

**Table 4**

Comparisons of Pharmacodynamic Parameter Ratios of Insulins Using Log Transformed Data (Data from Dr. Sun)

Pharmacodynamic Parameter	Study	Insulin Pair	Mean Ratio	90% Confidence Interval
Rmax	033	X-14 70/30 vs HI 70/30	1.197	1.125—1.274
	1086	X-14 70/30 vs X-14	0.763	0.719—0.813
	1086	X-14 70/30 vs X-14 50/50	NA	NA
	NA	X-14 70/30 vs —	NA	NA
AUC-glucose (0-t)	033	X-14 70/30 vs HI 70/30	0.975	0.902—1.055
	1086	X-14 70/30 vs X-14	0.925	0.869—0.990
	1086	X-14 70/30 vs X-14 50/50	NA	NA
	NA	X-14 70/30 vs —	NA	NA
AUC-glucose (0-6 hr)	033	X-14 70/30 vs HI 70/30	1.219	1.140—1.305
	1086	X-14 70/30 vs X-14	0.826	0.780—0.877
	1086	X-14 70/30 vs X-14 50/50	NA	NA
	NA	X-14 70/30 vs —	NA	NA

Rmax= maximal glucose utilization or maximal glucose infusion rate

AUC=area-under-the-curve

HI=human insulin

**Table 5**

Mean (CV) Times to Partial and Total Insulin AUC Values for X-14 70/30 and Human Insulin 70/30\*

Parameter T-AUC <sub>hr</sub>	X-14 70/30		Human Insulin 70/30		Ratio	
	Study 031	Study 033	Study 031	Study 033	Study 031	Study 033
25%	2.41 (22)	2.78 (21)	3.32 (14)	4.58 (16)	0.73	0.61
50%	5.45 (21)	7.16 (22)	6.80 (14)	9.85 (15)	0.81	0.73
75%	11.02 (16)	14.70 (11)	12.38 (15)	15.92 (9)	0.91	0.93
100%	23.83 (4)	24.00 (0)	24.00 (0)	24.00 (0)	0.99	1.00

\*T-AUC-100% are the times to reach the given % of the total AUC for each formulation

**Table 6**

Mean (CV) Times to Partial and Total Insulin AUC Values for X-14 70/30 and Human Insulin 70/30 as Compared to Human Insulin 70/30\*

Parameter T-AUC <sub>hr</sub>	X-14 70/30		Human Insulin 70/30		Ratio	
	Study 031	Study 033	Study 031	Study 033	Study 031	Study 033
25%	2.34 (23)	2.48 (30)	3.32 (14)	4.58 (16)	0.70	0.55
50%	5.39 (34)	6.08 (38)	6.86 (14)	9.85 (15)	0.79	0.62
75%	11.15 (40)	11.85 (36)	12.38 (15)	15.92 (9)	0.92	0.74
100%	15.81 (32)	15.66 (24)	24.00 (0)	24.00 (0)	0.66	0.65

\*T-AUC-100% for X-14 70/30 are the times when the same respective AUC values were achieved for human insulin .

**Table 7**

Mean (CV) Times to Partial and Total Glucose AUC Values for X-14 70/30 and Human Insulin 70/30\*: Study 033

Parameter T-AUC <sub>hr</sub>	X-14 70/30	Human Insulin 70/30	Ratio
25%	3.18 (15)	4.13 (17)	0.79
50%	6.48 (16)	8.33 (14)	0.79
75%	12.90 (14)	14.30 (12)	0.91
100%	23.98 (0)	24.00 (0)	1.00

\*T-AUC-100% are the times to reach the given % of the total AUC for each formulation

**Table 8**

Mean (CV) Times to Partial and Total Glucose AUC Values for X-14 70/30 and Human Insulin 70/30 as Compared to Human Insulin 70/30\*: Study 033

Parameter T-AUC <sub>hr</sub>	X-14 70/30	Human Insulin 70/30	Ratio
25%	3.31 (21)	4.13 (17)	0.81
50%	7.30 (36)	8.33 (14)	0.87
75%	12.70 (34)	14.30 (12)	0.91
100%	17.00 (25)	24.00 (0)	0.71

\*T-AUC-100% for X-14 70/30 are the times when the same respective AUC values were achieved for human insulin.

**Table 9**

Mean (CV) Times to Partial and Total Insulin AUC Values for X-14 70/30 and X-14\*: Study 1086

Parameter T-AUC	X-14	X-14 70/30	Ratio
25%	1.08 (24)	1.44 (20)	0.76
50%	1.74 (22)	2.61 (21)	0.68
75%	2.62 (24)	4.95 (20)	0.54
100%	10.00 (0)	24.00 (0)	0.42

\*T-AUC-100% are the times to reach the given % of the total AUC for each formulation

**Table 10**

Mean (CV) Times to Partial and Total Insulin AUC Values for X-14 70/30 and X-14 Insulin as Compared to X-14 70/30\*: Study 1086

Parameter T-AUC <sub>hr</sub>	X-14	X-14 70/30	Ratio
25%	0.84 (27)	1.44 (20)	0.59
50%	1.27 (30)	2.61 (21)	0.49
75%	1.66 (35)	4.95 (20)	0.34
100%	2.27 (48)	24.00 (0)	0.09

\*T-AUC-100% for X-14 70/30 are the times when the same respective AUC values were achieved for X-14.

*Table 11*

Mean (CV) Times to Partial and Total Glucose AUC Values for X-14 70/30 and X-14\*: Study 1086

Parameter T-AUC <sub>hr</sub>	X-14	X-14 70/30	Ratio
25%	1.91 (15)	2.17 (17)	0.89
50%	3.18 (16)	3.66 (14)	0.87
75%	4.78 (17)	5.70 (14)	0.85
100%	10.00 (0)	10.00 (0)	1.00

\*T-AUC-100% are the times to reach the given % of the total AUC for each formulation

*Table 12*

Mean (CV) Times to Partial and Total Glucose AUC Values for X-14 70/30 and X-14 as Compared to X-14\*: Study 1086

Parameter T-AUC <sub>hr</sub>	X-14	X-14 70/30	Ratio
25%	1.84 (24)	2.17 (17)	0.85
50%	3.07 (26)	3.66 (14)	0.84
75%	4.52 (29)	5.65 (13)	0.80
100%	5.52 (29)	10.00 (0)	0.55

\*T-AUC-100% for X-14 70/30 are the times when the same respective AUC values were achieved for X-14.

#### 10.4.3. Other comparators

-The sponsor did not compare X-14 70/30 with the most appropriate human insulin mixture 50/50. The latter is known to have a more rapid rate of absorption and onset of action than human insulin 70/30.

-The sponsor did not provide data comparing X-14 with neighboring members of the X-14 family: 50/50 and \_\_\_\_\_

\_\_\_\_\_ was one of the treatment arms in the 4-arm crossover study with X-14 and X-14 70/30.

-The sponsor did not compare X-14 70/30 with the most appropriate basal insulin, NPH.

### 11.--Study design for clinical trials

#### 11.1.--General

The sponsor conducted one three-month, parallel, open-label active control, 1:1 randomization clinical trial with the mixture proposed for registration (formulation #3): 038 (Table 13). The study were conducted outside the U.S (Table 14). Patients with both Type 1 and 2 diabetes were enrolled. Diabetic patients over the age of 17 were enrolled. All patients were to have had experience with insulin therapy. (See inclusion criteria.) Patients were then randomized to three months of treatment with an X-14 or human insulin mixture (Table 13). Injections of human insulin 70/30 were to be given 30 minutes before breakfast and supper; injections of X-14 70/30 were to be given 15 minutes or less before breakfast and supper. Injections could be given in the thigh or abdomen-per local custom. (Results were not to be stratified by injection site although it is known that PK-PD responses vary by injection site.) Patients performed home glucose

monitoring. Insulin doses were titrated to maximize glycemic control and minimize hypoglycemia. Patients were then eligible to enter extension trials 067. Longitudinal cross-reacting insulin antibody data are being collected in — extension trials.

**Table 13**

Design Features of the Clinical Study

Study	Insulin Type	Dosing	Study Type	Tx Arm Duration	Blinding	Glucose Measure	
038	X-14 70/30 vs human insulin 70/30	BID	parallel	3 months	no	HgbA1c	8-point glucometer profile

Tx=treatment

**Table 14**

Other Study Features

Study	# Investigators	# Countries	Conducted in U.S.	# Randomized Patients/Investigator
038	36*	4**	No	8.17*

\*does not include 3 investigators who did not enroll any patients

\*\*does not include an investigator from Switzerland who did not enroll any patients. The other countries include Austria, Germany, Ireland, and United Kingdom.

11.2.--Patient Selection Criteria

11.2.1.--Inclusion Criteria

Aged  $\geq 18$  years (except in Austria  $\geq 19$  years)

Diabetes mellitus-Type 1 or Type 2 for  $\geq 24$  months

Treatment with BID insulin for  $\geq 12$  months (The UK required patients to be using Novo mixes *a priori*.)

HgbA1c  $\leq 11\%$

BMI  $\leq 35$  kg/m<sup>2</sup>

11.2.2.--Exclusion Criteria

Insulin allergy

Profound insulin resistance: insulin dose  $\geq 1.4$  U/kg/d

Inability to do glucose monitoring

Class 3 or 4 cardiac disease or unstable angina or myocardial within the last year

Renal disease (creatinine  $\geq 1.7$  mg/dl)

Active proliferative retinopathy

Liver disease (ALT  $\geq 2x$  ULN [50 IU/l], alk phos  $\geq 2x$  ULN [144 IU/l])

History of pancreatitis

Pregnancy or risk of pregnancy or lactation

Use of oral anti-diabetic agents-- within 30 days of entry

Use of systemic steroids at the time of entry

Severe recurrent hypoglycemia (There were no established criteria.)

Did not exclude patients:

- at high risk of requiring systemic steroids
- using beta blockers
- who had been exposed previously to X-14
- with adrenal insufficiency
- autonomic neuropathy

### 11.3.—Patient Characteristics-Special Populations

35% of exposed patients were patients with Type 1 diabetes. The mean duration of diabetes was 15.3 years. 54% of exposed patients were male. The mean age for exposed patients was 56.6 years and is consistent with the study inclusion of patients with Type 2 diabetes. 1% of patients were non-Caucasian; these three patients were randomized to human regular insulin for treatment. The mean BMI was 27.4. 20% of the exposed population were smokers. The values of the important safety and efficacy parameters were similar for the treatment groups at baseline (Table 15).

