CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-017
21-018

MEDICAL REVIEW(S)

1. Medical Officer Review
1.1. Administrative Summary
1.1.1. NDA: #21017 and 21018
1.1.2. Review: #1
1.1.3. Submissions
1.1.3.1. Paper submission: 12/21/98
1.1.3.2. CANDA submission: none
1.1.3.3. Major amendment: none
1.1.3.4. Other submissions:
4/20/99 Safety update-2 submissions
9/10/99 Geriatric listing-2 submissions
9/22/99 Diskette #1
9/24/99 IODI-extension data
10/25/99 Diskette #2
10/31/99 FAX
11/8/99 Safety update-2 submissions
1.1.3.5. Review completed: 11/5/99
1.2. Drug Name
1.2.1. Generic names:
25% Insulin Lispro and 75% Insulin Lispro Protamine/low mix
50% Insulin Lispro and 50% Insulin Lispro Protamine/mid mix
1.2.2. Proposed trade names: Humalog Mix 25→Humalog Mix 75/25
Humalog Mix 50→Humalog Mix 50/50
1.3. Sponsor: Lilly Laboratories
1.4. Pharmacologic category: diabetic; insulin analogue
1.5. Proposed indications: Dosing BID
1.6. Dosage form and route of administration:
1.6.1. Dosage form: vials for injection and cartridges for use in specified pens.
1.6.2. Dosage: to be titrated
1.6.3. Route of administration: Subcutaneous
1.7. NDA drug classification: Standard
1.8. Important related drugs: human insulin (semi-synthetic and recombinant), Animal insulins, and insulin-like growth factor
1.9. Related reviews: #20563 original review and 8/31/98 supplements
1.9. Materials reviewed: Volumes:
NDA #21017 1-3, 73-80, 83-85, 89, and 90
NDA #21018 1-3, 22-24, 37, 42, 47-62, 64, and 65
1.10. Table of contents

2.--Introduction

The Diabetes Control and Complications Trial (DCCT) established that good glycemic control decreased the risk for long-term diabetic complications in patients with Type 1 diabetes mellitus. Intensive therapy was associated with lower HgbA1c values and better clinical outcomes than conventional therapy. Typically, intensive therapy involves pre-prandial dosing with a more rapid acting insulin in conjunction with a longer acting insulin to provide a basal level of control throughout the day. Four or more injections are required daily. Alternatively, patients utilize subcutaneous insulin infusions delivered by pump. A basal rate is based on the anticipated activity level. Insulin boluses are given for food consumption. Additional insulin is given in the event of unexpected hyperglycemia. Insulin rates/injection doses are reduced in the event of hypoglycemia.

Intensive therapy requires frequent monitoring of blood glucose. Fingerstick sampling is typically performed between four and six times per day. Some patients are unable or unwilling to use intensive therapy because of the number of insulin injections required, the complexities of pump use, and/or the number of glucose fingerstick checks. Unfortunately, tight glycemic control is also associated with increased risk of hypoglycemia. These patients and their physicians may elect to pursue conventional therapy with BID dosing regimens. Typically a rapid acting insulin is given in conjunction with a longer acting insulin e.g. NPH, lente, or ultralente at breakfast and with the evening meal. The rapid acting insulin provides glycemic control for the meal immediately following. The longer acting insulin provides insulin coverage for the mid-day meal, the pre-bedtime snack, and the nocturnal interval. If patients mix their own insulin, the ratio of rapid acting insulin to longer acting insulin can be adjusted for anticipated meal size and physical activity. Pre-mixed insulins have a fixed ratio. This may be perceived as "easier" by patients, and it reduces potential contamination of the short acting insulin vial with protamine, a compound use to delay absorption. Fixed ratio insulins, however, are less flexible, particularly for patients with erratic schedules. Most patients are unable to achieve tight glycemic control with BID insulin dosing and this is accentuated in patients using fixed ratio insulins.

The development of pre-mixed insulins incorporating the rapid acting insulin analogue, lispro, faced some unanticipated formulation-mixing problems. NPH insulin could not be directly added to lispro. Analysis of early data showed that the pharmacokinetics of lispro and human insulin NPH differed when the two insulins were mixed and when they were given as simultaneous, but separate, injections. The difference was most prominent when the protamine content of the NPH was higher. It has been hypothesized that the lispro insulin analogue molecules and the human insulin molecules reached a new equilibrium after mixing; some of the lispro was exchanged for human insulin-resulting in 4 insulin species: soluble lispro, soluble human regular, protamine associated lispro, and protamine associated human regular. The appearance of human regular was thought to account for the blunting of C-max and T-max. To avoid the formation of regular human insulin, the sponsor prepared an NPH equivalent with lispro, Neutral Protamine Lispro (NPL). NPL was mixed with lispro to prepare fixed ratio insulins that would have a more rapid onset of action than the currently available fixed dose insulins (70/30: 70% NPH+30% human

regular and 50/50: 50% NPH+50%human regular) and could be given immediately before meals (versus 30-45 minutes before meals).

The sponsor has developed two such fixed ratio insulins: mid-mix (50% lispro+50% NPL) and low mix (25% lispro+75% NPL). The sponsor has presented efficacy data from five trials: IODI, IODK, IODL, IODM, and IODN and extension trial data for IODI, IODK, and IODL. Three of the trials (IODK, IODM, and IODN) assessed the drug products being submitted for registration. Two of the trials (IODI and IODL) assessed products for which registration was not being sought[redacted] Because the primary goal of the NDA review was to assess long-term safety of lispro products, the antibody changes in from the IODI and IODL extension studies were included in the review.

3.--Prior Agreements
In lieu of extensive clinical testing, the sponsor was requested to provide:
a--pharmacokinetic and pharmacodynamic studies that would demonstrate that each mixture was distinct from the other lispro mixtures and from lispro as well as NPH (or NPL),
b--labeling that would show the how the lispro products compared to one another on a pharmacokinetic-pharmacodynamic (PK-PD) basis,
c--labeling that would show how the lispro products compared to the Humulin products on a PK-PD basis, (Head-to-head comparison studies would not be required.)
d—and multi-year studies to assess long-term changes in the levels of cross-reacting antibodies and the effect of these antibodies on the doses of insulin required to maintain comparable levels of glycemic control as measured by HgbA1c.

