFD 510 Endocrine and Metabolic Drugs

The MIXED Procedure

Class Level Information

Class	Levels	Values
TRGRP	2	HI IAsp
_PCENTER	50	

Without center —

Covariance Parameter Estimates (REML)

Cov Parm	Estimate
Residual	0.55790338

Model Fitting Information for HBA_10

Description	Value
Observations	845.0000
Res Log Likelihood	-939.460
Akaike's Information Criterion	-940.460
Schwarz's Bayesian Criterion	-942.766
-2 Res Log Likelihood	1878.920

Tests of Fixed Effects

Source	NDF	DDF	Type III F	Pr > F
TRGRP	1	744	4.71	0.0303
_PCENTER	49	744	1.62	0.0056
TRGRP*_PCENTER	49	744	0.97	0.5367
HBA_3	1	744	866.19	0.0001

ESTIMATE Statement Results

Parameter	Estimate	Std Error	DF	t	Pr > t	Alpha	Lower
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IAsp minus HI

-0.13553972

0.06246383

744

-2.17

0.0303

0.05

-0.2582

Lower C

ESTIMATE Statement Results

Upper C.I.

-0.0129

Least Squares Means

Effect	TRGRP	LSMEAN	Std Error	DF	t	Pr > t
TRGRP	HI	7.92031374	0.05151721	744	153.74	0.0001
TRGRP	IAsp	7.78477403	0.03532307	744	220.39	0.0001

ANA/DCD/035/EU/11AUG99/prianait.sas/prianait.tab

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Trial ID=ANA/DCD/036/USA

The MIXED Procedure

Class Level Information

Class	Levels	Values
TRGRP	2	HI IAsp
_PCENTER	51	┌

With center →

Covariance Parameter Estimates (REML)

Cov Parm	Estimate
Residual	0.56071859

Model Fitting Information for HBA_10

Description	Value
Observations	863.0000
Res Log Likelihood	-961.559
Akaike's Information Criterion	-962.559
Schwarz's Bayesian Criterion	-964.876
-2 Res Log Likelihood	1923.118

Tests of Fixed Effects

Source	NDF	DDF	Type III F	Pr > F
TRGRP	1	760	4.67	0.0309
_PCENTER	50	760	1.63	0.0047
TRGRP*_PCENTER	50	760	0.95	0.5711
HBA_3	1	760	871.60	0.0001

ESTIMATE Statement Results

Parameter	Estimate	Std Error	DF	t	Pr > t	Alpha	Lower
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IAsp minus HI

-0.13367743

0.06183067

760

-2.16

0.0309

0.05

Lower C

-0.2551

ESTIMATE Statement Results

Upper C.I.

-0.0123

Least Squares Means

Effect	TRGRP	LSMEAN	Std Error	DF	t	Pr > t
TRGRP	HI	7.91792186	0.05098763	760	155.29	0.0001
TRGRP	IAsp	7.78424443	0.03497549	760	222.56	0.0001

ANA/DCD/035/EU/11AUG99/prianait.sas/prianait.tab

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Figure 1. HgbA1c vs Weight-Males Study 035