**Table 15**

Mean Intent-to-treat Values for HgbA1c, Insulin Doses, and Cross-reacting Antibodies

Study 038 Treatment Group	HgbA1c (%)		Total Daily Dose (U/kg)		Cross-Reacting Antibodies+ (% Binding)	
	Baseline (n)	Baseline-with values for ITT (n)	Baseline (n)	Baseline-with values for ITT (n)	Baseline (n)	Baseline-with values for ITT (n)
-IDDM	8.39 48	8.46 46	0.622 49	0.627 47	13.06 49	12.99 46
HR-NIDDM	8.18 102	8.18 96	0.580 101	0.579 96	8.73 102	9.12 97
X14-IDDM	8.38 55	8.41 49	0.631 53	0.640 48	11.06 55	11.49 49
X14-NIDDM	8.07 84	8.07 81	0.561 85	0.562 83	9.74 85	10.08 82

The "baseline" values, but not the "baseline-with values for ITT", include the 3 patients treated with the wrong drug: #26, 83, and 574.

Baseline-with values for ITT refers to randomized patients with baseline values and a subsequent value for intent-to-treat assessment.

ITT=intent-to-treat

+It is not known whether these values include the non-specific antibodies.

No special population groups were studied.

### 11.4.---Numbers of Patients and Disposition

351 patients were screened. 294 patients were randomized. Three patients randomized to X-14 70/30 did not receive any drug. Two patients randomized to X-14 70/30 actually received human insulin 70/30 and completed the trial (#26 and #83). One patient was treated with human insulin 70/30 until the last month of the trial (#574). 279 (96%) had post-baseline data for intent-to-treat (ITT) analysis. 268 (92%) completed the trial. One patient (#720) completed the trial, but did not have endpoint HgbA1c data. Withdrawals were few and scattered throughout the trial (Table 16). The patterns of withdrawal were

similar for the two insulin products (Table 17). Twelve of the 23 patients who withdrew were NIDDM patients. The most common reasons for withdrawal during the trials was non-compliance. Seven patients were discontinued for adverse events. Two patients were withdrawn for rash.

**Table 16**

Duration of Patient Exposure to Experimental and Control Drug in Patients with Any Drug Exposure after Randomization

Treatment Arm	Duration in Study			Completers
	</=4 weeks	>4weeks, </=8 weeks	>8 weeks	
X-14 70/30	9	2	131 (129)*	124 (122)*
Human insulin 70/30	5	3	145 (144)*	144 (143)*

\*The patients treated with the wrong insulin were included in the group to which they were randomized.

**Table 17**

Discontinuation of Patients

Reason for Discontinuation	Patients Exposed to Drug in the Controlled Trial				
	# Patients			Duration of Treatment (days) for Each Drop-out (Individuals & Group)	
	X-14 mix	HI mix	Total	X-14 mix	HI mix
Non-compliance	5	3	8	21+9+13+14+13=70	80+35+15=130
Adverse event	4	3	7	8+84+63+32=187	14+2+29=45
Entry Criteria or Protocol Violation	2	2	4	55+28=83	71+51=122
Other	2	1	3	5+21=26	15
Lack of efficacy	1	0	0	15	

X-14=insulin aspart HI=human insulin

**11.5.— Drug Exposure in Extension Trials**

The sponsor did not supply complete information on the extension trials so these data were not reviewed.

**11.6--Study Drug Formulation**

Insulin X-14 70/30 has the empirical formula of C<sub>256</sub>H<sub>381</sub>N<sub>65</sub>O<sub>79</sub>S<sub>6</sub> and a molecular weight of 5825.8. Each milliliter of X-14 70/30 contains insulin aspart 100 units, 0.33 mg protamine sulfate, 36.4 mg mannitol, 1.25 mg dibasic sodium phosphate, 1.72 mg m-cresol, 1.5 mg phenol, zinc \_\_\_\_\_ adjusted to provide 32.7 ug/ml, \_\_\_\_\_ The pH is adjusted to 7.2—7.44.

**11.7.—Dose-Route-Administration**

All insulin was to be given as subcutaneous injections twice daily with the doses to be titrated as needed (Table 13). One patient (#501) required more injections per day than was permitted by the protocol Another had higher insulin requirements than permitted

(#245). Both were in the human insulin 70/30 treatment arm and were withdrawn from the study.

#### 11.8.-- Concomitant Medications

Patients using glucocorticoids, which can increase insulin resistance and the doses of insulin required to maintain glycemic control, were excluded from ANA/DCD/038,UK. Patients using beta blockers, which can mask the symptoms of hypoglycemia, were not excluded from ANA/DCD/038,UK. Oral antidiabetic agents were excluded from the ANA/DCD/038,UK study, but the period for exclusion, 1 month, was not long enough to exclude their impact on basal HgbA1c values. Patients who had participated in other insulin aspart product studies or who had used commercially available insulin aspart were not specifically excluded. Prior exposure to X-14 could have had an impact on cross-reacting antibody levels.

There were no drug interaction studies-although the sponsor recorded the use of concomitant drugs with some of the hyperglycemic events (Vol.46, p244).

#### 11.9.—Safety Studies and Parameters

Physical exams were conducted at study entry. Patients were to have undergone a retinal exam at or three months prior to screening. There was no specific assessment of diabetic neuropathy. Vital signs and weight measurements were taken at each subsequent visit. The exit physical did not include a formal fundoscopic exam. Electrocardiograms were obtained at entry and exit. Routine clinical chemistry, hematologic, and lipid tests were obtained at baseline and at the end of each treatment arm. Patients were to conduct serial home glucose monitoring and to report hypoglycemia.<sup>1</sup> There were no specific criteria for monitoring or assessing hyperglycemia. Urine ketones were to be measured with each visit using ketostix. Anti-insulin antibodies, in particular, cross-reacting insulin antibodies, were assessed at baseline and endpoint.

<sup>1</sup>Hypoglycemia was defined by the sponsor as:

Minor--symptoms consistent with hypoglycemia with or without serum/blood glucose confirmation

Major A--symptoms of hypoglycemia with impaired consciousness that required third party assistance

Major B-- symptoms of hypoglycemia with impaired consciousness that required third party intervention with IV glucose or glucagon

#### 11.10.—Efficacy Variables

HgbA1c values, the parameter of glycemic control accepted by the Division, were obtained at baseline and at endpoint. In addition, unblinded patients were to conduct a home glucose profile with sampling done before meals, 90 minutes after meals, before bedtime, and at 2 A.M. Measures were to be obtained on three days in the week prior to the baseline, 8 week, and 12 week visits. The sponsor assessed the mean glucose, glucose excursion, fasting glucose, and post-prandial glucose with these glucometer readings.

#### 11.11.—Statistical Analysis

Active controls were employed because of the absolute requirement for insulin in Type 1 patients. The controls were human insulin mixtures. The study was open-label to permit

administration of the human regular insulin mixes 30 minutes prior to meals and X-14 mixes within 10 or 15 minutes of meal ingestion. Although the sponsor used a non-inferiority comparison for HgbA1c:  $H_0: d > 0.6\%$ , and the alternative  $H_1: d < 0.6\%$ , rigorous statistical analysis was not undertaken because a) the equivalence of lispro and human regular insulin had been previously established, b) the trials were open-label, and c) the variability due to injection site differences was not controlled.

#### 11.12.—Inspections

Inspections of the clinical sites were not initially requested because the clinical study was not the pivotal study. A cross-over PK-PD study that assesses the differences from neighboring insulins: X-14 50/50 mix and \_\_\_\_\_ or NPH would be the most appropriate study for inspection. In May 2000, the sponsor submitted data from a 4-arm cross-over PK-PD study site in Germany. Because the sponsor provided data only from the X-14 and X-14 70/30 arms and did not have a \_\_\_\_\_ arm or NPH arm, the study was deemed to be inadequate. The request to inspect this site was withdrawn because of these inadequacies.

#### 11.13.—Amendments

*September 18, 1997*

The X-14 70/30 insulin was to be administered within 10 (not 15) minutes of the beginning of a meal.

*January 21, 1998*

A German version of the quality of life questionnaire was to be used in Austria, Germany, and Switzerland.

*February 4, 1998*

In Austria, the trial was restricted to patients at least 19 (not 18) years of age.

*November 5, 1997*

In Ireland, the trial was restricted to patients who had not received another investigational drug within the last 4 (not 3 months).

*January 15, 1998*

In the UK, the trial was restricted to patients who had used NovoNordisk mixtures (not other brands and not self-prepared mixtures BID) for at least 12 months. Patients were expected to continue on these NovoNordisk mixtures between baseline and study baseline, the mixtures would not be provided by NovoNordisk during this interval.

*April 2, 1998*

The list of local trial monitors for Austria, Germany, and Switzerland was modified.

*July 7, 1998*

The list of investigators for Austria, Germany, and Switzerland was modified.

#### 12.—Efficacy Results

Glycemic control as measured by HgbA1c was less than optimal at baseline (Table 15). Mean values exceeded 8%. Glycemic control did not improve substantially during the clinical trial (Tables 18-20). The maximal decrease in HgbA1c was 0.2%. There were no clinically significant differences between the treatment groups for HgbA1c at endpoint and the change in HgbA1c over the duration of the study whether an intent-to-treat or

completer analysis was performed. There were no gender differences for the change in HgbA1c over the duration of the study for patients with NIDDM (Table 21). The same, however, cannot be said for patients with IDDM who were treated with X-14 70/30. The glucose control in the women deteriorated. The small size of this subgroup may contribute to this deviant observation and limits the detection of any interaction between and gender and glycemic control.

Insulin doses were increased for all treatment groups, but did not account for all of the changes in glycemic control. The dose increase was greater for patients in the X-14 70/30 arms. The difference in dose was 0.07 U/kg/d for patients with IDDM and 0.02 U/kg/d for patients with NIDDM. These differences were statistically significant for the IDDM patients. Additional data support the need for higher doses of X-14 70/30 insulin to achieve comparable changes in glycemic control. Patients with IDDM in the human insulin 70/30 arm had a decrease in HgbA1c of 0.20% with an increase in daily insulin dose of 0.012 U/kg/d: ratio -17.09. Patients with NIDDM in the X-14 70/30 arm had a comparable decrease in HgbA1c of 0.18% with an increase in daily insulin dose of 0.041 U/kg/d: ratio -4.38. Patients with IDDM in the human insulin 70/30 arm had a decrease in HgbA1c of 0.20% with an increase in daily insulin dose of 0.012 U/kg/d: ratio -17.09. Patients with NIDDM in the human insulin 70/30 arm had a decrease in HgbA1c of 0.10% with an increase in daily insulin dose of 0.026 U/kg/d: ratio -3.86. In practical terms, the mean differences in dose increases were approximately 1 to 5 U/day for a 70 kg person receiving X-14 as opposed to human insulin. These values are similar to those observed in the original X-14 NDA.