4.--Objectives
The sponsor has sought to show that:
a--the PK-PD profiles of mid-mix and low mix are distinct from other lispro products,
b--there were no major differences in glycemic control for patients treated with lispro mixtures vs Humulin mixtures, and
c--the levels of cross-reacting antibodies did not increase over time.

5.--CANDA
There was no CANDA submission. Additional data were provided on EXCEL spread sheets.

6.--Chemistry issues
Recombinant lispro insulin analogue is produced in E. coli using DNA technology is similar to that employed by the sponsor for the production of other insulin products. Neutral protamine lispro is produced by adding protamine to lispro. Neutral protamine lispro and lispro are combined in fixed ratios to prepare mid-mix and low mix insulins. The specifications for the low mix permit the soluble component to range from[redacted] U/ml at expiry. The specifications for the high mix permit the soluble component to range from[redacted]U/ml at expiry. (The width of these ranges are the subject of outstanding

questions raised by the Division chemists.) The suspension is then buffered with a phsophate buffer to a final pH of 7.0 to 7.8. Both cartridges and vials are filled with pre-mixed suspensions prepared in this way.

7.--Pre-clinical Issues

The sponsor did not conduct any additional pharmacology studies in support of these NDAs.

8.--Pharmacokinetic-Pharmacodynamic Issues

In a five-way cross-over glucose clamp study in normal volunteers (IODJ; n=31), lispro, medium mix (50/50), low mix (25/75), and NPL were shown to have distinct pharmacokinetic profiles. Pharmacokinetic profiles were defined as distinct if there was a 20% differences in the log transformed pharmacokinetic parameters of insulin pairs. (See table 1.) The glucose profiles, as measured by glucose infusion rate, were, not unexpectedly, less distinct. (See table 2.) In this study, which used 0.3 U/kg of insulin, high mix (75/25) was pharmacokinetically distinct from lispro and medium mix. The high mixture was not glucodynamically distinct from either lispro or the medium mix. Its profile was essentially the same as that of the medium mix.

In a four-way cross-over glucose clamp study, in Type1 diabetic patients (IOGI; n=12; 0.3 U/kg), the glucose infusion rates associated with NPL were distinct from that of the low mix and mid mix and the mid mix was distinct from the low mix.

In a two way cross-over study in normal volunteers (IOBS; n=8; 0.4 U/kg), NPL was shown to have a somewhat earlier C-max than NPH, but otherwise had a similar pharmacokinetic profile.

Table 1

Comparisons of Pharmacokinetic Parameters of Insulins in the Lispro Family Using Log Transformed Ratios (Data from Dr. Fossler)

Pharmacokinetic Parameter	Insulin Pair	Mean Ratio	90% Confidence Interval
AUC-insulin(0-t)	Low Mix vs NPL	101.2	91.8—111.7
	Mid Mix vs Low Mix	111.9	101.5—123.5
	High Mix vs Mid Mix	87.8	79.6—96.9
	Lispro vs High Mix	102.0	92.5—112.5
AUC-insulin(0-5 hr)	Low Mix vs NPL	160.2	149.3—171.9
	Mid Mix vs Low Mix	140.6	131.1—150.9
	High Mix vs Mid Mix	121.8	113.6—130.7
	Lispro vs High Mix	138.7	129.3—148.9
Cmax-insulin	Low Mix vs NPL	175.4	158.9—193.7
	Mid Mix vs Low Mix	164.1	148.6—181.2
	High Mix vs Mid Mix	130.0	117.7—143.5
	Lispro vs High Mix	149.7	135.5—165.3

Table 2
Comparisons of Pharmacodynamic Parameters of Insulins in the Lispro Family Using Log Transformed Ratios (Data from Dr. Fossler)

Pharmacodynamic Parameter	Insulin Pair	Mean Ratio	90% Confidence Interval
Rmax	Low Mix vs NPL	126.5	114.9—139.1
	Mid Mix vs Low Mix	113.8	103.5—125.2
	High Mix vs Mid-Mix	108.8	98.9—119.7
	Lispro vs High Mix	113.2	102.9—124.5
AUC-glucose (0-t)	Low Mix vs NPL	119.0	105.8—133.9
	Mid Mix vs Low Mix	96.7	85.9—108.8
	High Mix vs Mid Mix	97.9	87.0—110.1
	Lispro vs High Mix	83.0	73.7—93.3
AUC-glucose (0-5)	Low Mix vs NPL	173.9	154.5—195.7
	Mid Mix vs Low Mix	122.6	109.0—138.0
	High Mix vs Mid Mix	112.7	100.2—126.8
	Lispro vs High Mix	114.6	101.8—128.9

Rmax=maximal glucose utilization or maximal glucose infusion rate

In a three way cross-over glucose clamp study in normal volunteers (IOCM; n=6; 0.3 U/kg), self-mixed combinations of low mix, mid mix, and high mix were shown to be pharmacokinetically similar to the same insulin combinations when given as pre-mixtures in IODJ. (Patients were crossed-over to other extemporaneous mixtures. They were not crossed over to the comparable pre-mixture.)

The sponsor did not do direct, head-to-head glucose clamp studies comparing mid mix with human insulin 50/50 or low mix with human insulin 30/70[1] or 20/80. Rather a subset of patients (n=11) with Type 1 diabetes who were part of the clinical trial IODM (mid-mix vs 50/50 at breakfast and low mix vs 30/70) were assessed for free insulin levels and postprandial glucose levels. (It is not clear how these patients were selected.) Patients were crossed-over for the two insulin regimens, 50/50 and mid mix. Patients were given the human insulin doses 30 minutes before breakfast administration and the insulin analogue immediately before breakfast administration. The meals consisted of actual foodstuff and attempts were made to standardize them for the individual patient. Patients were not given a standard Sustacal challenge. The pharmacokinetic and pharmacodynamic profiles were similar for the two insulin mixtures after correction for the time of injection.