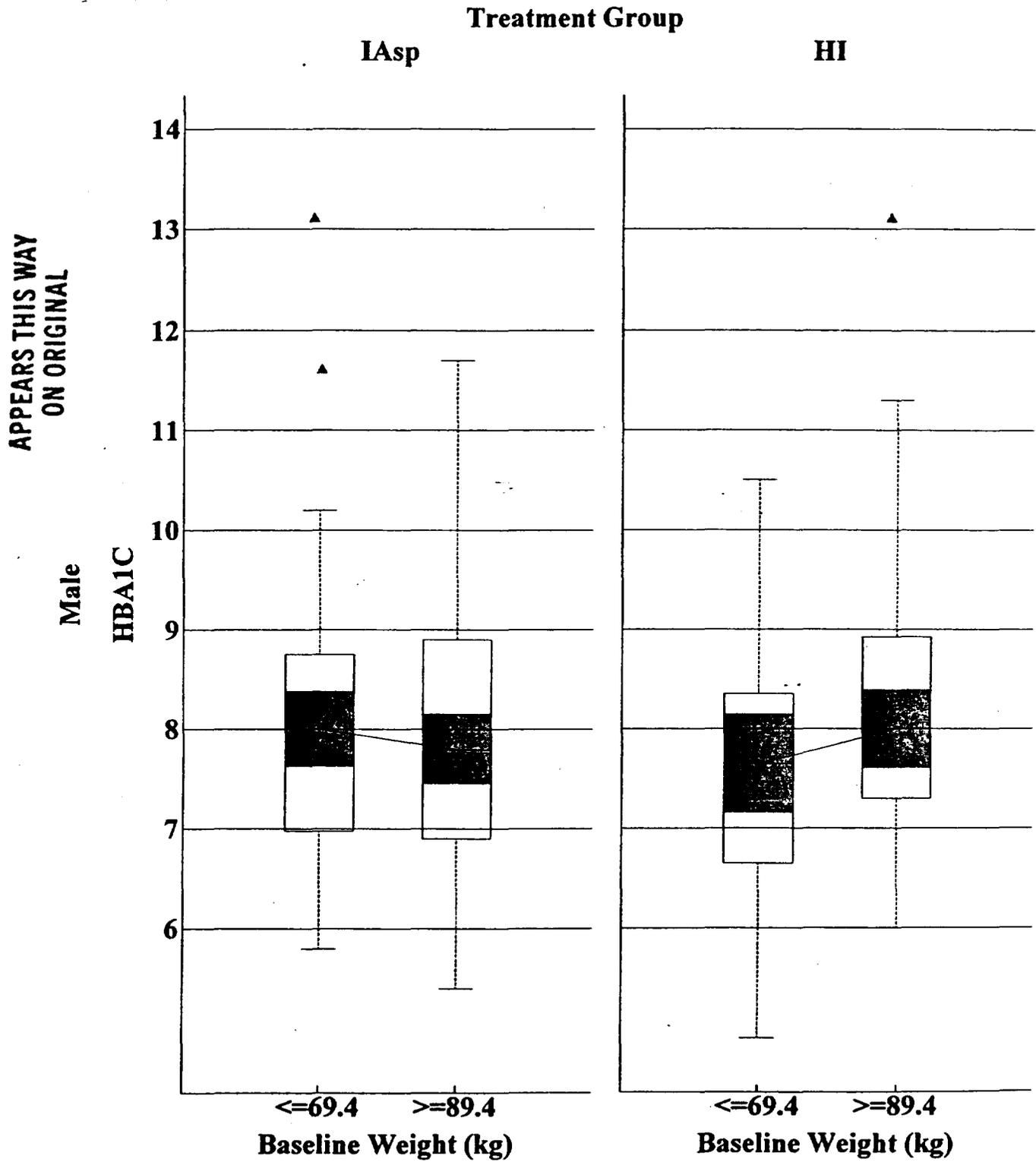


Figure 2. HgbA1c vs Weight-Females Study 035

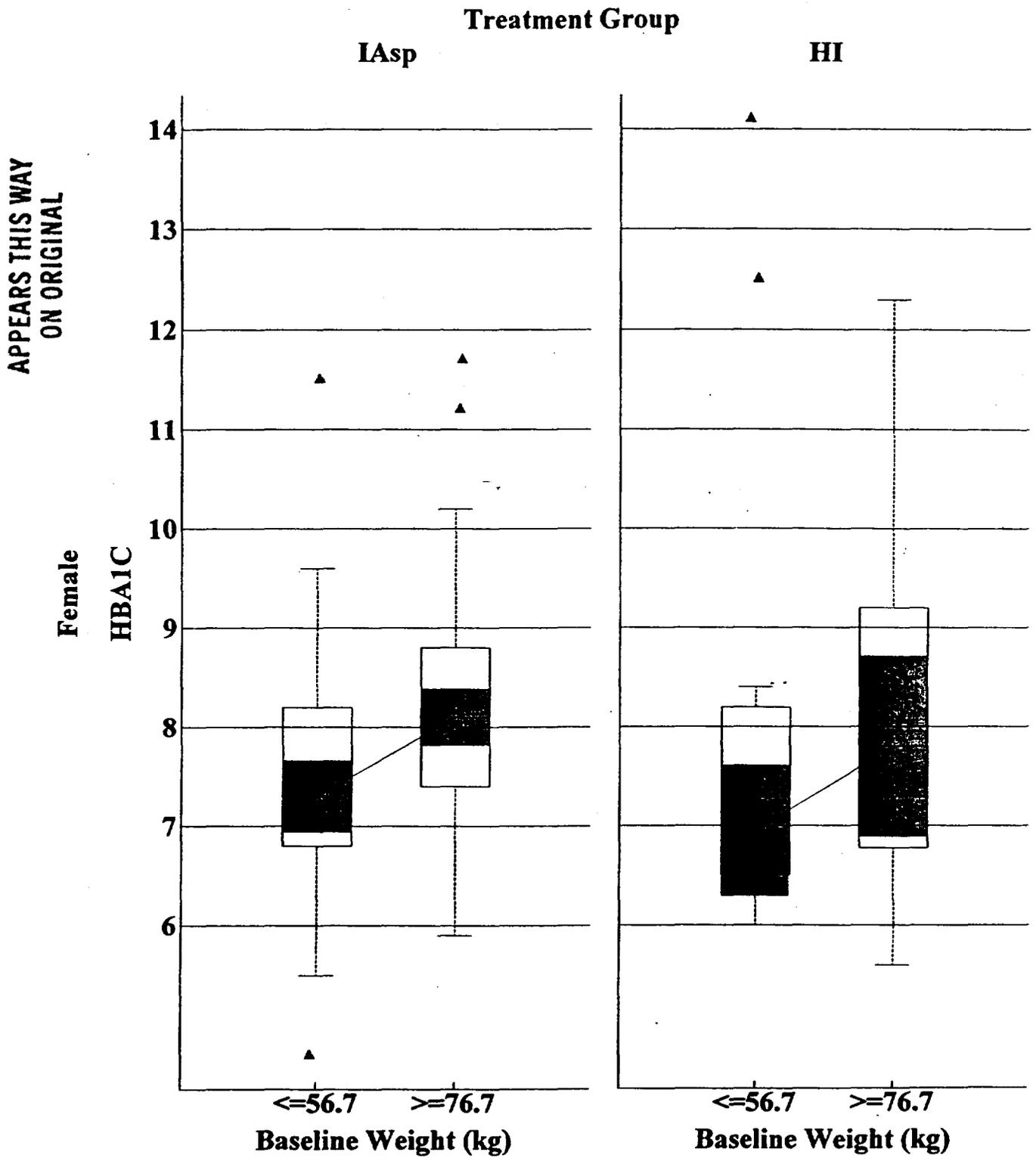