*Table 18*

Mean Intent-to-treat Values for HgbA1c and Insulin Doses\*

Study 038 Treatment Group	HgbA1c (%)				Dose (U/kg/day)			
	Baseline- All*	Baseline- With at least 1 fu Value	Endpoint	Delta	Baseline- All*	Baseline- With at least 1 fu Value	Endpoint	Delta
X-14 70/30 IDDM (n exposed=53)	8.34	<b>8.41</b>	8.42	0.01	0.628	0.638	<b>.713</b>	<b>0.074</b>
N=	53	49	49	49	53	48	48	48
HI 70/30 IDDM (n exposed=49)	8.39	8.46	8.26	<b>-0.20</b>	0.622	0.627	0.639	0.012
N=	49	46	47	46	49	47	47	47
P=	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	0.14	0.005
X-14 70/30 NIDDM (n exposed=85)	8.07	8.07	<b>7.92</b>	<b>-0.18</b>	0.561	0.562	0.603	<b>0.041</b>
N=	84	81	82	81	85	83	83	83
HI 70/30 NIDDM (n exposed=101)	8.16	8.19	8.08	-0.10	0.578	0.579	0.605	0.026
N=	101	96	96	96	100	96	97	96
P=	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

\*Does not include the 3 patients who were treated with the wrong insulin: #26, 83, and 574.

HI=Human insulin

**Table 19**

Mean Intent-to-treat Values for HgbA1c, Insulin Doses, and Cross-reacting Antibodies in Patients Who Had Values for All Parameters at Baseline and Study Exit\*

Study 038 Treatment Group	HgbA1c (%)			Total Daily Dose (U/kg)			Cross-Reacting Antibodies+ (% Binding)		
	Baseline	Endpoint	Delta	Baseline	Endpoint	Delta	Baseline	Endpoint	Delta
X14-IDDM n=48	8.41	8.41	-0.002	0.638	<b>0.713</b>	<b>0.075</b>	11.71	<b>26.79</b>	<b>15.08</b>
HI-IDDM n=45	8.45	<b>8.28</b>	<b>-0.17</b>	0.619	0.628	0.009	12.26	12.66	0.40
	P=N.S.	P=N.S.	P=N.S.	P=N.S.	P=0.089	P=0.003	P=N.S.	P=0.001	P=5.4x10-6
X14-NIDDM n=80	8.08	<b>7.89</b>	<b>-0.20</b>	0.564	0.606	<b>0.042</b>	10.24	<b>18.98</b>	<b>8.74</b>
HI-NIDDM n=95	8.19	8.08	-0.11	0.578	<b>0.604</b>	0.026	9.28	9.69	0.41
	P=N.S.	P=N.S.	P=N.S.	P=N.S.	P=N.S.	P=N.S.	P=N.S.	P=0.002	P=3.7x10-5

\*Does not include the 3 patients who were treated with the wrong insulin: #26, 83, and 574. Analysis showed that exclusion of these patients did not substantively change the analysis.

+It is not known whether these values include non-specific antibodies.

X-14=X-14 70/30 HI=Human insulin 70/30

**Table 20**

Mean Values for HgbA1c, Insulin Doses, and Cross-reacting Antibodies in Patients Who Had Values For All Parameters at Baseline and 12 weeks-Completers\*

Study 038 Treatment Group	HgbA1c (%)			Total Daily Dose (U/kg)			Cross-Reacting Antibodies+ (% Binding)		
	Baseline	Endpoint	Delta	Baseline	Endpoint	Delta	Baseline	Endpoint	Delta
X14-IDDM n=47	8.42	8.39	-0.03	0.638	<b>0.713</b>	<b>0.075</b>	5.42	<b>26.31</b>	<b>15.44</b>
HI-IDDM n=44	8.46	<b>8.27</b>	<b>-0.19</b>	0.618	0.627	0.010	12.18	12.68	0.50
	P=N.S.	P=N.S.	P=N.S.	P=N.S.	P=0.094	P=0.004	P=N.S.	P=0.002	P=5.2x10-6
X14-NIDDM n=76	8.11	<b>7.92</b>	<b>-0.19</b>	0.556	0.602	<b>0.046</b>	9.48	<b>18.13</b>	<b>8.65</b>
HI-NIDDM n=93	8.17	8.06	-0.11	0.574	<b>0.601</b>	0.027	9.33	9.75	0.42
	P=N.S.	P=N.S.	P=N.S.	P=N.S.	P=N.S.	P=N.S.	P=N.S.	P=0.005	P=5.8x10-5

\*Does not include the 3 patients who were treated with the wrong insulin: #26, 83, and 574. Analysis showed that exclusion of these patients did not substantively change the analysis.

+It is not known whether these values include non-specific antibodies.

X-14=X-14 70/30 HI=Human insulin 70/30

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*Table 21*

HgbA1c Results by Gender

Study 038	HgbA1c (%) Baseline	HgbA1c (%) Endpoint	HgbA1c (%) Delta	N=
X-14 70/30 IDDM-male	8.53	8.43	-0.10	31
X-14 70/30 IDDM-female	<b>8.21</b>	<b>8.41</b>	<b>+0.20</b>	18
HI 70/30 IDDM-male	8.35	8.17	-0.16	33
HI 70/30 IDDM-female	8.71	8.47	-0.24	14
X-14 70/30 NIDDM-male	7.95	7.79	-0.18	44
X-14 70/30 NIDDM-female	8.23	8.05	-0.17	39
HI 70/30 NIDDM-male	8.12	8.04	-0.08	46
HI 70/30 NIDDM-female	8.22	8.10	-0.12	51

\*Does not include the 3 patients who were treated with the wrong insulin: #26, 83, and 574.

The sponsor collected fasting and post-prandial glucose data (Table 22). The latter included 90 minute post-prandial glucose levels, glucose excursions (the 90 minute post-prandial glucose minus the pre-prandial glucose level), the 90 minute post-prandial areas-under-the-curve (AUC) for glucose, and the mean glucose profiles (a composite of glucometer readings obtained before meals, 90 minutes after meals, at bedtime, and at 2 A.M). The meaning of these glucose parameters remains uncertain. No glucose measurements were made via a laboratory. They are all derived from glucometer readings, which are not known for their precision and accuracy, and these readings are collected by the patients in an unblinded fashion. The fasting glucose readings were higher in patients with IDDM who were on X-14 70/30 than in patients with IDDM who were on HI 70/30. A similar finding was observed with IDDM patients treated with another short acting insulin analogue and a night-time basal insulin and was presumed to occur because of the shorter duration of the insulin analogue than human regular insulin. Curiously, this finding was not replicated in the patients with NIDDM as it was with the other insulin analogue. Furthermore, the mean glucose profiles did not correlate well with another well validated estimate of mean glucose exposure, HgbA1c. Similarly, none of the r values for other glucose parameters, fasting glucose, 90-minute-post-breakfast glucose, glucose excursion, and AUC<sub>breakfast to 90 minutes</sub> exceeded 0.6.—suggesting that these parameters lack clinical significance and/or that the self-collected glucose values were not accurate or representative of the true values for the parameters (Tables 22-24, Figures 1—8).

It should be noted that in a small, two week, cross-over study (046) with serial glucose measurements in 13 patients with NIDDM, the maximal post-prandial glucose for breakfast and supper were higher by ~18—54 mg/dl for patients using human insulin 70/30, but that maximal post-lunch glucose differences were higher by ~36 mg/dl for patients using X-14 70/30 insulin (Vol. 1, p286). (See graphic display in appendix 1.) Mean nocturnal glucose measurements exceeded 120 mg/dl and did not vary by treatment arm. These data suggest that there are temporal differences in the profiles of glucose lowering for the two different insulin mixtures, but that no one fixed insulin mixture

provides lower glucose values throughout the entire day. Hence, the limited correlation observed between post-prandial parameters and HgbA1c.

*Table 22*

Glucose Parameters (Derived from Glucometer Readings) and Their Relationship to HgbA1c

Treatment/ Statistical Parameter	Glucose Parameters					
	HgbA1c (%)	Fasting (mmol/L)	90 Min PP (mmol/L)	Glucose Excursion (mmol/L)	AUC-90 Min (mmolxhr/L)	Mean (mmol/L)
IDDM, X-14 70/30						
<b>Mean</b>	<b>~8.4</b>	<b>9.75</b>	<b>10.25</b>	<b>0.47</b>	<b>14.93</b>	<b>8.88</b>
R=		0.42	0.12	-0.24	0.29	0.24
N=		46	46	45	45	37
IDDM, HI 70/30						
<b>Mean</b>	<b>~8.2</b>	<b>7.70</b>	<b>11.12</b>	<b>3.42</b>	<b>14.12</b>	<b>8.58</b>
R=		0.39	0.52	0.25	0.56	0.50
N=		44	42	42	42	36
P=		0.01	N.S.	0.003	N.S.	N.S.
NIDDM, X-14 70/30						
<b>Mean</b>	<b>~7.9</b>	<b>8.48</b>	<b>10.08</b>	<b>1.60</b>	<b>13.93</b>	<b>8.53</b>
R=		0.25	0.35	0.21	0.36	0.40
N=		76	75	75	75	69
NIDDM, HI 70/30						
<b>Mean</b>	<b>~8.0</b>	<b>8.39</b>	<b>11.03</b>	<b>2.65</b>	<b>14.56</b>	<b>9.16</b>
R=		0.18	0.21	0.07	0.21	0.42
N=		92	91	91	92	86
P=		N.S.	0.12	0.05	N.S.	0.069

Patient values were included if they had an endpoint value for the particular glucose parameter and HgbA1c level. HgbA1c values varied slightly because the variances in the sample size for the glucose parameter—particularly the mean glucose profile.

R=Correlation coefficient of glucose parameter with HgbA1c

Fasting=Fasting glucose

PP=Post-prandial

Glucose excursion=90 minute post-breakfast glucose minus the fasting glucose (*Typically the most distinct excursions can be found in the morning because there is less carry-over from the prior insulin dose, e.g. Vol., p286.*)

AUC=area-under-the-curve estimate of glucose exposure at breakfast and for the subsequent 90 minutes

Mean=Mean glucose determined from glucometer logs with glucose measured at 8 time-points

*Table 23*

Relationship Between the Change in HgbA1c and the Mean Glucose at Endpoint\*

	Delta HgbA1c (Last Visit-Baseline)(%)	Mean Glucose (mmol/l)	Correlation Coefficient	N=
IDDM X-14 70/30	-0.05	8.83	0.14	37
IDDM Human Insulin 70/30	-0.21	8.68	0.14	35
NIDDM X-14 70/30	-0.21	8.54	0.02	68
NIDDM Human Insulin 70/30	-0.15	9.16	0.22	86

\*Eight point glucose profile as self-measured by patients using glucometers

*Table 24*

Relationship Between the Change in HgbA1c and the Glucose Excursion (90 Minute Post Breakfast Glucose Minus Fasting Glucose) at Endpoint\*

	Delta HgbA1c (Last Visit-Baseline)(%)	Glucose Excursion (mmol/l)	Correlation Coefficient	N=
IDDM X-14 70/30	-0.007	0.47	-0.09	45
IDDM Human Insulin 70/30	-0.27	3.37	-0.03	41
NIDDM X-14 70/30	-0.21	1.62	-0.03	74
NIDDM Human Insulin 70/30	-0.12	2.65	0.17	91

\*Glucose excursion as self-measured by patients using glucometers

### 13.--Safety Results

#### 13.1.—General

The controlled studies were not sufficiently powered to identify adverse events other than those previously identified: hypoglycemia, changes in cross-reacting antibodies, and changes in alkaline phosphatase levels. The nature and number of adverse events as well as the number of withdrawals due to adverse events appeared to be comparable for the two treatment groups (Tables 25-26).