Similarly, in IOFX, 31 patients with Type 1 diabetes were treated with a dose of insulin, 30/70 or low mix, standardized to the patient respectively 30 minutes or immediately

[1] A modified glucose clamp study (IOHL) comparing low mix versus 30/70 was conducted in Type 2 patients. High variability was observed and, reportedly, it was not possible to increase sample size. The data were not included for review. (Safety-update11/8/99)

prior to a supper standardized to the patient. pharmacokinetic and pharmacodynamic profiles were similar for the two insulin mixtures after correction for the time of injection.

No comparable studies were done for low mix and 20/80.

9.--Study design for clinical trials

9.1.--General

The sponsor conducted three six-month, cross-over, open-label active control, 1:1 randomization clinical trials with the mixtures proposed for registration: IOAK, IODM, and IODN. (See table 3.) All studies were conducted outside the U.S. (See table 4.) Type 2 diabetic patients were enrolled in all three studies. Type 1 patients were enrolled in IODK and IODM. Diabetic patients between the ages of 18 and 75 were enrolled in IODK and IODM. Diabetic patients between the ages of 18 and 70 were enrolled in IODN. All patients were to have had experience with insulin therapy. (See inclusion criteria.) During the lead-in 0—4 week lead-in period, patients were started on human insulin mixtures. Patients were then randomized to three months of treatment with a lispro mixture or human insulin mixtures. (See table 3.) Patients performed home glucose monitoring. Insulin doses were titrated to maximize glycemic control and minimize hypoglycemia. Patients were then eligible to enter extension trials for IODK. (See table 5.) Longitudinal cross-reacting insulin antibody data were collected in three extension trials.

Table 3

Design Features of Clinical Studies

Study	Insulin Type	Dosing	Study Type	Tx Arm Duration	Blinding	Glucose Measure
IODK	20/80 mix vs lispro low mix	BID	cross-over	3 months	no	HgbA1c
IODM	50/50 mix vs lispro mid-mix 30/70 mix vs lispro low mix	at breakfast at supper	cross-over	3 months	no	HgbA1c
IODN	30/70 mix vs lispro low mix	BID	cross-over	3 months	no	HgbA1c

Tx=treatment

20/80=20% human regular insulin+80% human insulin NPH (not marketed in U.S.)

30/70=30% human regular insulin+70% human insulin NPH (marketed in U.S.)

Table 4

Other Study Features

Study	# Investigators	# Countries	Conducted in U.S.	# Randomized Patients/Investigator
IODI	19	5	No	8.7
IODK	21	5	No	6.0
IODL	14	5	No	10.7
IODM	19	5	No	5.3
IODN	12	3	No	7.4

Table 5
Design Features of Extension Studies

Study	Insulin Type	Duration	Both Treatment Arms Eligible[1]	Insulin Dose Recorded	Antibodies	Measurement of HgbA1c
IODI[1]	Lispro ac NPL basal	12 months	No	Yes	Yes	No
IODK	Low mix BID	18 months	No	Yes	Yes	No
IODL	High mix ac NPH basal	18 months	No	No	Yes	No

[1]IODI was a 12 month parallel study. Only patients who had received lispro products were eligible for entry into the extension trial.
AC=before meals

9.2.--Patient Selection Criteria
9.2.1.--Inclusion Criteria
Aged 18-75 years inclusive (IODN)
18-70 years inclusive (IODK, IODM)
Diabetes mellitus-Type 1 or Type 2 (IODI, IODK, IODM)
Type 1 (IODL)
Type 2 (IODN)
Diabetes duration-2 years (IODK, IODL, IODM)
Prior insulin regimen-BID (IODI)
BID for at least 120 days (IODM)
QD or BID for at least 120 days (IODK)
Experience with insulin mixes (self-mix, commercial mix) (IODN)
Intensive insulin therapy for at least 120 days (IODL)
HgbA1c <150% of the ULN (unspecified central lab) (IODK, IODN)
≤9.5% (by [redacted]) (IODM)

9.2.2.--Exclusion Criteria
Insulin allergy
Profound insulin resistance
BMI >35 kg/m2 (IODK, IODM)
Two hypoglycemic episodes requiring intervention by a third party within the last six months
Cerebrovascular or severe peripheral vascular disease (IODK, IODM)
Class 3 or 4 cardiac disease
Renal disease (creatinine >2 mg/dl, transplantation, or dialysis)
Proliferative retinopathy (IODK, IODM)
Liver disease (including SGOT >2x ULN[IODK, IODM] >3x ULN [IODN])
Hematologic problems or adrenal insufficiency
History of cancer (other than skin cancer) (IODM)

Use of oral anti-diabetic agents– within 30 days of entry (IODK, IODM)
--within 14 days of visit 1 (IODN)
Use of systemic steroids or high risk of requiring systemic steroids
--for longer than one week (IODK, IODM)
--for longer than two weeks (IODN)
Use of beta blockers (IODK, IODM)
Participation on other studies with lispro (but not necessarily prior exposure to lispro products) (IODK, IODM)
Pregnancy or risk of pregnancy or lactation

9.3.—Patient Characteristics-Special Populations
59, 37, and 0% of randomized patients respectively were Type 1 patients in studies IODK, IODM, and IODN. (See table 6.) 46, 55, and 45% of randomized patients respectively were male in studies IODK, IODM, and IODL. (See table 6.) In IODK, the mean age for patients was 47.0 years (range 18.8–70.6 years). In IODM, the mean age was 51.8 years (range 18.9—70.4 years). In IODN, the mean patient age was somewhat older 60.0 years (range 26.2—73.7 years) and was consistent with the study inclusion of only Type 2 patients. In these three studies, 54 patients (~13%) were >64 years, and 46 patients (~11%) were >65 years.

No special population groups were studied.