Figure 3. 90 minute post-breakfast blood glucose vs Weight-Males Study 035

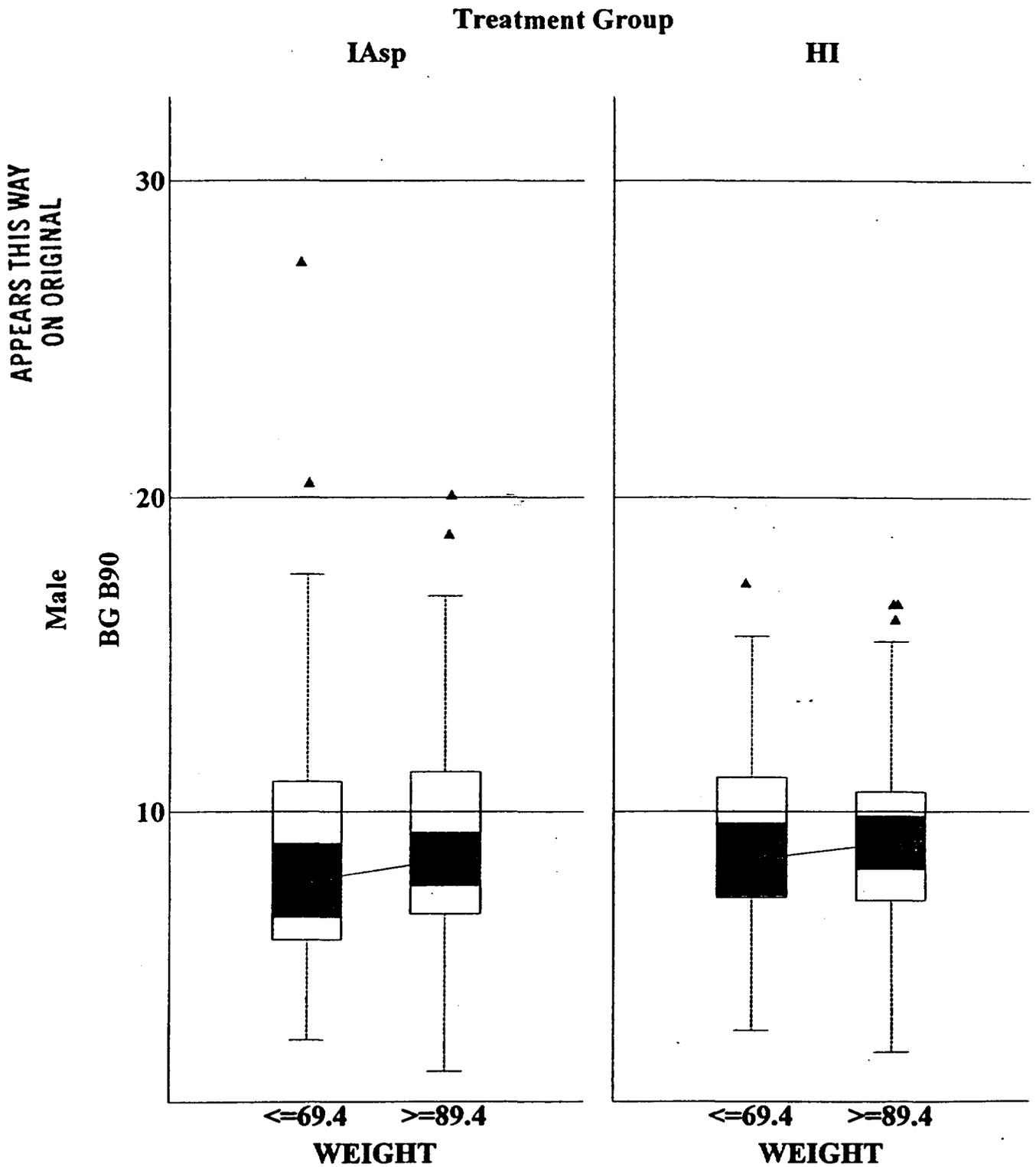


Figure 4. 90 minute post-breakfast blood glucose vs Weight-Females Study 035