The extension studies were intended to provide long-term safety results—with the emphasis directed at the effect of antibodies on a) systemic-local allergic reactions and b) glycemic control and insulin doses. The raw data and results of these extension studies were not available for review.

Table 25

Drop-outs Due to Adverse Events

Tx	Pt #	Age	Gender	Event	Duration of Tx at Onset (Days)	Duration of Event (Days)
X-14	82	71	F	Diarrhea	2	10
X-14	170	68	M	Arterial thrombosis	83	6
X1-4	883	64	M	Rash, parasthesia	17/33	45/29
X-14	761	?	?	Unspecified	63	?
HI	389	47	F	Abdominal & back pain, nausea	6	9/16/38
HI	716	74	F	Neuropathy	4	81
HI	778	69	F	Rash-erythema	14	31

Tx=treatment Pt=patient F=female M=male HI=human insulin

Table 26

Serious Adverse Events

Tx	Pt #	Age	Gender	Event	Duration of Tx at Onset	Resulted in Withdrawal
X-14	81	47	M	Peripheral ischemia	49	No
X-14	170	68	M	Arterial thrombosis	83	YES
X1-4	411	55	M	Viral infection	8	No
X-14	818	63	M	Skin ulceration	3	No
HI	64	75	M	Hypoglycemia	7	No
HI	64	75	M	Hypoglycemia	12	No
HI	146	53	M	Urinary tract infection	51	No
HI	518	69	F	Bundle branch block	77	No
HI	567	67	F	Cranial nerve lesion	59	No
HI	572	75	F	Pancreatic carcinoma	-92	No
HI	716	74	F	Neuropathy	4	YES
HI	765	61	F	Uterine cancer	61	No
HI	864	66	F	Angina	52	No

Tx=treatment Pt=patient F=female M=male HI=human insulin

13.2.--Hypoglycemia

For the purposes of this review, hypoglycemia was defined as requiring intervention from a third party and/or having a blood glucose  $\leq 36$  mg/dl (2 mmol/L). This definition is relatively specific for clinically significant events and minimizes problems due to the relative inaccuracy of the home glucose meters and open-label nature of the trial. (See the minutes of the and the 1996 Winter and 1998 Spring E & M Advisory Committee meetings.)

Hypoglycemia, as is typical, was more common in the Type 1 patients (Table 27). Regardless of treatment arm, the median number of hypoglycemic events requiring third party intervention was zero for patients with IDDM. Hypoglycemia requiring third party intervention was limited to 15--20% of the exposed populations for both treatment arms. The overall rates of hypoglycemia requiring third party intervention, however, were approximately four times greater than the rates predicted by the DCCT for intensively

managed IDDM patients with HgbA1c values of ~8-8.5%, 0.40-0.45 events per patient-year regardless of treatment arm.

**Table 27**

**Glycemic Control versus Hypoglycemia**

(Hypoglycemia=glucose  $\leq$ 36 mg/dl and/or requiring intervention from a third party)

Study 038 Treatment Group	HgbA1c (%)		Hypoglycemia--# Events							
	End	Delta	During Treatment Arm				During Final Month			
			Total	Blood Glucose <math>\leq 2</math> mmol/L	Events Not Self Treated W/o Rx*	IV Glucose or Glucagon	Total	Blood Glucose <math>\leq 2</math> mmol/L	Events Not Self Treated W/o Rx*	IV Glucose or Glucagon
X-14—IDDM Exposed=			32	18	8	6	6	0	2	4
N=			16	11	7	4	4	0	1	3
HI—IDDM Exposed=			42	18	18	6	11	4	4	3
N=			17	12	7	5	6	3	3	3
X-14—IDDM Exposed=			11	5	6	0	4	1	3	0
N=			7	5	3	0	2	1	1	0
HI—NIDDM Exposed=			20	8	10	2	5	3	2	0
N=			11	5	6	1	4	2	2	0

HI=human regular insulin compounds

\*W/o =without

X-14=insulin aspart compounds

\*Rx=IV glucose or glucagon

Hypoglycemia was less frequent in Type 2 patients, who typically have lower rates of hypoglycemia (Table 27). The median number of median number of hypoglycemic events requiring third party intervention was zero for patients with NIDDM. Hypoglycemia requiring third party intervention was limited to 3--8% of the exposed populations. There were only 2 events that required treatment with glucagon or IV glucose. These were found in the human insulin 70/30 group which had ~25% more patients than the X-14 70/30 treatment arm. The overall rates of hypoglycemia requiring third party intervention were similar to the rates predicted by the DCCT for intensively managed IDDM patients with HgbA1c values of ~8-8.5%.

Lastly, the occurrence of hypoglycemic events by time of day was similar regardless of treatment arm. The adjusted ANOVA of 2 A.M. glucometer readings did not show any difference by treatment group: 8.12 mmol/L (Vol.1, p296).

**13.3.--Acidosis/Severe Hyperglycemia**

In study 038, there were no cases of hyperglycemia or acidosis requiring hospitalization; It is unclear as to whether systematic monitoring was done for less serious cases of hyperglycemia or ketosis because neither the protocol nor the submission elaborates on this issue. Urine ketones were assessed at each visit at 2, 4, 8, and 12 weeks. Given the sporadic nature of ketosis, few events would be uncovered this way. Furthermore, it

would not identify hyperglycemia in patients with Type 2 diabetes. Although the number of patients with Type 1 diabetes was limited, the average glycemic control, as measured by HgbA1c, was mediocre at best so some hyperglycemia would have been expected. There were 9 cases (#4, 26, 33, 73, 102, 152, 169, 323, and 437; mean age 43 years; range 25-71) of flu-like illness for patients treated with X-14 70/30 and 5 (#27, 146, 290, 413, and 501; mean age 61 years; range 41-71) for patients treated with human insulin 70/30 (Vol. 32, p306-7). It is not known whether any of these were presentations of DKA.

#### 13.4.--Allergic Reactions

There were no anaphylactoid reactions during study 038.<sup>1</sup> There were several reactions that may be consistent with allergic reactions:

a--A 42 year old female (#433) developed pruritus on the "neck and skin" four days after starting X-14 70/30. The duration of the pruritus was unclear. The patient was not discontinued.

b--A 26 year old female (#323) developed pruritus 25 days after starting X-14 70/30. The duration of the pruritus was unclear. The patient was not discontinued.

c--A 64 year old male (#883) developed persistent "eruption of the skin on the trunk" 17 days after starting X-14 70/30. The patient was discontinued.

d--A 70 year old male (#73) developed a rash 80 days after starting X-14 70/30. The duration of the rash was unclear. The patient was not discontinued.

e--A 71 year old male (#152) developed a rash 59 days after starting X-14 70/30. The duration of the rash was unclear. The patient was not discontinued.

f--A 69 year old female (#778) developed a persistent "exanthem" 14 days after starting study drug human insulin 70/30. The patient was discontinued. The patient appears to have been on insulin mixtures prior to study 038.

There were no narratives available and the CRF were brief and illegible so that further conclusions about the nature of the events cannot be made--except that increased cross-reacting antibody levels do not appear to be associated with increased risk for rash or systemic allergic reactions. (See samples in appendix 2.)

There was insufficient information to determine whether there was a treatment difference in skin injection site reactions.

<sup>1</sup> There was another report of persistent "allergy" that occurred in a 63 year old female after 83 days of treatment with a still blinded drug in study — safety update, p025.

#### 13.5.--Deaths

There were no deaths in the 12 week controlled trial although two patients died during the extension studies. One patient (#235) from the human insulin 70/30 treatment arm died of disseminated non-Hodgkins lymphoma one day after diagnosis during the extension trial (067). Another patient (#147) treated with X-14 70/30 reportedly died of cardiac failure (Safety update: p12, 20). In the first case, not attribution could be made to the drug product. In the second case, the patient appears to have been ineligible for the study

because of a history of renal failure. Advanced complications of diabetes likely contributed significantly to the patient's demise.

### 13.6--Antibodies

Cross-reacting antibodies were previously shown to be antibody species that changed the most with exposure to X-14. (See NDA #20986 review.) Similar changes were not predictably seen with X-14--specific antibodies. It was not known whether the introduction of protamine, which is commonly acknowledged to be antigenic, would enhance or mute these antibody responses.

Cross-reacting antibody levels were higher in those patients treated with X-14 70/30 (Tables 19 and 20). Similar findings were present in the intent-to-treat population (Table 28), the intent-to-treat population with baseline and exit values for HgbA1c, insulin dose, and cross-reacting antibodies, and in the population that had baseline and 12 week values for HgbA1c, insulin dose, and cross-reacting antibodies. These findings are consistent with those in the original NDA and with other insulin analogues.

Table 28

Mean Intent-to-treat Values for Cross-reacting Antibodies at Baseline and Exit

	Cross-reacting Antibodies (% Binding)			
	Baseline- All*	Baseline- With at least 1 fu Value	Endpoint	Delta
X-14 70/30 IDDM (n=53)	10.99	11.49	26.28	14.79
N=	53	49	49	49
HI 70/30 IDDM (n=49)	13.05	12.99	13.31	0.32
N=	49	46	46	46
P=	N.S.	N.S.	0.002	5x10-6
X-14 70/30 IDDM (n=85)	9.74	10.08	8.70	8.60
N=	85	82	8.2	8.2
HI 70/30 IDDM (n=101)	8.82	9.12	9.58	0.46
N=	101	97	97	97
P=	N.S.	N.S.	0.002	3.4x10-5

\*Does not include the 3 patients who were treated with the wrong insulin: #26, 83, and 574.

HI=Human insulin

To assess the clinical importance of cross-reacting antibodies, the changes in antibody levels were divided into tertiles and the mean levels of changes in HgbA1c and insulin dose of the respective antibody groups calculated (Tables 29 and 30). The patients with the greatest antibody increases with X-14 70/30 use did not experience a deterioration in glycemic control. Nor did they require more insulin than patients in the lowest tertile to achieve a comparable decrease in HgbA1c glucose. The study, however, was too short to assess long-term effects of insulin analogue+protamine on antibody formation.

**Table 29**

Qualitative and Quantitative Serial Changes in Antibody Binding Versus the Associated Serial Changes in the Mean Total Daily Insulin Doses and Glycemic Control in Patients Treated with X-14 70/30 Insulin Mixture: Patients with Post Baseline Measurements in All Three Categories.