Table 6
Number of Patients

Study	Entered	Randomized							Extension			
		Type 1	Type 2	Male	Female	Total	Drop-out LP	Drop-out HR	Type 1	Type 2	Total	Drop-out
IODI	197	102	64	112	54	166	10	6	42	21	63	3
IODK	192	75	52	59	68	127	7	2	33	27	60[1]	12
IODL	157	141	0	78	63	141	1	2	75	0	75	
IODM	124	37	63	55	45	100	3	0	—	—	—	—
IODN	110	0	89	42	40	89	2	7	—	—	—	—

[1]includes patients from IOFC, the extension study for IODK in France
Type 1 and Type 2 refer to the type of diabetes
LP=lispro compounds HR=human insulin compounds

9.4.---Numbers of Patients and Disposition
127, 100, and 89 patients were randomized to studies IODK, IODM, and IODN respectively. (See table 6.) The randomized patients represented 66, 81, and 81% respectively of the patients evaluated for entry. The drop-out rate was less than 10% for all studies for which information was available. 63, 60, and 75 patients entered the extension studies for IODI, IODK, and IODL. The extension trial patients represented 38, 47, and 53% respectively of the patients randomized to the controlled portions of IODI, IODK, and IODL. The drop-out rate was less than 10% for the extension studies for which information was available. The most common reasons for withdrawal during the

controlled portion of the trials and the extension trial were lack of efficacy or physician decision. (See table 7.) No patients were discontinued for adverse reactions.

Table 7
Discontinuation of Patients

	Controlled Trial					Extension	
	# Patients			Mean Duration of Tx (days)		# Patients	Mean Duration of Tx (days)
	LP mix	HR mix	Total	LP mix	HR mix		
IODK							
Lack of efficacy	4	0	4	43.8	—	4	305
M.D. decision	0	0	0	—	—	4	319
Entry criteria not met	2	1	3	45.5	28	0	—
Protocol violation	0	1	1	—	91	1	485
Adverse event	0	0	0	—	—	1	277
Other	1	0	1	27	—	2	397.5
IODM							
Lack of efficacy	1	0	1	31	—		
M.D. decision	0	0	0	—	—		
Entry criteria not met	0	0	0	—	—		
Protocol violation	0	0	0	—	—		
Adverse Event	0	0	0	—	—		
Other	2	0	2	24.5	—		
IODN							
Lack of efficacy	0	0	0	—	—		
M.D. decision	0	2	2	—	38		
Entry criteria not met	1	1	2	12	7		
Protocol violation	0	1	1	—	36		
Adverse event	0	0	0	—	—		
Other	1	3	4	43	89		

Tx=treatment LP=lispro HR=human insulin M.D.=physician

9.5.— Drug Exposure in Extension Trials*

Table 8
Exposure to NPL or NPL mixtures by number of days

Study	Days				
	1–27	28—90	91–182	183–365	>365
Combined	3	2	5	45	143
IODI	0	0	1	42	20
IODK[1]	1	1	3	2	53
IODM	2	1	1	1	70

[1]Includes patients in IOCF (France)
*The tabular exposure data for the controlled portion of the clinical trials that was presented by the sponsor appears to include exposure to the active controls as well as exposure to the experimental insulins.

9.6--Study Drug Formulation
Insulin lispro has the empirical formula of C257H383N65O77S6 and a molecular weight of 5808. Each milliliter of mid-mix contains insulin lispro 100 units, 0.19 mg protamine sulfate, 16 mg glycerin, 3.78 mg dibasic sodium phosphate, 2.20 mg m-cresol, zinc oxide content adjusted to provide [redacted] ionic zinc, 0.89 mg phenol, and qV water. Each milliliter of low mix contains insulin lispro 100 units, 0.28 mg protamine sulfate, 16 mg glycerin, 3.78 mg dibasic sodium phosphate, 1.76 mg m-cresol, zinc oxide content adjusted to provide 0.025 mg ionic zinc, [redacted] mg phenol, and qV water. The pH is adjusted to 7.0—7.8.

9.7.—Dose-Route-Administration
All insulin was to be given as subcutaneous injections twice daily with the doses to be titrated as needed. (See table 3.) In IODK, five patients using lispro mixtures and two patients using human regular mixtures changed the insulin regimen or administered additional doses that were not allowed by protocol. In IODM, nine patients using lispro mixtures and eight patients using human regular mixtures changed the insulin regimen or administered additional doses that were not allowed by protocol.

9.8.-- Concomitant Medications
Extended use of glucorticoids, which can increase insulin resistance and the doses of insulin required to maintain glycemic control, were excluded from IODK, IODM, and IODN. Beta blockers, which can mask the symptoms of hypoglycemia, were excluded from IODK and IODM, but not IODN. Oral antidiabetic agents were excluded from the trials, but the washout period was not long enough to exclude their impact on basal HgbA1c values. Prior participation in lispro product studies was excluded, but it is unclear as to whether patients could have been exposed to commercially available lispro. Prior exposure could have had an impact on cross-reacting antibody levels.

There were no drug interaction studies during IODK, IODM, or IODN.

9.9.—Safety Studies and Parameters
Physical exams were conducted at study entry. There was no specific assessment of diabetic retinopathy or neuropathy. Vital sign and weight measurements were taken at each subsequent visit. There was no exit physical. Electrocardiograms were obtained at entry. Routine clinical chemistry and hematologic tests were obtained at baseline and at the end of each treatment arm. Patients were to conduct serial home glucose monitoring and to report hyperglycemia and hypoglycemia. Anti-insulin antibodies, in particular, cross-reacting insulin antibodies, were assessed at baseline and the end of each three month treatment arm in IODK and IODM. Antibodies were to be intermittently assessed during extension trials; each six months during the IODI and IODK extensions; pre-

sumably every 14 weeks during IODL.[1] Insulin dose levels were obtained to help assess the clinical importance of the cross-reacting antibodies were recorded during the controlled and during the extension studies for IODI and IODK, but not IODL. Changes in glycemic control to assess the clinical significance of anti-insulin levels and changes were not obtained.

[1]Some of the presented protocol information suggest that the extension trial for IODI, IODK, and IODL were intended to be 24 months in length and that visits were to be scheduled at six month intervals. The extension trial for IODI appears to have been further extended by amendment for an additional 24 months, but most patients were discontinued prematurely (Visits 102 to 105).