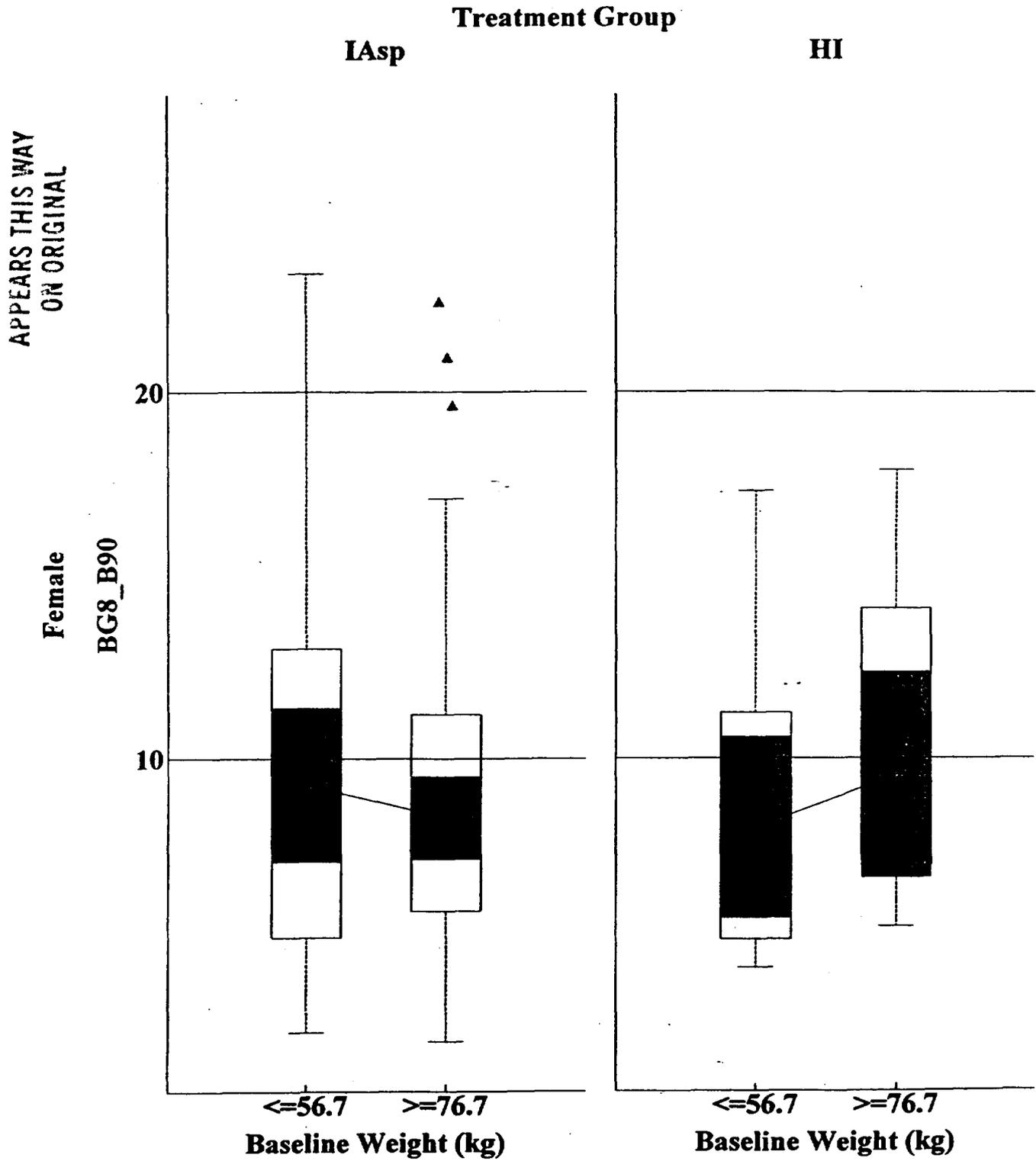


Figure 5. Glucose excursion vs Weight-Males Study 035

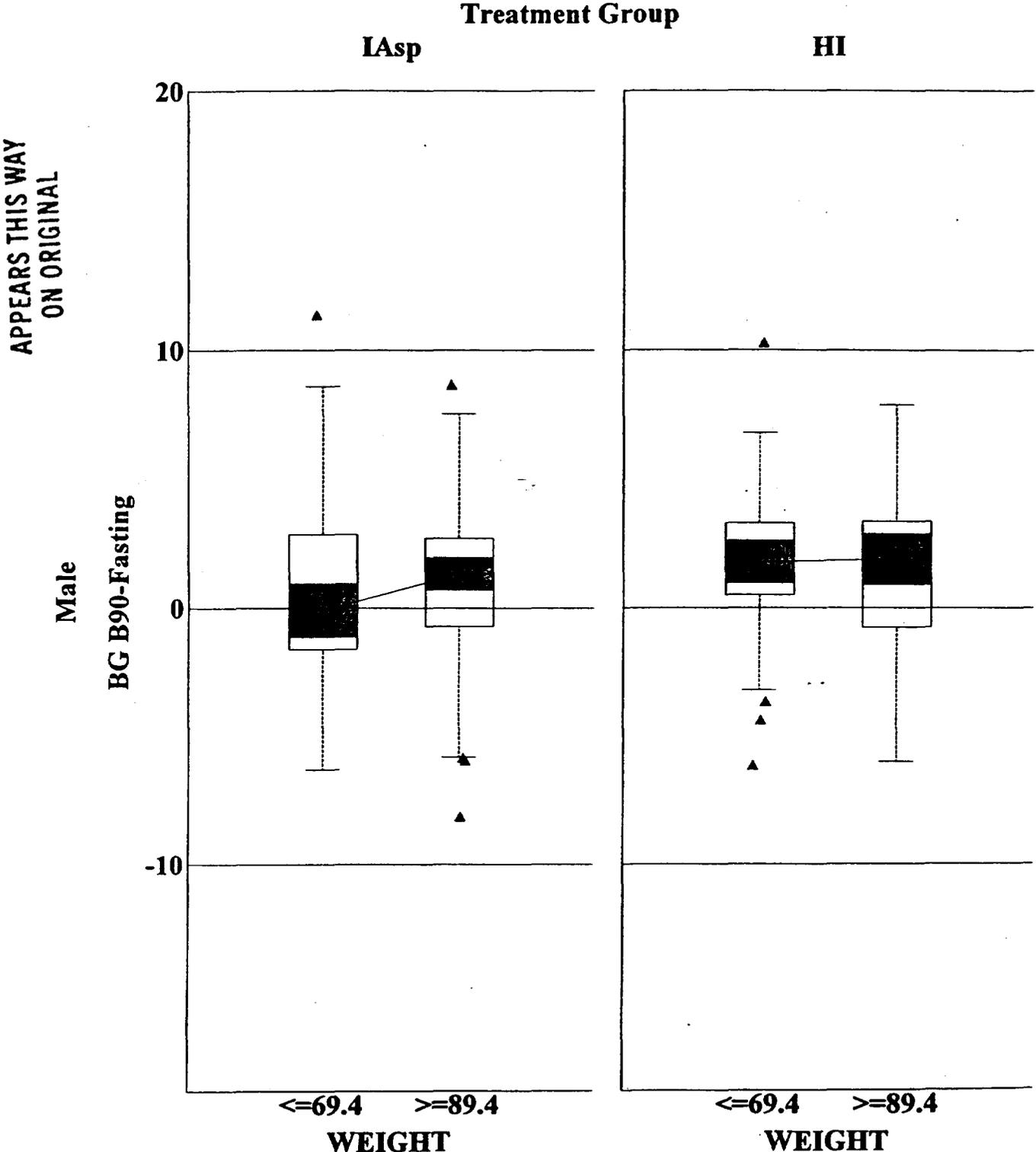