Study 038 Treatment Group	Antibody Group	N=	Antibody Delta (% binding)	Antibody Range (% binding)	Dose Delta (U/kg)	HgbA1c Delta (%)
IDDM	Top-Tertile	16	38.92	23.22—70.74	0.069	-0.21
	Mid-Tertile	16	7.54	0.58—23.15	0.084	0.23
	Bottom-Tertile	16	-1.21	-8.24—0.29	0.073	0.03
NIDDM	Top-Tertile	26	8.90	5.44—62.27	0.048	-0.22
	Mid-Tertile	27	1.45	0.10—5.37	0.049	-0.15
	Bottom-Tertile	27	-1.42	-10.90—0.10	0.030	-0.22

**Table 30**

Qualitative and Quantitative Serial Changes in Antibody Binding Versus the Associated Serial Changes in the Mean Total Daily Insulin Doses and Glycemic Control in Patients Treated with X-14 70/30 Insulin Mixture: Patients Who Completed the Study.

Study 038 Treatment Group	Antibody Group	N=	Antibody Delta (% binding)	Antibody Range (% binding)	Dose Delta (U/kg)	HgbA1c Delta (%)
IDDM	Top-Tertile	15	39.97	25.59—70.74	0.101	-0.13
	Mid-Tertile	16	8.96	1.03—23.22	0.057	0.14
	Bottom-Tertile	16	-1.06	-8.24—0.58	0.070	-0.04
NIDDM	Top-Tertile	25	26.15	5.44—62.27	0.049	-0.22
	Mid-Tertile	25	1.50	0.15—5.37	0.051	-0.14
	Bottom-Tertile	26	-1.30	-10.90—0.10	0.038	-0.20

Extensive interpatient variability for cross-reacting antibody binding was observed in a related compound. The short duration of the study did not permit serial tracking of individual patient antibody, insulin dose, or HgbA1c levels over time. It is not yet known whether patients with high antibody levels will maintain these levels over time and whether any future increases in antibody levels are limited to those with already significantly elevated values. It is not yet known whether there was any bias in the entry into or the subsequent drop-out in the extension was related to prior antibody levels. Reversibility of the antibody changes could not easily be assessed because of the parallel study design. Patients in the X-14 70/30 treatment arm who did continue into the extension study were not assessed with post-discontinuation antibody levels.

### 13.7.--Clinical Laboratory Studies

Laboratory including routine clinical chemistry studies. Except for alkaline phosphatase, there were no clear trends for aberrations in lab results by treatment group when means from the various treatment periods and studies were assessed. These findings suggest a

difference in the levels of alkaline phosphatase (Table 31). The magnitude of the differences is small, and no patient had pathologic levels ( $\geq 2 \times \text{ULN}$ ), but this finding is consistent with the small, but persistent increases in alkaline phosphatase in the patients with Type 1 diabetes observed in the controlled and extension trials for the parent compound, X-14. It is not known whether the enzyme is derived from a hepatic or bony source.

**Table 31.**  
Changes in Alkaline Phosphatase

	Baseline	Endpoint	Delta
IDDM, X-14 70/30	55.00	54.38	-0.62
IDDM, HI 70/30	54.33	51.02	-3.30
		P=N.S.	P=0.07
NIDDM, X-14 70/30	59.04	57.21	-1.83
NIDDM, HI 70/30	57.36	54.52	-2.84
		P=N.S.	P=N.S.

#### 14.—Reviewer's Commentary

a) U.S insulin manufacturers have known since the late 1980s that they must show a 20% difference in the PK-PD profiles from neighboring insulins within a family line to be permitted to market their product. The sponsor has shown with single-dose cross-over data in normal volunteers that the proposed X-14 insulin mixture is pharmacokinetically distinct from human insulin 70/30 when an  $\text{AUC}_{\text{insulin (0-90 min)}}$  parameter was employed. Pharmacodynamic data were not presented. In addition, the sponsor conducted single-dose euglycemic clamps in normal volunteers using X-14 70/30 versus human insulin 70/30. Similarly, pharmacokinetic differences were apparent when  $\text{AUC}_{\text{insulin (0-90 min)}}$  parameter was employed. It should be noted that the sponsor has carefully selected AUC time intervals that will highlight these differences. The sponsor has also presented selected data from a 4-way cross-over study and shown that X-insulin is distinct from the X-14 70/30 mix. The sponsor, however, has not presented data that show the distinctiveness of X-14 70/30 from the most logical nearest comparators: \_\_\_\_\_ or X-14 50/50. Furthermore, although the sponsor touts more rapid absorption and onset than human insulin 70/30, it is not clear that the PK-PD profile differs from that of human insulin 50/50.

The sponsor should not be allowed to imply or infer that X-14 70/30 is distinct from its nearest comparators. Such inferences will be made by clinicians who read the composition section of any label and or the drug name itself. In addition, the sponsor should include a table that outlines the PK-PD profiles of the various insulins available from NovoNordisk. This will enable clinicians to better select the appropriate insulin for their individual patients. NovoNordisk already has such a product reference guide in print.

b) The PK-PD studies outlined above were done with formulations that differed from the to be marketed formulations. There were no bridging studies. Glucose data collected

collected by the patients in parallel treatment arms suggests that the glucose lowering was more rapid in the X-14 70/30 mixture group than in the human insulin 70/30 mixture use group, but interpretation is limited because of the self-collected nature of the data and because the determinations were made with glucometers.

c) The serial glucose sampling data from study 046 is limited because it was done in 13 patients with NIDDM who likely have confounding endogenous insulin secretion, but the study does suggest that there are temporal differences in the profiles of glucose lowering for the two different insulin mixtures. Unfortunately, it suggests that no one fixed insulin mixture provides lower glucose values, or even glucose excursions, throughout the entire day. Hence, the limited correlation between post-prandial parameters and HgbA1c. There may also be a limited correlation between post-prandial parameters and HgbA1c because the magnitude of difference between the glucose values for the two insulin preparations is relatively small and the duration of difference is relatively short. There may be insufficient time for pathologic glycosylation to occur-limiting the clinical significance of any rapid glucose lowering.

d) Fixed ratio human insulin mixtures cannot provide optimal glucose control because most patients do not have fixed dietary intake/metabolic demands and cannot predict the timing and relative dosing of insulin required for more than a single meal. The convenience of BID dosing, however, may outweigh concerns for tight glycemic control in some patients. Convenience may be further enhanced by immediate pre-meal (versus 30 minute pre-meal) dosing. The HgbA1c data suggest that glycemic control was less than optimal—regardless of treatment mixture. Glycemic control appeared to be equivalent whether the X-14 70/30 mixture or the human insulin 70/30 was employed. Increased insulin doses (~1-6 U/day) may be required to achieve comparable glycemic control when the X-14 mixture is utilized. Similar increased dose needs were observed with X-14 in the original NDA.

e) Hypoglycemia rates also appear to be similar for X-14 70/30 and human insulin 70/30 mixtures. The timing of hypoglycemic events appeared to be similar—regardless of whether a lispro mixture or a comparable human insulin mixture was employed. Curiously, the rates of hypoglycemia appear to exceed those predicted by the DCCT. This may reflect the limitations of a BID dosing regimen with any fixed insulin combination or a higher degree of reporting in this study than in the DCCT.

f) Cross-reacting antibody levels appeared to be higher with the X-14 70/30 product than with human insulin 70/30 product. These differences were apparent despite the parallel design that was employed. The treatment associated differences for such antibodies can tend to be observed more clearly in studies with a cross-over design because there is a high degree of inter-patient variability in such anti-insulin antibody measurements. The antibody findings are consistent with that of the original NDA for X-14 insulin.

g) Cross-reacting antibody levels may increase over time. The sponsor did not submit raw data from the extension study. They intend to submit data in 2001. This limits the kind of conclusions that can currently be made regarding long-term exposure.

h) The significance of cross-reacting insulin antibodies remains uncertain. In the controlled portion of the registration trial, most patients had low levels of cross-reacting antibodies. More patients treated with X-14 70/30 had higher levels of cross-reacting antibodies than patients treated with human insulin 70/30, but the number of patients with higher antibody levels was not limited to isolated outliers. Most importantly, patients with increases in antibody binding did not clearly have increased insulin needs to achieve comparable glycemic control.

i) The range of X-14 permitted in the mixtures suggest that PK-PD profile may vary by as much as  $\pm$  % from batch to batch. With these variations, patients could receive relatively more rapid acting X-14 component and experience unexpected hypoglycemia early in the post-prandial period. Conversely, patients could receive relatively less rapid acting X-14 component and experience unexpected hyperglycemia early in the post-prandial period and more hypoglycemia late in the post-prandial period. This problem will be more clinically significant in patients with the lowest glucose levels, in other words, the best glycemic control.

j) The addition of new mixtures to the widening array of insulin products potentially increases the risk for errors in dispensing and self-administration. The development of a self-explanatory label, unique packaging, and an educational program for professionals and patients would reduce problems.

#### **15.--Regulatory Conclusions**

a) The X-14 70/30 mix may differ from other insulin formulations like NPH, ~~\_\_\_\_\_~~, and X-14 50/50, but the sponsor has not established this and should not be allowed to imply this. Additional studies are needed.

b) Even if the sponsor can establish that this insulin differs from insulins in the X-14 family, the sponsor cannot state or imply that the insulin will provide superior post-prandial glycemic control.

c) The sponsor should not be allowed to imply that X-14 70/30 has more rapid onset of action than human insulin mixtures. Its profile is likely to be similar to that of human insulin 50/50.

d) The sponsor did not provide long-term safety data regarding the clinical significance of cross-reacting antibodies.

**RECOMMENDATION: APPROVABLE WITH STUDIES TO SHOW DISTINCTIVENESS OF X-14 70/30 COMPARED TO OTHER INSULIN PRODUCTS AND WITH CHANGES IN THE LABEL.**

## 16.—Label Review

### 16.1. General

The labels should be primarily pharmacokinetic-pharmacodynamic labels. The labels should include comparative pharmacokinetic and glucodynamic data for the family of X-14 insulin products and the family of human insulin products.

The label should concentrate on the attributes of this particular insulin and how it compares to other insulins. It should not be a guide for the management of diabetes. Nor should it be a guide for the properties of and general use of insulin.

### 16.2. Specific

#### Mechanism of Action

The primary activity of NovoLog 70/30 is the regulation of glucose metabolism. Insulins, including NovoLog 70/30, exert their specific action through binding to insulin receptors. NovoLog 70/30 blood glucose by facilitating cellular uptake of glucose into skeletal muscle and fat, simultaneously inhibiting the output of glucose from the liver.