9.9.—Efficacy Variables

HgbA1c values, the parameter of glycemic control accepted by the Division, were obtained at baseline and the end of each treatment arm. In addition, unblinded patients were to conduct a home glucose profile with sampling done before meals, two hours after meals, before bedtime, and at 3 A.M. Measures were to be obtained on three non-consecutive days including one weekend day prior to visits at baseline, one month, and the end of the treatment arm.

9.10.—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 lispro mixes immediately before meals. Rigorous statistical analysis was not undertaken because equivalence of lispro and human regular insulin had been previously established and because the trials were open-label.

9.11.—Inspections

No inspections were conducted.

9.12.--Amendments

A subset set of patients with Type 1 diabetes at a single Dutch site in IODM were to undergo additional pharmacokinetic-pharmacodynamic testing.

The patients in IODI who completed the 24 month extension study were given the option to enter an additional 24 extension study. (The extension appears to have been truncated by the sponsor.)

10.--Efficacy Results

Glycemic control as measured by HgbA1c was less than optimal at baseline. Glycemic control did not improve substantially during the three clinical trials. (See tables 9 and 10.) There were no clinically significant differences between treatment groups for HgbA1c at endpoint and the change in HgbA1c over the duration of the three studies. The largest difference between treatment arms at endpoint was present in IODK and actually favored Humulin 20/80 over the lispro low mix. Although the difference was statistically

significant (p=0.007), the magnitude of the difference was less than 0.2%. Similarly, the largest difference in the HgbA1c delta between treatment arms was present in IODK and favored Humulin 20/80. Again the difference was statistically significant (p=0.016), but the magnitude of difference was small (<0.3%). The differences in glycemic control were not achieved by use of more human regular insulin. The additional amount of lispro mix compared to human insulin mix used in the three studies ranged from 0.005 to 0.028 U/kg/d (intent-to-treat) or 0.003 to 0.018 U/kg/d (patients with values for all parameters). The differences for the dose at endpoint and the dose delta were not statistically significant except for study IOAK. The mean dose differences were <3 U/d for a 70 kg person. These values are similar to those observed in the original lispro NDA.

Table 9
Mean Intent-to-treat Values for HgbA1c, Insulin Doses, and Cross-reacting Antibodies

Study/ Treatment	HgbA1c (%)			Total Daily Dose (U/kg)			Cross-Reacting Antibodies (% Binding)		
	Baseline	Endpoint	Delta	Baseline	Endpoint	Delta	Baseline	Endpoint	Delta
IODK									
HR	8.04 n=124	7.91 n=119[1]	-0.13 n=119	0.525 n=125	0.514 n=119[2]	-0.004 n=119[3]	7.12 n=118	6.11 n=117[4]	-0.53 n=113[5]
LP	7.98 n=124	8.11 n=122	0.12 n=121	0.508 n=123	0.542 n=124	0.030 n=122	6.96 n=121	7.95 n=119	0.06 n=116
IODM									
HR	7.60 n=98	7.57 n=95	0.00 n=94	0.585 n=97	0.599 n=97	0.015 n=96[6]	7.57 n=98	5.95 n=95	-0.99 n=94[7]
LP	7.73 n=98	7.72 n=98	-0.03 n=96	0.587 n=99	0.604 n=97	0.025 n=96	6.90 n=98	7.36 n=98	-0.07 n=96
DN									
HR	8.03 n=83	8.05 n=86	-0.02 n=80[8]	0.590 n=87	0.642 n=83	0.047 n=82[9]	—	—	—
LP	8.04 n=84	7.82 n=81	-0.17 n=79	0.617 n=85	0.658 n=80	0.029 n=80	—	—	—

HR=human regular insulin compounds LP=lispro insulin compounds
[1]p=0.106 [2]p=0.28 [3]p=0.001 [4]p=0.14 [5]p=0.18 [6]p=0.36 [7]p=0.085 [8]p=0.33 [9]p=0.39.

Table 10
Mean Values for HgbA1c, Insulin Doses, and Cross-reacting Antibodies in Patients Who Had Values For All Parameters at Baseline and Endpoint

Study/Treatment	HgbA1c (%)			Total Daily Dose (U/kg)			Cross-Reacting Antibodies (% Binding)		
	Baseline	Endpoint	Delta	Baseline	Endpoint	Delta	Baseline	Endpoint	Delta
IODK (n=104)									
HR	8.09	7.96[1]	-0.126[2]	0.516	0.513[3]	-0.003[4]	6.68	6.07[5]	-0.61[6]
LP	8.00	8.14	0.132	0.503	0.531	0.027	6.60	6.83	0.23
IODM (n=92)									
HR	7.56	7.58[7]	0.174[8]	0.582	0.598[9]	0.163[10]	7.11	6.12[11]	-1.00[12]
LP	7.72	7.68	0.047	0.576	0.601	0.025	6.96	6.91	-0.04
IODN (n=70)									
HR	7.97	7.85	-0.121[13]	0.586[14]	0.627[15]	0.041[16]	---	---	---
LP	7.91	7.75	-0.166	0.604	0.639	0.035	---	---	---

HR=human regular insulin compounds LP=lispro insulin compounds
[1]p=0.007 [2]p=0.016 [3]p=0.012 [4]p=0.02 [5]p=0135 [6]p=0.34
[7]p=0.18 [8]p=0.62 [9]p=0.70 [10]p=0.53 [11]p=0.035 [12]p=0.08
[13]p=0.34 [14]p=0.81 [15]p=0.33 [16]p=0.82

11.--Safety Results

11.1.--The controlled studies were not sufficiently powered to identify adverse events other than those previously identified. 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.

11.2.--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.)

The vast majority of hypoglycemic events were accompanied by a documented blood glucose level. In Study IODM, blood glucose values were missing for only three events in patients using human regular mixtures and six events in patients using lispro mixtures. There were no such undocumented events in IODK or IODM.

Over the duration of the studies and during the last month of the study, when dosing was more likely to be at equilibrium levels, the mean number of hypoglycemic events per patient per month was less than 0.5—regardless of treatment. (See table 11.) Similarly, the median number of events was zero for both treatment arms of the study. The low number of events in IODN reflects the limitation of the study to Type 2 patients. The

minimally higher number of total hypoglycemic events for 20/80 in IODK may reflect the correspondingly slightly lower HgbA1c levels. Similarly, the minimally higher number of total hypoglycemic events for low mix in IODN may reflect the corresponding slightly lower HgbA1c levels. This relationship was not present for IODM, but may reflect the spurious findings that can occur with small numbers of patients.