Figure 6. Glucose excursion vs Weight-Females Study 035

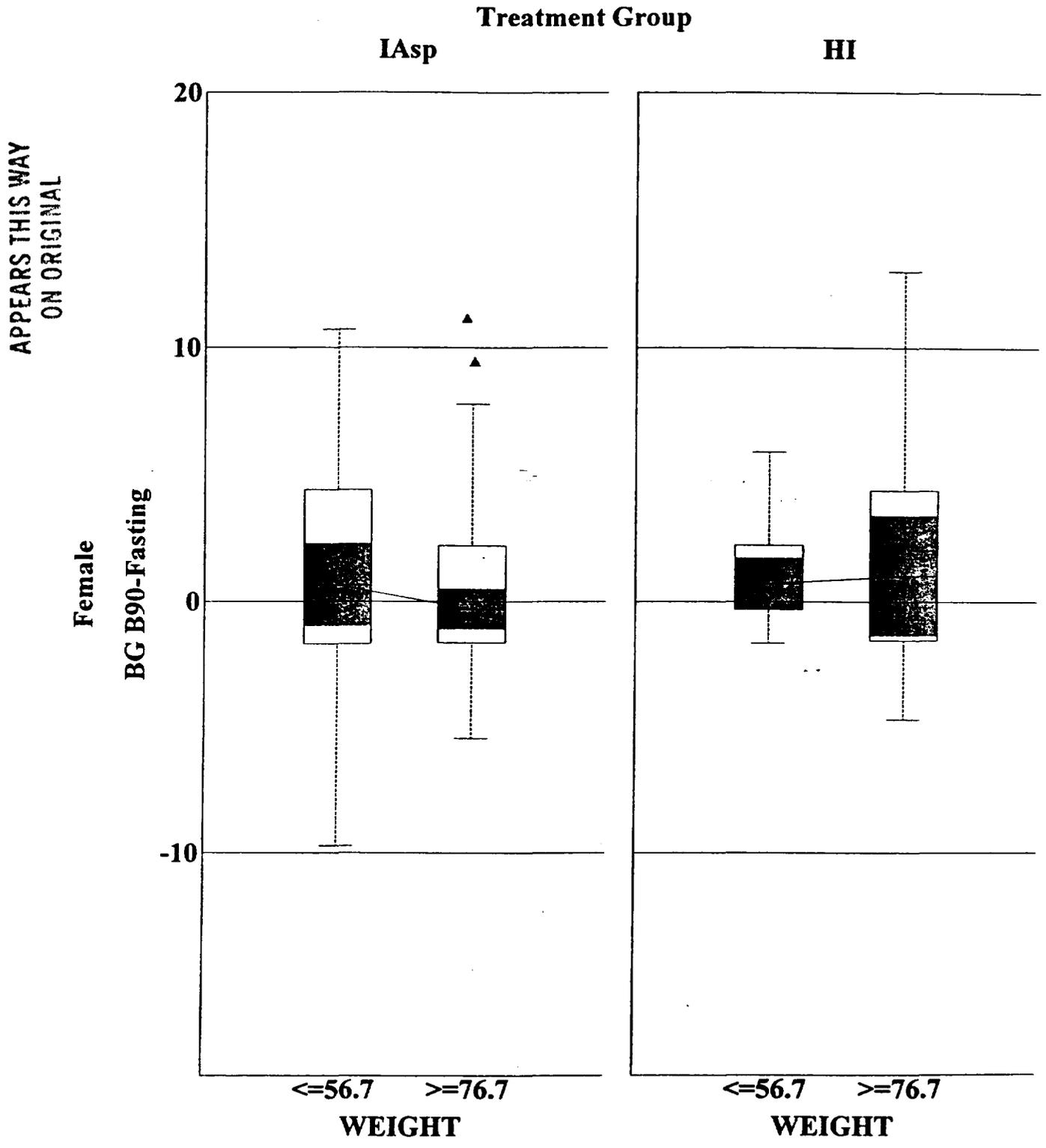


Figure 7. HgbA1c vs 90 minute post-breakfast blood