NovoLog 70/30. In standard biological assays in mice and rabbits, one unit of NovoLog has the same glucose lowering effect as one unit of regular human insulin. However, the effect of NovoLog 70/30 is more rapid in onset compared to human insulin 70/30 due to its faster absorption after subcutaneous injection.

The sponsor implies equipotency of X-14 and human regular insulin based on animal data.

--Comment: The sponsor did not provide any human data.

The sponsor states that the glucose lowering effect occurs sooner because of faster absorption through the skin.

--Comment: This is likely true when compared to 70%NPH+30%human regular insulin. It may not be true compared to 50%NPH+50%human regular insulin.

#### Pharmacokinetics

The single substitution of amino acid proline with aspartic acid at position B28 in NovoLog reduces the molecules tendency to form hexamers with regular human insulin.

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The sponsor states that "The insulin aspart in the soluble \_\_\_\_\_ of \_\_\_\_\_ 70/30 is absorbed more rapidly from the subcutaneous layer than \_\_\_\_\_ human insulin. The remaining 70% is in a crystalline form as insulin aspart protamine which has a \_\_\_\_\_ prolonged absorption profile \_\_\_\_\_"

--Comment. The sponsor has not actually established these data. They are inferred.

*The relative bioavailability of \_\_\_\_\_ compared to NovoLog and human insulin 70/30 indicates that they are absorbed to similar \_\_\_\_\_*

The mean half life (t1/2) of \_\_\_\_\_ : 70/30 was about 8—9 hours \_\_\_\_\_ Serum insulin levels returned to baseline 15—18 hours after a subcutaneous dose. \_\_\_\_\_

The sponsor included some textual information on the PK comparisons of X-14 70/30 and human insulin 70/30.

--Comment: The sponsor did not include any comparative PK data with other members of the X-14 insulin family or NPH. The sponsor did not include PK graphics. Instead they included glucodynamic data from 13 patients with NIDDM. The effect on the glucodynamics is exaggerated by the scale of the glucose axis. Any PK-PD data from this population will be confounded by endogenous insulin secretion.

Distribution and elimination \_\_\_\_\_ has a low binding to plasma proteins, 0-9%, similar to regular insulin. After subcutaneous administration in normal volunteers (n=24), \_\_\_\_\_ was more rapidly eliminated with an average apparent half-life of 81 minutes compared to 141 minutes for regular human insulin.

--Comment: Biopharm should comment.

#### Pharmacodynamics

The sponsor has included graphic pharmacodynamic data from normal volunteers.

--Comment: the sponsor did not include information on the scatter of the data for the two 70/30 insulins, indicated the time of injection, or provided a scale or descriptor for the Y axis.

#### Special Populations: Children and adolescents

--Comment: \_\_\_\_\_

#### Gender

The sponsor states that \_\_\_\_\_

--Comment: The sponsor has not established that there are no gender differences. The gender disparity for the changes in HgbA1c observed in the patients with IDDM treated with X-14 70/30 was not seen in the IDDM patients treated with human insulin 70/30 or the NIDDM patients treated with X-14 70/30 insulin. Although this is likely a result of the small sample size, the sponsor has not yet provided data to refute the finding.

--Comment: Even if HgbA1c values were the same for male and female patients, gender differences could be postulated for the temporal aspects of PK-PD because women have more SQ tissue which may make the differences between human insulins and X-14 insulins smaller.

#### Renal impairment

The sponsor provides extensive information on insulin and renal dysfunction.

--Comment: The sponsor should just state that the effect of renal impairment on the PK of X-14 70/30 has not been assessed—similar to the wording in the lispro mix labels. (The lispro mix labels include information on impaired renal function and the drug disposition of lispro in patients with NIDDM.)

#### Hepatic impairment

The sponsor provides extensive information on insulin and renal dysfunction.

--Comment: The sponsor should just state that the effect of hepatic impairment on the PK of X-14 70/30 has not been assessed—similar to the wording in the lispro mix labels. (The lispro mix labels include information on impaired hepatic function and the drug disposition of lispro in patients with NIDDM.)

#### Clinical Studies

--Comment: Although the sponsor could potentially state that glycemic control as measured by HgbA1c and hypoglycemia as assessed by events requiring intervention by a third party appear to be comparable for human insulin 70/30 and X-14 70/30, such statements were not included in the lispro mix labeling because sponsors were told that mixture labels would be primarily pharmacokinetic and dynamic in nature. Furthermore, in the 3 month trial with ~300 patients, no glucose assessments were made by a laboratory. The only glucose assessments were glucose meter readings obtained by patients in an open-label trial on 3 days. Among patients who submitted the 8 point glucose profiles, there were patients who did not submit all 8 values. It is unclear as to whether patients could discard selected 8-point profiles because sampling could occur on a single day over a one week period. The validity of the glucose profile can also be questioned because the measured glucose profile was somewhat higher for the patients on

human insulin 70/30, reported mean: 9.12 mmol/L, than for X-14 70/30, reported mean 8.75, and the reported ITT ANOVA HgbA1c for patients on human insulin 70/30, 8.12%, was numerically less than the reported ITT ANOVA HgbA1c for X-14 70/30, 8.14 (Vol.1, p 293). Furthermore, there was no correlation between the 90 minute post-breakfast glucose, post-breakfast glucose excursion, mean glucose level and the validated endpoint parameter, HgbA1c. Hypoglycemia rates were comparable for the two insulins. It could also be noted that the self-collected 2 AM glucose data do not support the Sponsor's contention in the initial NDA that there was less nocturnal hypoglycemia. Mean glucose values were 8.12 mmol/L for both insulins (Vol. 1, p 296). The sponsor may not include data from the two week study 046 with its 13 patients with NIDDM (Vol. 1, p286). The study is too small and too short to be assessed as a clinical trial. However, it should be noted that post-prandial glucose parameters were noted be greater in magnitude after lunch for patients treated with X-14 70/30 and greater after breakfast and dinner for patients treated with human insulin 70/30. Nocturnal glucose values were not hypoglycemic and were comparable for the two treatment groups.

The sponsor states that

#### Indications and Usage

\_\_\_\_\_ 70/30 is indicated for the treatment of patients with diabetes mellitus for the control of hyperglycemia.

--Comment: The statement \_\_\_\_\_

\_\_\_\_\_ should be deleted. The sponsor did not submit data to the initial NDA submission comparing human regular insulin and X-14 70/30. The sponsor does have some data \_\_\_\_\_ More appropriate comparators include NPH and/or \_\_\_\_\_ and X-14 50/50 or human insulin 50/50. It should also be noted that the reference (from volume 46, p184) cited by the sponsor compares data from human regular insulin and X-14. The lispro 75/25 mix label compares the onset and duration of action for lispro 75/25 and human insulin 70/30 and indicates that this is achieved by adding lispro to a lispro protamine suspension. The duration of action for X-14 70/30 may be somewhat shorter than that of human insulin 70/30 as suggested by the higher fasting glucose (glucometer) levels in the patients with IDDM.

#### Warnings

Precautions

--Comments: The sections for renal impairment, hepatic impairment, and allergy should parallel the comparable sections in the Division amended label for X-14.

--Comment: There were two cases of rash in which the patients were discontinued. The patient using the X-14 mixture had pruritus; the patient using the human insulin 70/30 mixture did not. There were also several other persistent skin reactions, and these were most prevalent in patients using the X-14 mixture. Unfortunately, the documentation for all of these reactions was poor. It would be better to use the Novolog label phrasing for severe reactions.

--Comment: The sponsor did not systematically assess for local injection site reactions so they cannot dismiss their potential occurrence.

Precautions-Antibody production

--Comment: The animal data suggest that X-14 70/30 and NPH are more antigenic than human insulin 70/30. Because of the protamine in X-14 70/30, the comparative data from the 70/30 clinical trial should be included in the label. The sponsor cannot use 12 month data from X-14 in any label without presenting it for formal review. All that has been presented is a small summary and graph.

Information for patients-Laboratory tests

--Comment: The need to monitor blood glucose and HgbA1c is standard language.

Information for patients-Drug interactions

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Mixing of insulins

--Comment: The sponsor appropriately states that X-14-70/30 should not be mixed with other insulins.

Carcinogenicity

--Comment: PharmTox should comment.

Pregnancy

--Comment: PharmTox should comment.

Pregnancy-Nursing mothers

The sponsor states that it is not known whether X-14 70/30 is excreted into human milk.

--Comment: The sponsor should not comment on dosing in lactating/nursing mothers.

Geriatric use

Clinical studies of 70/30 did not include sufficient numbers of aged 65 and over to determine whether they respond differently younger

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

--Comment: The sponsor has limited glucose data, but some of these data are similar to that from another analogue mix which suggests that the early glucose lowering effect appears to be less in the patients with Type 2 diabetes than in patients with Type 1 diabetes. The former tend to be older than the latter. It is not known whether this is related to poorer glycemic control and/or more insulin resistance or increased obesity in the patients with Type 2 diabetes. Furthermore, it is known that the composition of the skin and the supporting tissues changes-especially in those aged  $\geq 75$  years.

Adverse Reactions

.....Other: .....

--Comments: This section should follow the Division recommended format for the X-14 label. Small differences in alkaline phosphatase were observed in study 038 as well. The statistical significance was not as great—in part because of the smaller study population. Data from the extension studies was not available to more completely assess the persistence of this enzyme level difference in the population as a whole and in individual patients.

Dosage and administration

*NovoLog Mix 70/30 is intended only for subcutaneous administered intravenously.*

*NovoLog Mix 70/30 should not be*

*NovoLog Mix 70/30 will vary among patients and should be determined by the health care professional familiar with the patient's metabolic needs, eating habits, and other lifestyle variables. As with all insulins, the duration of action will vary according to the dose, injection site, blood flow, temperature, and level of physical activity.*

*regimens of*

Summary of            Properties of Insulin Products (Pooled Cross-study Comparison)\*

<i>Insulin Products</i>	<i>Dose, U/kg</i>	<i>Time of peak activity, hours after dosing</i>	<i>Percentage of Total Activity occurring in the First 4 Hours</i>
<i>NovoLog</i>			
<i>Novolin R</i>			
<i>Novolin 50/50</i>			
<i>NovoLog Mix 70/30</i>			
<i>Novolin 70/30</i>			
<u>          </u>			
<u>          </u>			
<u>          </u>			
<i>Novolin N</i>			

\*The information supplied in table 1 indicates when peak activity can be expected and the percent of the total insulin activity occurring during the first 4 hours.

-Specifics of the studies from which the table was derived.

-The values represent means with ranges provided in the parentheses.

--Comment: With the proliferation of insulin compounds on the market, the label will be an important source of data for the physician attempting to find a pharmacodynamic profile appropriate for the patient. For example, Novolin 50/50 may be equivalent to X-14 70/30.

--Comment: Because this is a fixed combination, titration to good control without hypoglycemia is problematic. Indeed the relatively high rates of hypoglycemia in both treatment arms may reflect the limitations of a BID dosing regimen with a fixed insulin combination.