- Patients were able to self treat most of the above hypoglycemic events regardless of the treatment used. (See table 11.) In IODK, only 11 episodes required intervention from a third party. Six patients were being treated with human insulin mixes; five were being treated with lispro insulin mixes. Whether patients were able to self treat was unknown in five events in which the treatment insulin was 20/80 and in four events in which the treatment insulin was low mix. In IODM, there were 17 events that required third party intervention. In seven of the events, the patients were being treated with human insulin mixes. In 10 of the events, the patients were being treated with lispro mixtures. Whether patients were able to self treat was not known for two patients; one of whom was using lispro mixtures. In IODN, there were no episodes requiring third party assistance and only one episode, in a patient using low mix, for which the degree of outside intervention was not known.

Table 11
Glycemic Control versus Hypoglycemia
(Hypoglycemia=glucose ≤36 mg/dl and/or requiring intervention from a third party)

Study	Treatment	HgbA1c (%)		Hypoglycemia					
				During Treatment Arm				During Final Month	
		Endpoint	Delta	# Events	# Events Not Self Treated	IV Glucose or Glucagon or Coma	# Patients	# Events	# Patients
IODK	HR	7.91	-0.13	121	6	1	37	27	17
	LP	8.11	0.12	104	5	0	40	48	18
IODM	HR	7.57	0.00	47	7	2	20	23	12
	LP	7.72	-0.03	52	10	2	27	15	12
IODN	HR	8.05	-0.02	25	0	0	14	8	7
	LP	7.82	-0.17	31	0	0	13	15	9

HR=human regular insulin compounds
LP=lispro insulin compounds

The number of episodes requiring third party intervention: 28 events in 316 patients for 6 months (or 0.18 events per patient-year) was less than the rate predicted by the DCCT for patients with a HgbA1c of ~8%, 0.45 events per patient-year. Again, this likely reflects the inclusion of Type 2 patients, who typically have lower rates of hypoglycemia.

The number of very serious hypoglycemia events was very small-regardless of treatment. In all three studies combined, there were only five events that required treatment with glucagon or IV glucose OR in which the patient was comatose. (See table 11.) In four of the events, the treatment drugs were human insulin mixtures; in two of the events, the treatment drugs were lispro mixtures.

Lastly, the occurrence of hypoglycemic events by time of day was similar regardless of treatment arm. The vast majority of events occurred during the day and were especially clustered at mid-day. (See figures 1—3.)

11.3.--Acidosis/Severe Hyperglycemia

In IODK, there were 3 cases of hyperglycemia or acidosis requiring hospitalization; two in patients using 20/80; one in patients using lispro low mix. In IODM and IODN there were no cases of hyperglycemia or acidosis requiring hospitalization.

11.4.--Allergic Reactions

There were no discontinuations in IODK, IODM, and IODN for systemic allergic reactions or significant local reactions. There was insufficient information to determine whether there was a treatment difference in minor allergic reactions or skin injection site reactions. Patients with increased cross-reacting antibody levels did not appear to bear increased risk for systemic allergic reactions.

11.5.--Deaths

There were no deaths in IODK, IODM, or IODN. There have been 17 deaths in related studies:

A 61 yo M German patient (412-4061) being treated with lispro and NPL insulins in IODI died of suicide.
A 66 yo F Indian patient (358-3588) being treated with mid and low mix insulins in IOHO died from a presumed myocardial infarction after presently with a new onset cough.
A 70 yo M Indian patient (358-3605) being treated with mid and low mix insulins in IOHO died with congestive hear failure.
A 67 yo F Mexican patient (370-3727) being treated with glibenclamide and metformin in study IOHI presented in cardiac arrest.
A 59 yo M Russian patient (460-4608) being treated with low mix in IOGZ died of unexpectedly of acute heart failure.
A 64 yo M Polish patient (181-1820) being treated with low mix in IOHY died of cardiac problems.
A 69 yo M Canadian patient (852-8532) being treated with NPH during IOME experienced four serious episodes of hypoglycemia during the lead-in period and died of a CVA three weeks after randomization.
Eleven German patients of 1000 patients treated with low mix during a post-marketing surveillance study S003 died: CVA (4), myocardial infarction-cardiac failure (3), multi-system organ failure (1), pulmonary insufficiency (1), pneumonia (1), worsening of pancreatic cancer (1), and Moschkowitz Syndrome (1).

11.6--Antibodies

Cross-reacting antibodies were previously shown to be antibody species that changed the most with exposure to lispro. (See NDA #20563 review.) Similar changes were not predictably seen with lispro-specific antibodies. Because of significant inter-patient variability, the differences in antibody levels were not clearly seen in the parallel studies submitted to the NDA. Differences, however, were apparent in the large cross-over

studies like IOAG and were present despite treatment period. It was not known whether the introduction of protamine, which is commonly acknowledged to be antigenic, would enhance or mute these antibody responses.

Although there tended to be treatment-associated differences in the level of cross-reacting antibody binding and in the change of binding from baseline, antibody levels did not clearly rise with lispro mixture treatment in IODK and IODM. (See tables 3 and 4.) Similar findings were present in the intent-to-treat population and in the population that had baseline and endpoint values for HgbA1c, insulin dose, and cross-reacting antibodies. There is no obvious explanation for this observation.

To assess the clinical importance of cross-reacting antibodies, the changes in antibody levels were divided into three categories: an increase of ≥1% binding, a decrease of ≥1% binding, and essentially no change in % binding and the mean levels of changes in HgbA1c and insulin dose of the respective antibody groups calculated. (See table 12.) Although the patients in IOAK with the greatest antibody increase experienced a small deterioration in glycemic control despite an increase in insulin dose. This, however, was not true in IODM. Nor was the inverse relationship true for IODK patients with an antibody decrease. Unfortunately, the relatively small number of patients with complete data sets limits the ability to generalize these conclusions.