glucose by treatment group

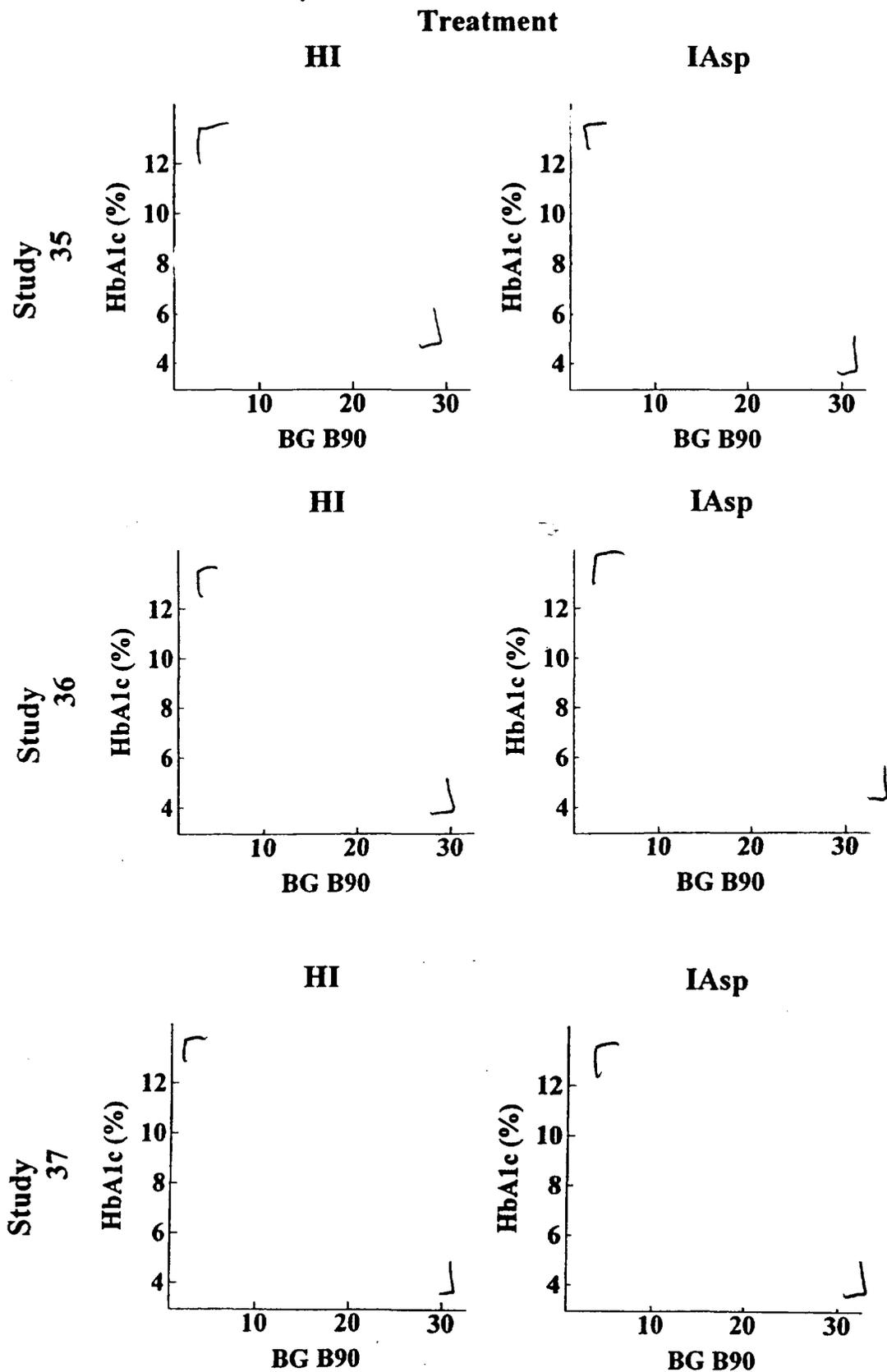
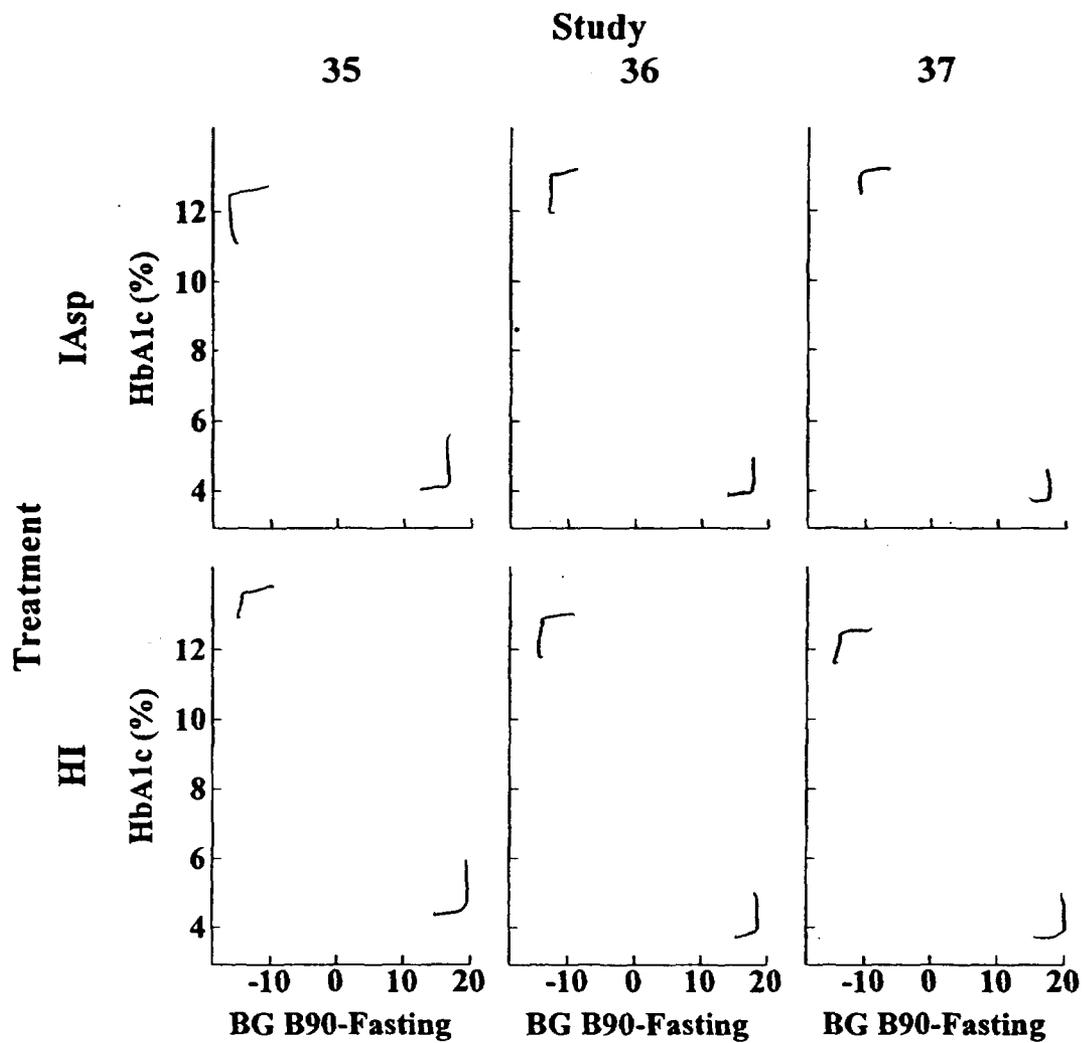
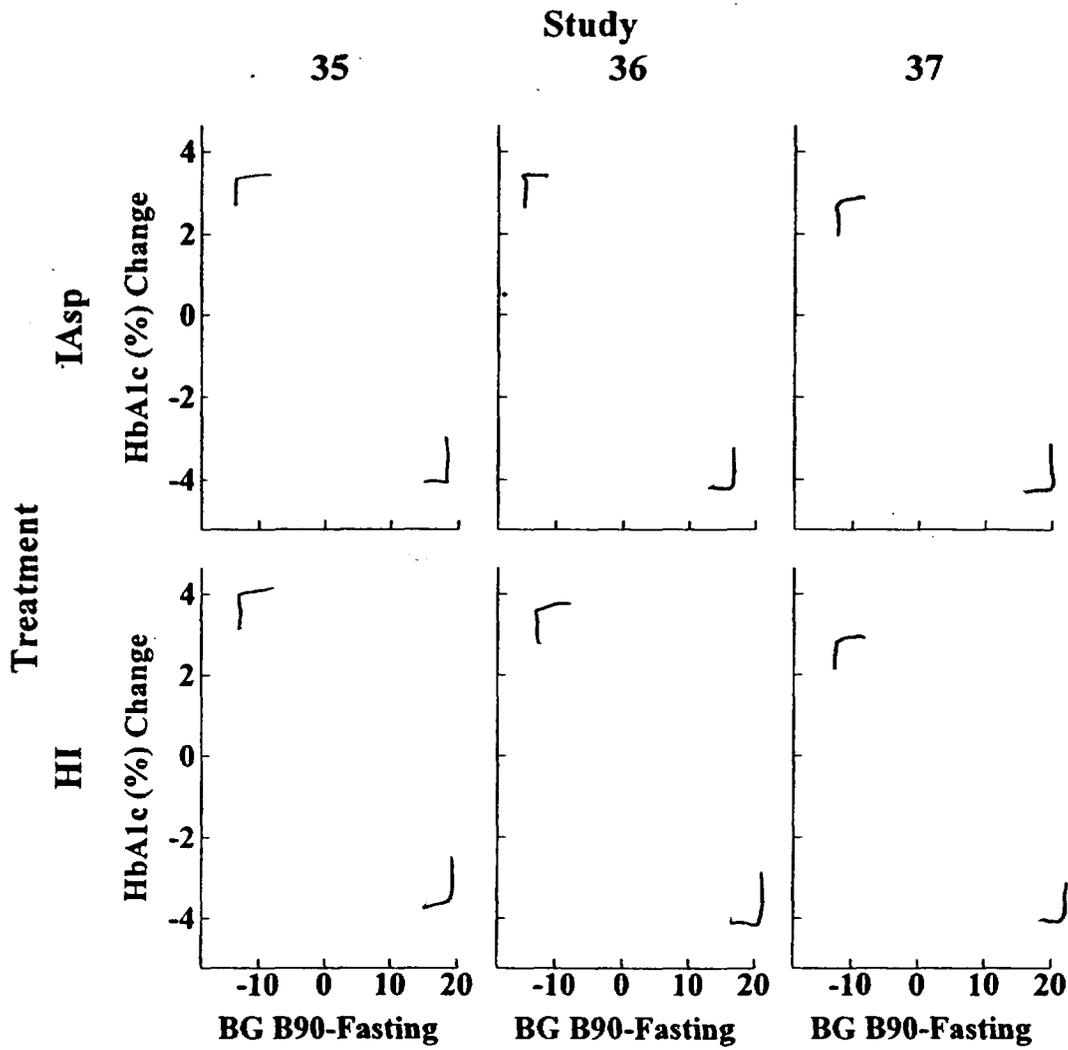