--Comment: Information on drug activity should be in the preceding paragraph.

--Comment: The sponsor provides extensive instructions for cartridge use that uses language directed at the patient. Most of this should be included in the patient brochure.

How supplied

70/30 is available in the following package sizes: each presentation containing 100 Units of insulin aspart per mL (U-100).

10 ml

3 ml PenFill cartridges

3 ml Prefilled syringe

--Comments: none

**/S/**

Elizabeth Koller, M.D.

**/S/**  
8/11/00

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ON ORIGINAL**

## 15.1.--Figure Legends

Figure 1. HgbA1c versus Glucose Excursion in IDDM Patients Treated with X-14 70/30  
The HgbA1c at endpoint was compared to the glucose excursion derived from the 90 minute post-breakfast glucometer reading minus the fasting glucometer reading at endpoint. The r value was not consistent with an association.

Figure 2. HgbA1c versus Glucose Excursion in IDDM Patients Treated with Human Insulin 70/30  
The HgbA1c at endpoint was compared to the glucose excursion derived from the 90 minute post-breakfast glucometer reading minus the fasting glucometer reading at endpoint. The r value was not consistent with an association.

Figure 3. HgbA1c versus Glucose Excursion in NIDDM Patients Treated with X-14 70/30  
The HgbA1c at endpoint was compared to the glucose excursion derived from the 90 minute post-breakfast glucometer reading minus the fasting glucometer reading at endpoint. The r value was not consistent with an association.

Figure 4. HgbA1c versus Glucose Excursion in NIDDM Patients Treated with Human Insulin 70/30  
The HgbA1c at endpoint was compared to the glucose excursion derived from the 90 minute post-breakfast glucometer reading minus the fasting glucometer reading at endpoint. The r value was not consistent with an association.

Figure 5. HgbA1c versus AUC-Glucose in IDDM Patients Treated with X-14 70/30  
The HgbA1c at endpoint was compared to the glucose area-under-curve derived from the endpoint fasting and 90 minute post-breakfast glucometer readings. The r value was not consistent with an association.

Figure 6. HgbA1c versus AUC-Glucose in IDDM Patients Treated with Human Insulin 70/30  
The HgbA1c at endpoint was compared to the glucose area-under-the-curve derived from the endpoint fasting and 90 minute post-breakfast glucometer readings. The r value was not consistent with an association.

Figure 7. HgbA1c versus AUC-Glucose in NIDDM Patients Treated with X-14 70/30  
The HgbA1c at endpoint was compared to the glucose area-under-the-curve derived from the endpoint fasting and 90 minute post-breakfast glucometer readings. The r value was not consistent with an association.

Figure 8. HgbA1c versus AUC-Glucose in NIDDM Patients Treated with Human Insulin 70/30

The HgbA1c at endpoint was compared to the glucose area-under-the-curve derived from the fasting and 90 minute post-breakfast glucometer readings. The r value was not consistent with an association.