Table 12
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 Lispro Insulin Mixtures.

Study	Antibody Group	N=	Antibody Delta (% binding)	Antibody Range (% binding)	Dose Delta (U/kg)	HgbA1c Delta (%)
IODK	≥1% binding	25	8.74		0.049	0.16
	~1% binding	51	0.01		0.012	0.04
	≤1% binding	31	-4.10		0.038	0.18
IODM	≥1% binding	16	2.64		-0.040	-0.37
	~1% binding	48	-0.13		0.001	-0.06
	≤1% binding	28	-3.96		0.025	-0.10

Because of the extensive interpatient variability for cross-reacting antibody binding, individual patient antibody levels were tracked over time for studies IODI, IODK, and IODL. (See figures 4—10.) Similarly, insulin dose levels (U/kg) were tracked over time for patients in IODI and IODK. (See figures 11—15.) Visual inspection of the serial antibody levels confirmed the high antibody binding for a relatively small number of patients. Although only 198 of 354 patients eligible for entry into the extension trials actually entered the trials, there was no apparent bias in the drop-out that related to prior antibody levels. In addition, although the level of antibody binding could vary widely for a given patient, particularly those with higher binding levels, the mean level of binding appeared to remain relatively constant over time. There was no apparent trend for large

increases in % binding, >5%, over time. (See tables 13 and 14.) The insulin doses in IODK appear to increase somewhat over time, but the small number of patients and the absence of concomitant HgbA1c values limit any interpretation.

Table 13
Mean Cross-reacting Antibody Levels in Patients with Both Antibody Levels and Insulin Dose Levels at the 6 Month Endpoint in the Controlled Trial (IODL) and the End of the Extension Trial (Only in Patients Exposed to Lispro)

Study	N=	Total Daily Insulin Dose (U/kg)		Cross-reacting Antibodies (% Binding)	
		6 Mo Endpoint in Controlled Trials	End of the Extension Trials	6 Mo Endpoint in Controlled Trials	End of the Extension Trials
IODI (parallel study)	38	0.696	0.704	12.22	13.01
IODK HR tx first	36	0.493	0.509	6.58	7.51
IODK LP tx first	16	0.480	0.503	8.60	9.26

HR=human insulin preparations LP=lispro insulin preparations
Tx=treatment Mo=month

Table 14
Mean Cross-reacting Antibody Levels and Insulin Dose Levels in Patients with Antibody Levels at the 6 Month Endpoint in the Controlled Trials and the End of the Extension Trials OR with Insulin Dose Levels at the 6 Month Endpoint in the Controlled Trials and the End of the Extension Trials (Only in Patients Exposed to Lispro)

Study	Total Daily Insulin Dose (U/kg)			Cross-reacting Antibodies (% Binding)		
	6 Mo Endpoint in Controlled Trials	End of the Extension Trials	N=	6 Mo Endpoint in Controlled Trials	End of the Extension Trials	N=
IODI (parallel study)	0.711	0.713	61	11.38	11.27	53
IODK HR tx first	0.504	0.516	33	6.58	7.51	26
IODK LP tx first	0.480	0.503	16	8.60	9.26	16
IODL HR tx first	—	—	—	8.82	9.55	34
IODL LP tx first	—	—	—	8.62	8.01	33

HR=human insulin preparations LP=lispro insulin preparations
Tx=treatment Mo=month

11.7.—Clinical Laboratory Studies

Laboratory including routine clinical chemistry studies, CPK, and a CBC were obtained in patients in IODK and IODM, but not IODN. There were no clear trends for aberrations in lab results by treatment group when means from the various treatment periods and studies were assessed.

12.—Reviewer's Commentary

a) The sponsor has established with glucose clamp data that the proposed lispro insulin mixtures, low mix (25/75) and mid-mix (50/50), are pharmacokinetically, although not pharmacodynamically, distinct from one another and from lispro and NPL. In meal studies in Type 1 diabetic patients, low mix appears to be pharmacokinetically and pharmacokinetically similar to 30/70 human insulin mix after adjustments for the earlier insulin injection time associated with 30/70. The sponsor did not conduct head-to-head PK studies comparing 50/50 human insulin mix with mid-mix. The PK-PD studies conducted on a subset of IODM patients were not submitted to Biopharm Review Package. It is likely that mid-mix and 50/50 human insulin mix will have similar profiles after correction for the time of injection.

b) 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 data suggest that glycemic control was less than optimal—regardless of treatment mixture. Glycemic control appeared to be equivalent whether a lispro mixture or a comparable human insulin mixture was employed. Increased insulin doses (~1-2 U/d) may be required to achieve comparable glycemic control when lispro mixtures are utilized.

c) Hypoglycemia rates also appear to be similar lispro insulin mixtures and human insulin mixtures. The timing of hypoglycemic events appeared to be similar—regardless of whether a lispro mixture or a comparable human insulin mixture was employed.

d) Cross-reacting antibody levels appeared to be higher with lispro products than with human insulin products. This is consistent with the findings in the cross-over studies of the original NDA. Cross-over study assessment is important because there is a high degree of inter-patient variability in such anti-insulin antibody measurments.

e) Cross-reacting antibody levels may increase over time. The increases appear to be small in magnitude. The small numbers of patients in the extension studies, however, limits generalized conclusions.

f) The significance of cross-reacting insulin antibodies remains uncertain. In the controlled portions of the registration trials, patients with increases in antibody binding did not clearly have increased insulin needs to achieve comparable glycemic control. The

absence of HgbA1c levels and sometimes insulin dose levels, as well as the small numbers of patients in the extension trials, restricts the conclusions that may be drawn about the long-term impact of antibody response.

g) The wide range of lispro permitted in the mixtures suggest that PK-PD profile may vary from batch to batch. Patients could experience unexpected hyperglycemia or hypoglycemia. This problem will be more clinically significant in patients with the best glycemic control. The chemists are addressing this wide specification range with the sponsor.

h) 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 will reduce problems.

13.--Regulatory Conclusions

a) The mid-mix and low mix lispro insulin mixtures appear to be approvable on the basis of the pharmacokinetic studies.

b) The sponsor did not meet the agreements for providing long-term safety data regarding antibodies.