Figure 8. HgbA1c vs Glucose excursion Studies 035, 036, and 037



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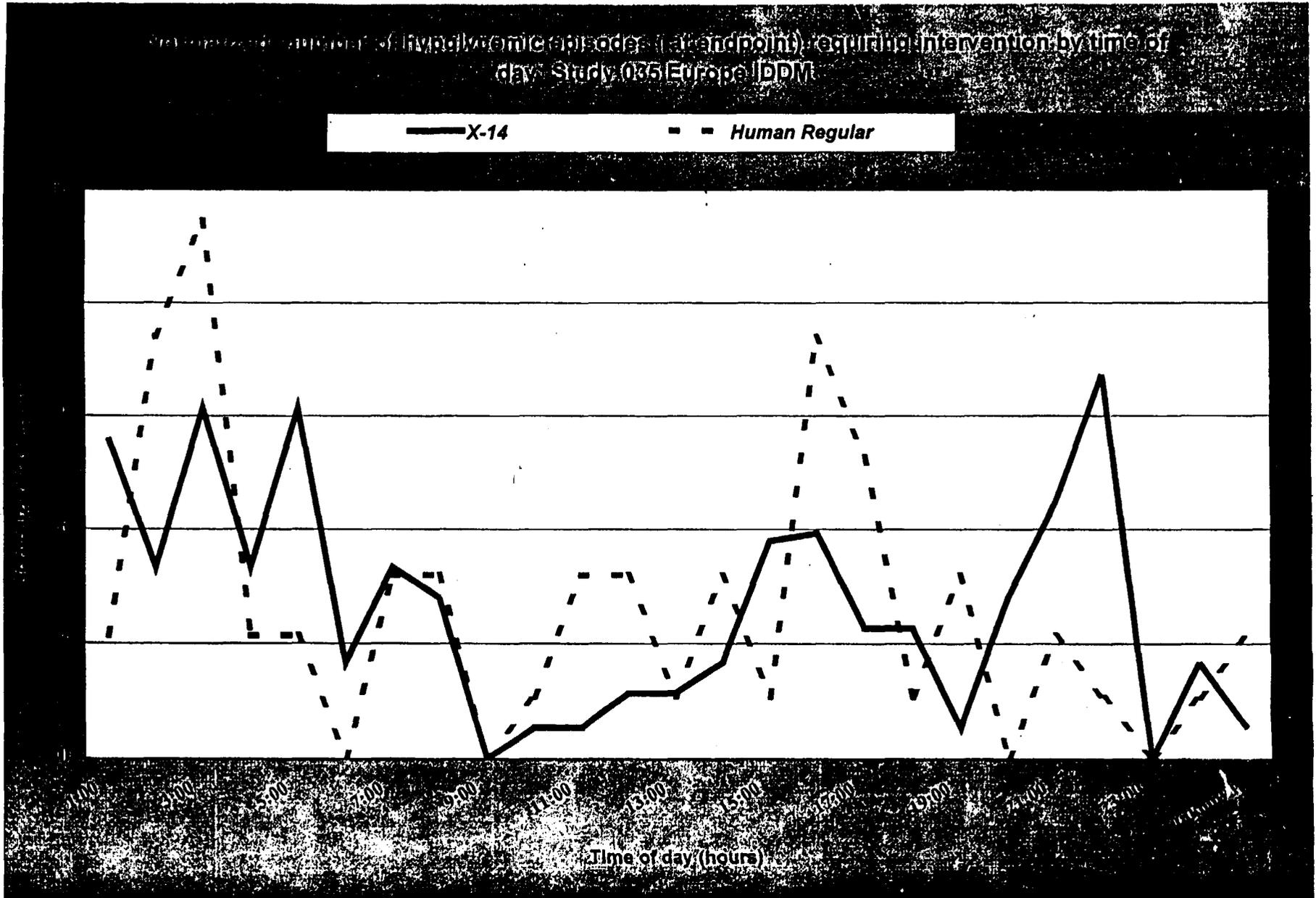
Figure 9. Delta HgbA1c vs Glucose excursion Studies 035, 036, and 037



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Figure 10. Hypoglycemic-like events (normalized) vs Time of day Study 035

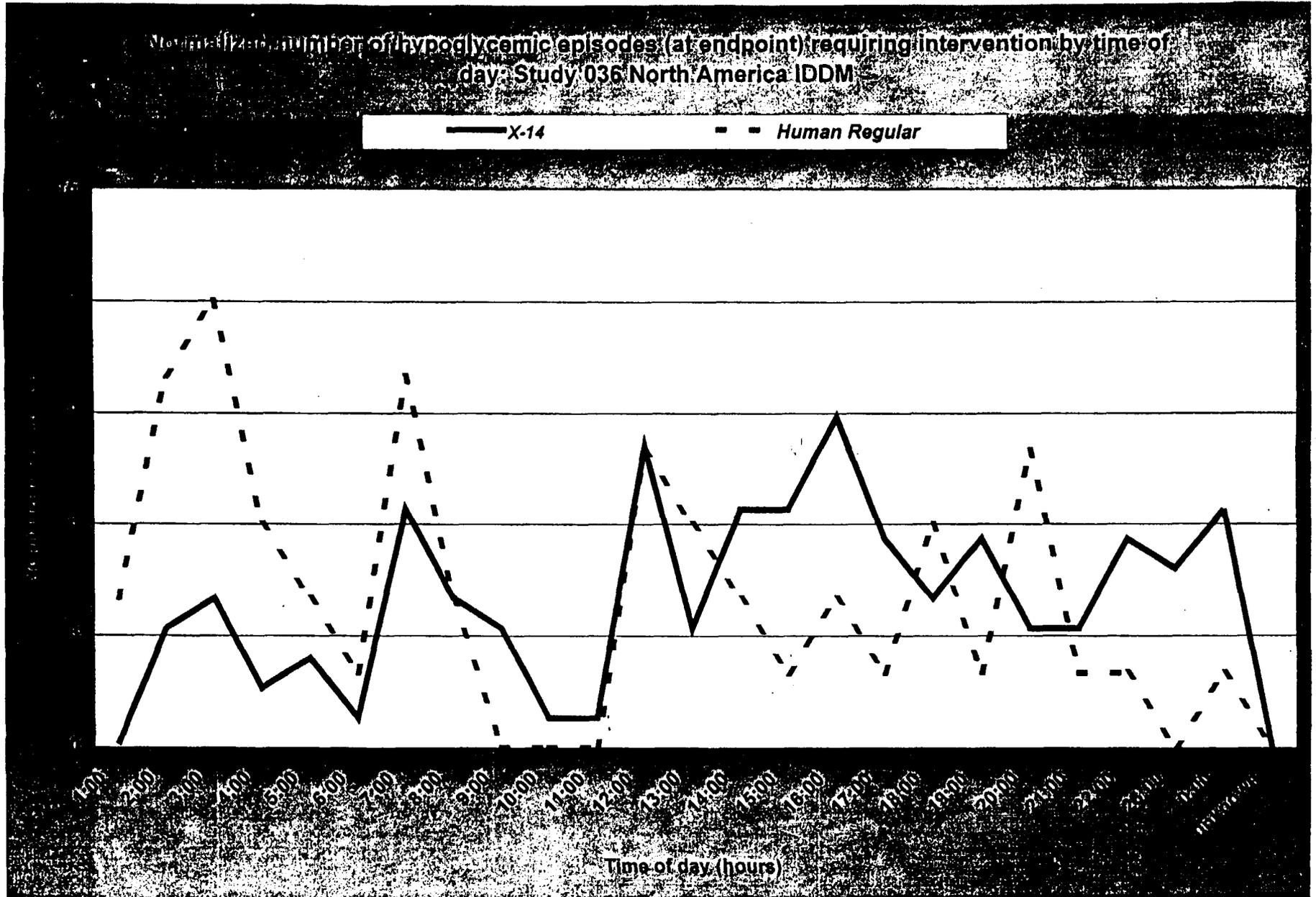
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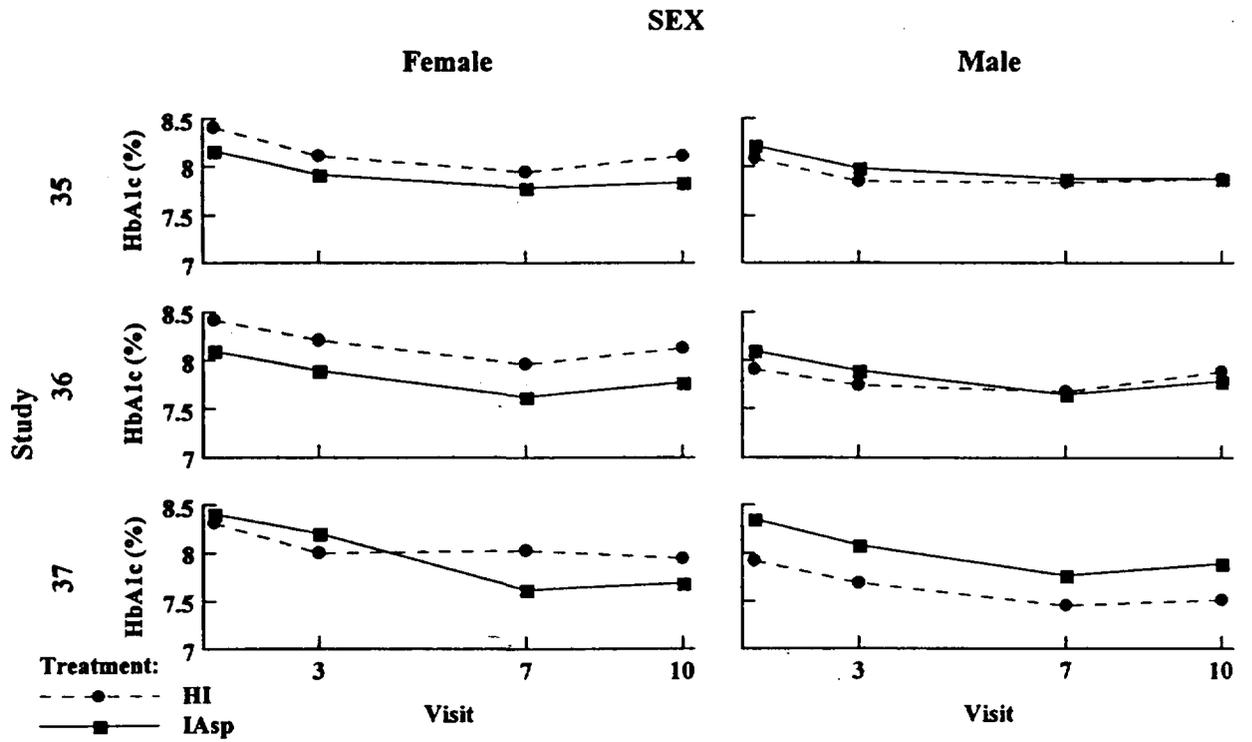
Fig . Hypoglycemic-like events (normalized) vs Time of day y 036