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Fig. 1

### HgbA1c versus Glucose Excursion (X-14 70/30) in IDDM Patients (Parallel Trial)

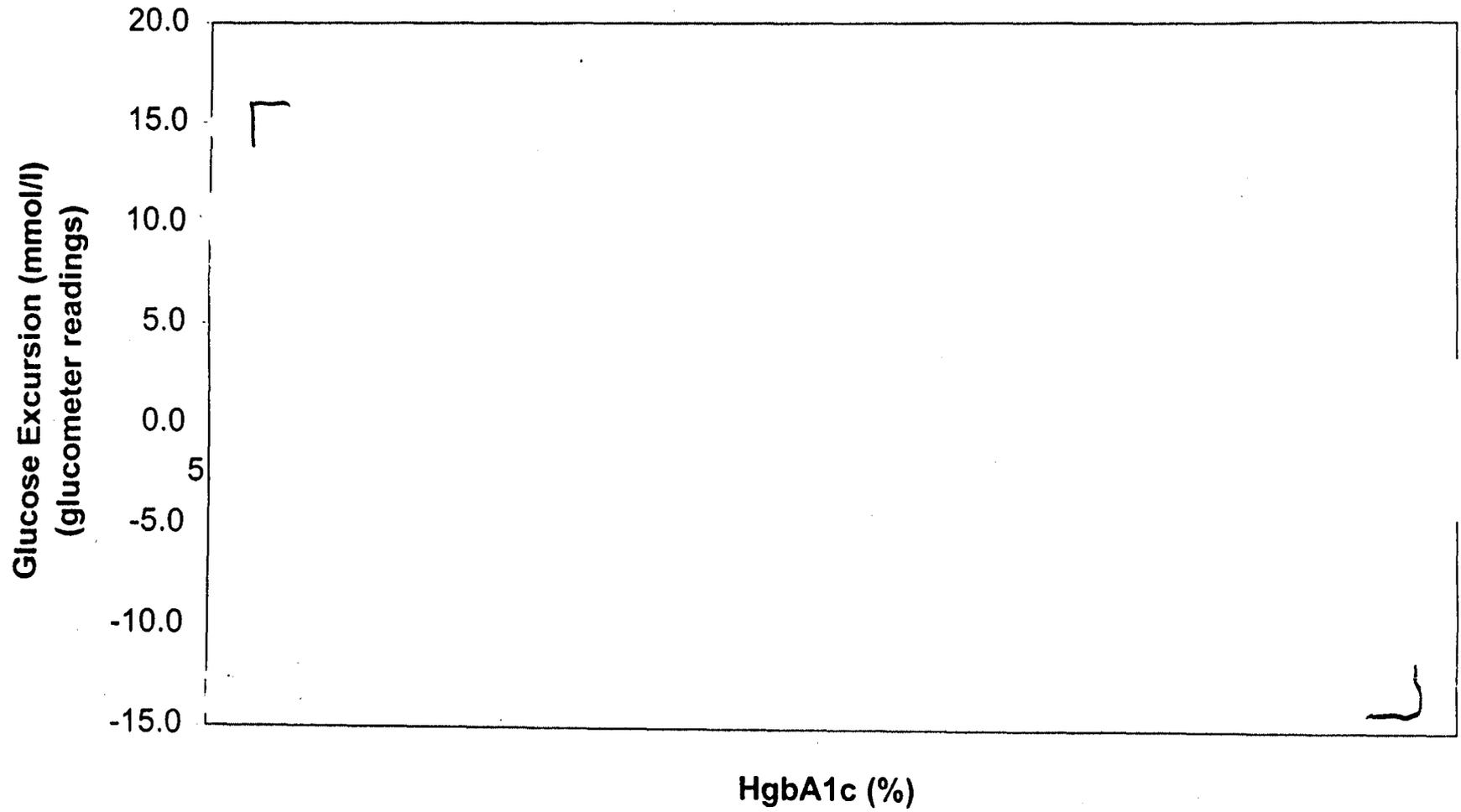


Fig. 5

### HgbA1c versus AUC-Glucose-90 Minute (X-14 70/30) in IDDM Patients (Parallel Trial)

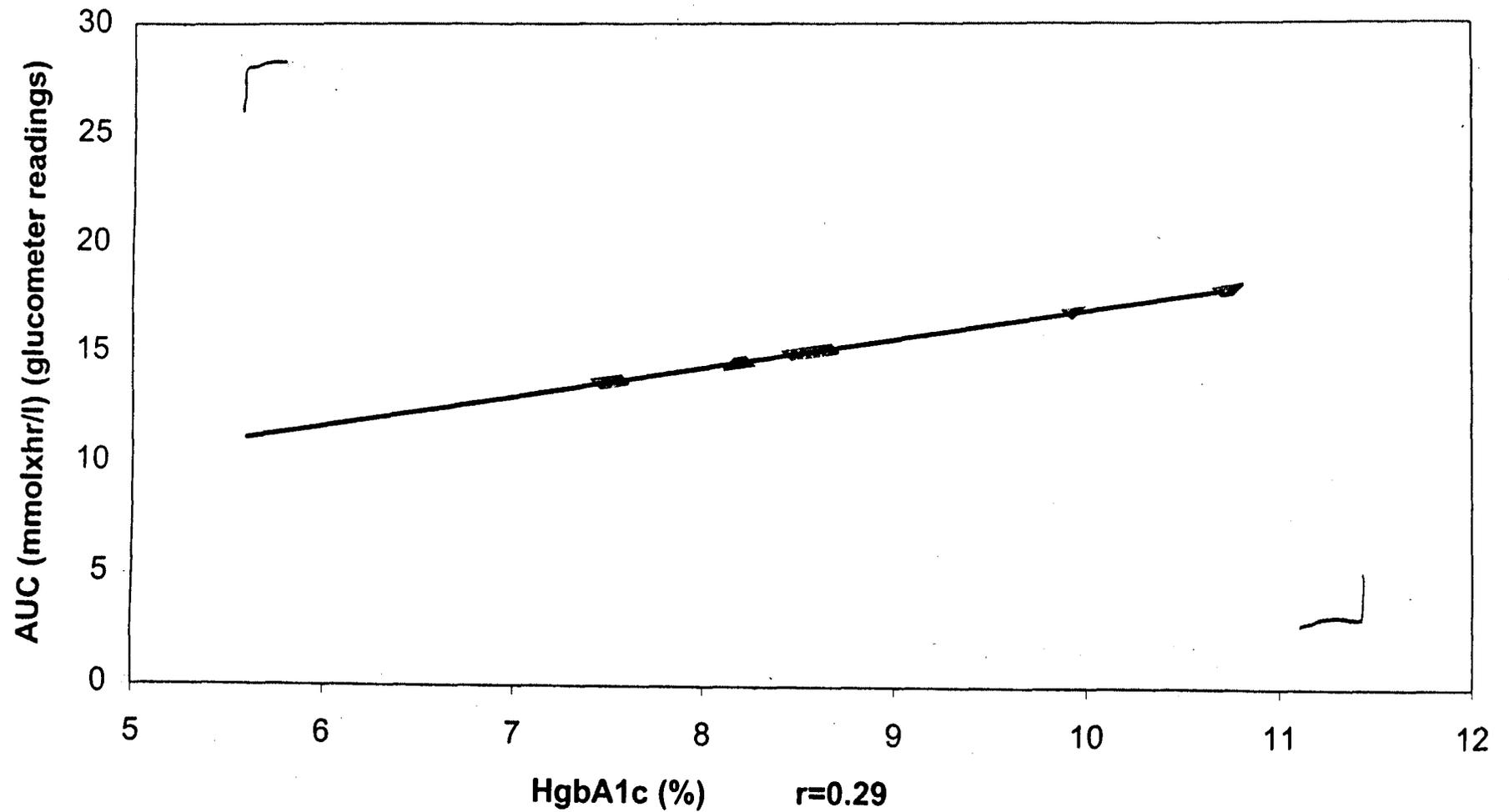


Fig. 7

### HgbA1c versus AUC-Glucose-90 Minute (X-14 70/30) in NIDDM Patients (Parallel Trial)

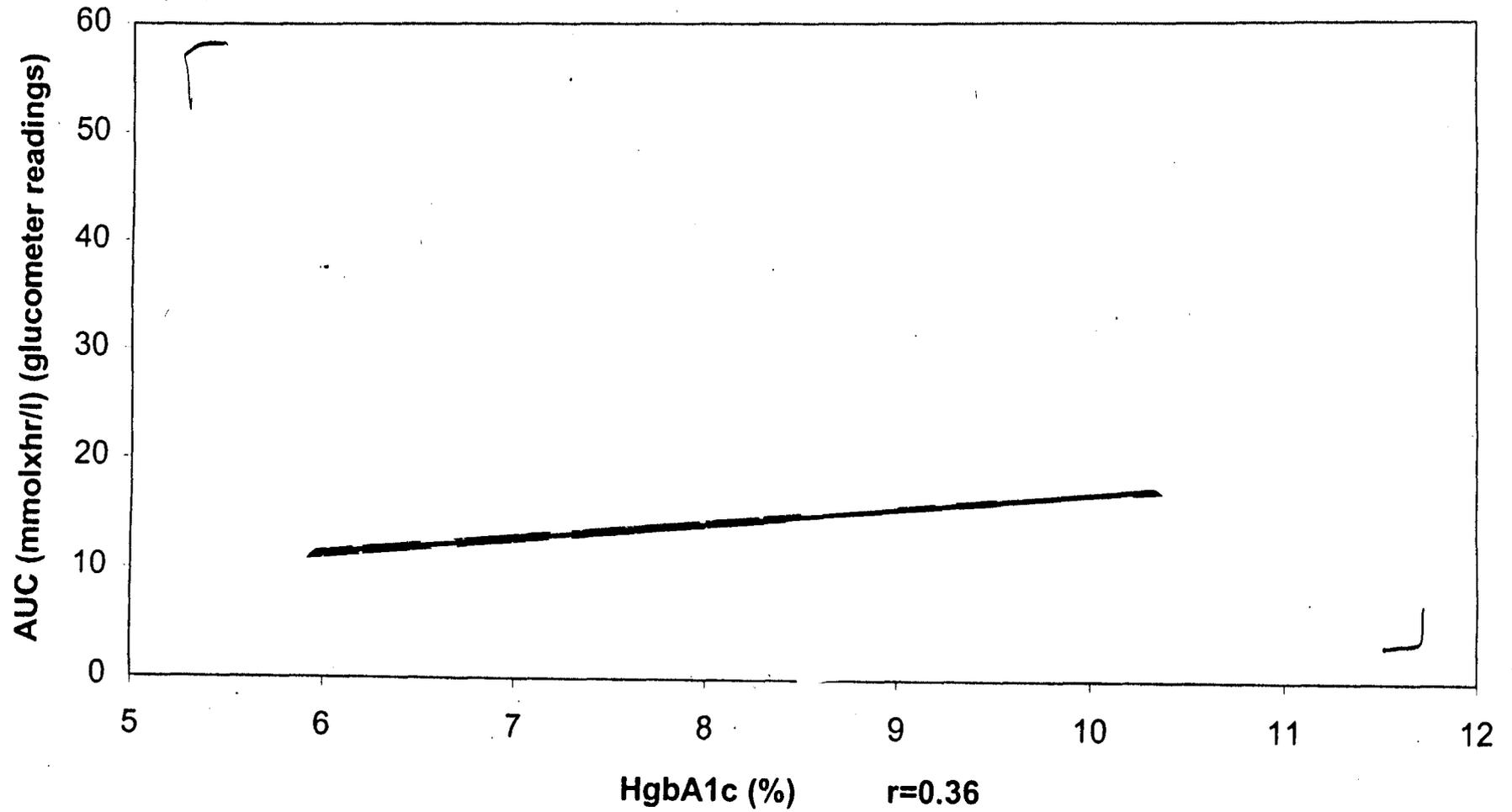
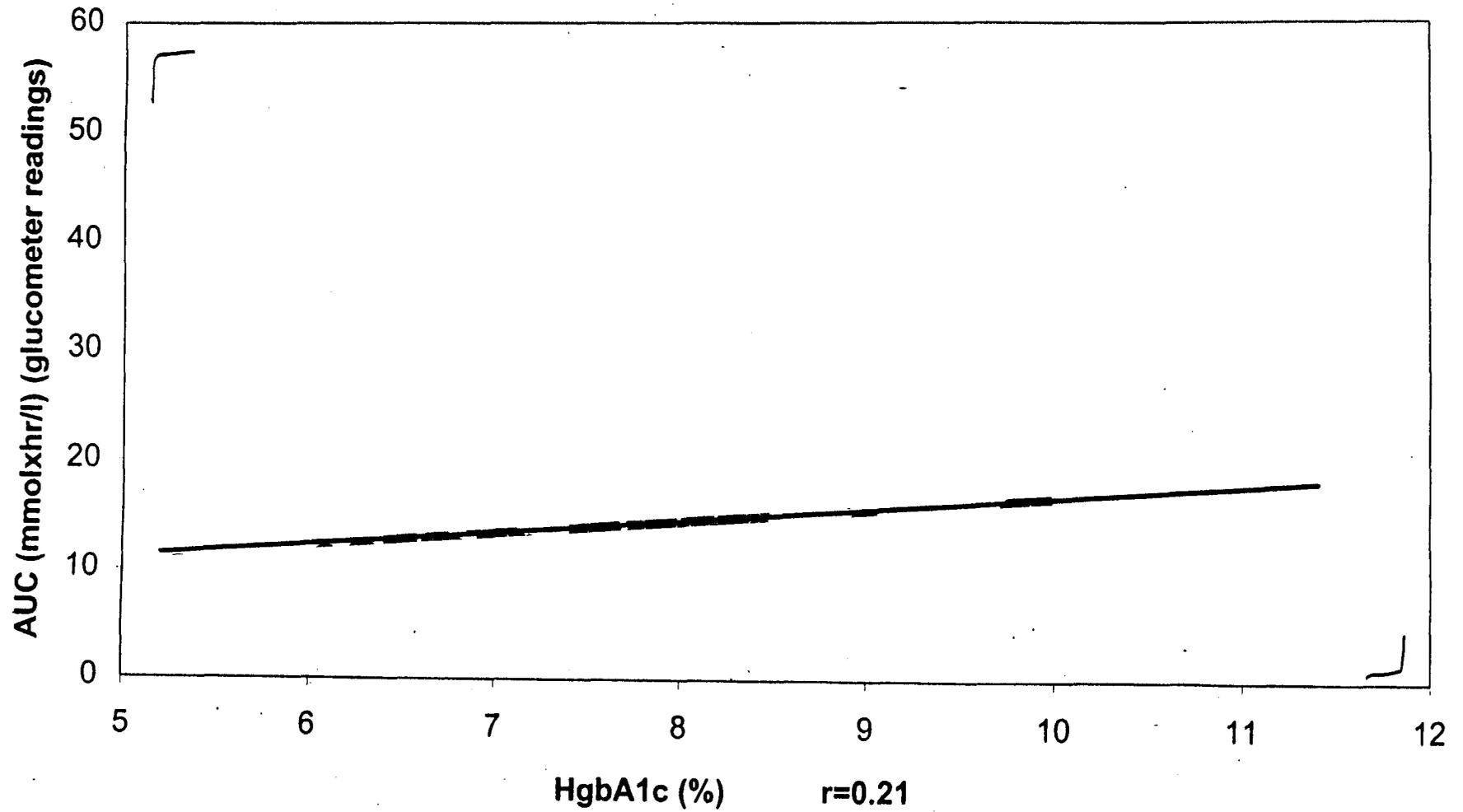
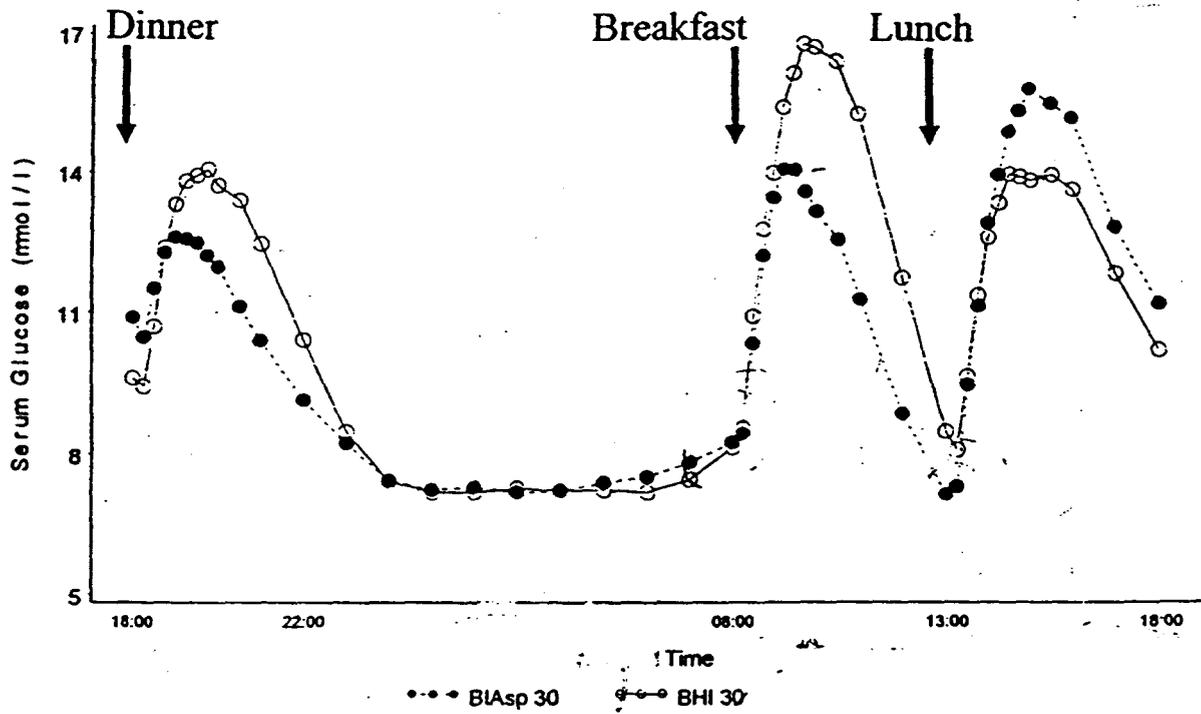


Fig. 8

### HgbA1c versus AUC-Glucose-90 Minute (Human Insulin 70/30) in NIDDM Patients (Parallel Trial)



Appendix 1  
Glucose Sampling over 24 hours in 13 Patients with NIDDM



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Appendix 2  
Sample Case Report Form

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