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Figure 12. HgbA1c vs Gender Studies 035, 036, and 037



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NDA 20,896
NovoLog
Insulin Aspart

NovoNordisk
Phone (609) 987-5800
Received 8/6/99
Forwarded 8/10/99
Reviewed 8/16/99

MEDICAL OFFICER'S REVIEW OF A NDA SAFETY UPDATE

1. Summary

This submission includes safety information on deaths, serious adverse events, adverse event withdrawals and pregnancies. Deaths and pregnancy's information encompasses all studies (until 6/18/99) and the other AE only refer to ongoing studies (until 4/29/99.) The randomization scheme in the well-controlled studies was 2:1.

The number of patients exposed to NovoLog is 2246 (1874 type 1) for a total 1564 patients years (~1618 p/years in type 1).

One patient exposed to NovoLog died during the study (myocardial infarction.) Four subjects died in the control arms (myocardial infarct [1] sudden death [2] and cerebral hemorrhage [1]) In the well controlled studies, the sponsor claims that the was "no difference of AE withdrawals between the two treatment groups" (NovoLog vs. regular insulin.)

After three month of exposure the level of cross-reactive antibodies was higher in the NovoLog treated patients. These levels decreased significantly from 3 to 12 months and returned to baseline levels.

In the completed studies 1 subject on NovoLog withdrew from the study due to an AE (accidental injury).

In the ongoing studies (Phase 3, 050/EU) 11/567 (NovoLog) and 2/186 (regular) withdrew due to an AE.

In the phase 3b studies _____, and _____, six subjects on regular insulin withdrew (n=1, n=2/181, n 3/211). Four patients on NovoLog withdrew (n=1/185, n=3/211.)

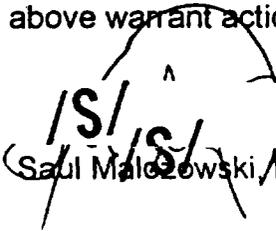
Regarding severe AE the rate of those in all studies does not differ between NovoLog and regular insulin. It appears, however, that subjects receiving NovoLog has a higher incidence of hypoglycemic and coma events that those receiving regular insulin in study 050 (Novolog=10, regular n=0.) The underlying reasons for these differences are difficult to elucidate.

Twenty-five pregnancies occurred during the studies. Twelve were on NovoLog, 12 on regular and one is unknown. Two patients in each major group did not deliver at the time of reporting. Normal deliveries were seen in 11 subjects (NovoLog 7, regular 4) elective abortions were performed in three subjects (NovoLog 2, regular 1), one baby was born with asphyxia in the NovoLog group, while in the regular group there was one spontaneous abortion, one baby was born with hypospadias, and two with hypoglycemia, and one had hypoglycemia and heart abnormalities.

In summary, the data presented by the sponsor suggest that:

- 1) The safety profile of NovoLog is similar to its comparators
- 2) The AE withdrawal pattern for NovoLog was similar to its comparators
- 3) The outcomes of the pregnancies are supportive for the safety of NovoLog although the number of patients exposed as well as the scrutiny received was modest.
- 4) The number of hypoglycemic events associated with NovoLog was higher in study 050.

Finally, the Medical Officer has to evaluate this report to assess whether the information summarized above warrant action that may affect the proposed labeling of this product.


Saul Malozowski, M.D., Ph.D.

cc: NDA Arch.
HFD-510-file
HFD-510/EKoller/JRhee/SMalozowski/8/15/99

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