RECOMMENDATION: APPROVABLE WITH CHANGES IN THE LABEL.

14.—Label Review

The labels are primarily pharmacokinetic-pharmacodynamic labels. The labels include glucose infusion rates for the family of human insulin products and the family of lispro insulin products. The graphs for the two insulin families of products are sequentially placed in the label, and the axes have the same scale. This does permit some direct comparisons by the prescribing physician, which will be utilitarian. The sponsor, however, did not do head-to-head comparisons of mid-mix with human insulin 50/50-[redacted] The sponsor states that: [redacted] It would be more correct for the sponsor to state that, although direct comparison studies have not been performed, it is likely that a) Humalog Mix50 has a more rapid onset of glucose-lowering activity than Humulin 50/50 when dosed immediately before meals and b) the duration of activity of the two insulin products is similar. Similar statements were made in the low mix label. Although a head-to-head comparison study [redacted] was conducted, that information was not included in the label. If adequate head-to-head information is available that should be included in the label.

In addition to the graphic data, it may be helpful for the sponsor to present PK-PD data in a tabular format with parameters that may better describe insulin, e.g. the time to insulin-AUC-25%, insulin-AUC-50%, insulin-AUC-75%, and insulin-AUC-100% as well as the

time to glucose-AUC-25%, glucose-AUC-50%, glucose-AUC-75%, and glucose-AUC-100%. Because t-max and C-max may not be very utilitarian in very short acting insulins and especially in very long-acting insulins, the AUC-derived parameters may better describe the temporal profile of insulin absorption and action and permit comparison between a broad range of insulins.

The sponsor should not include information from the Humalog trials when discussing special populations including age, gender, obesity, renal impairment, and hepatic impairment. Later in the label, under Precautions, the sponsor states that the mixtures have not been studied in pediatric patients and that the numbers of geriatric patients were insufficient to provide appropriate guidelines.

The sponsor indicates that cross-reacting antibodies increase. They do not indicate that the increase is typically greater in patients using lispro products (versus human insulin products). There are no claims regarding temporal changes in the antibodies.

/S/
Elizabeth Koller, M.D.

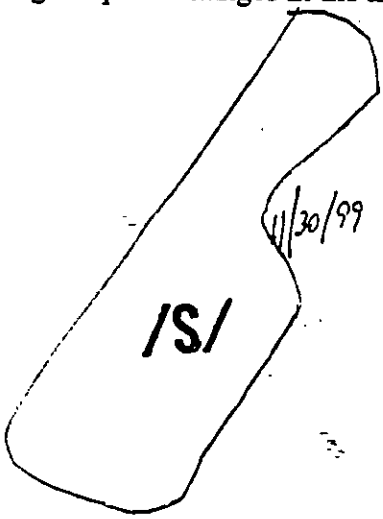

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Figure Legends

Figure 1. Hypoglycemia by time of day. The number of hypoglycemic events during the treatment arm at any given hour were normalized or expressed as a percentage of total hypoglycemic events for that treatment during Study IODK. The time of day was expressed in military clock format. Hypoglycemic events were displayed as a relative distribution of events throughout the day by treatment.

Figure 2. Hypoglycemia by time of day. The number of hypoglycemic events during the treatment arm at any given hour were normalized or expressed as a percentage of total hypoglycemic events for that treatment during Study IODM. The time of day was expressed in military clock format. Hypoglycemic events were displayed as a relative distribution of events throughout the day by treatment.

Figure 3. Hypoglycemia by time of day. The number of hypoglycemic events during the treatment arm at any given hour were normalized or expressed as a percentage of total hypoglycemic events for that treatment during Study IODN. The time of day was expressed in military clock format. Hypoglycemic events were displayed as a relative distribution of events throughout the day by treatment.

Figure 4. Cross-reacting antibody levels. The serial cross-reacting antibody binding levels for individual patients were tracked over time in IODI and the IODI extension study. The experimental treatment arm used lispro and NPL.

Figure 5. Cross-reacting antibody levels. The serial cross-reacting antibody binding levels for individual patients were tracked over time in IODK and the IODK extension study. The patients were exposed to lispro mixtures during the first three months of the six month controlled portion of the trial.

Figure 6. Cross-reacting antibody levels. The serial cross-reacting antibody binding levels for individual patients were tracked over time in IODK and the IODK extension study. The patients were exposed to lispro mixtures during the second three months of the six month controlled portion of the trial.

Figure 7. Cross-reacting antibody levels. The serial cross-reacting antibody binding levels for individual patients were tracked over time in IODL and the IODL extension study. The patients were exposed to lispro mixtures (75% lispro+25% NPL before meals) during the first three months of the six month controlled portion of the trial.

Figure 8. Cross-reacting antibody levels. The serial cross-reacting antibody binding levels for individual patients were tracked over time in IODL and the IODL extension study. The patients were exposed to lispro mixtures during the first three months of the six month controlled portion of the trial. The patients with extremely high antibody binding levels (>25%) were excluded.

Figure 10. Cross-reacting antibody levels. The serial cross-reacting antibody binding levels for individual patients were tracked over time in IODL and the IODL extension study. The patients were exposed to lispro mixtures during the second three months of the six month controlled portion of the trial. The patients with extremely high antibody binding levels (>20%) were excluded.

Figure 11. Total daily insulin levels (U/kg). The serial total daily insulin dose levels for individual patients were tracked over time in IODI and the IODI extension study. The experimental treatment arm used lispro and NPL.

Figure 12. Total daily insulin levels (U/kg). The serial total daily insulin dose levels for individual patients were tracked over time in IODK and the IODK extension study. The patients were exposed to lispro mixtures during the first three months of the six month controlled portion of the trial.

Figure 13. Total daily insulin levels (U/kg). The serial total daily insulin dose levels for individual patients were tracked over time in IODK and the IODK extension study. The patients were exposed to lispro mixtures during the second three months of the six month controlled portion of the trial.

Fig. 1 Hypoglycemia by Time of Day (20/80 vs Low Mix; IODK)

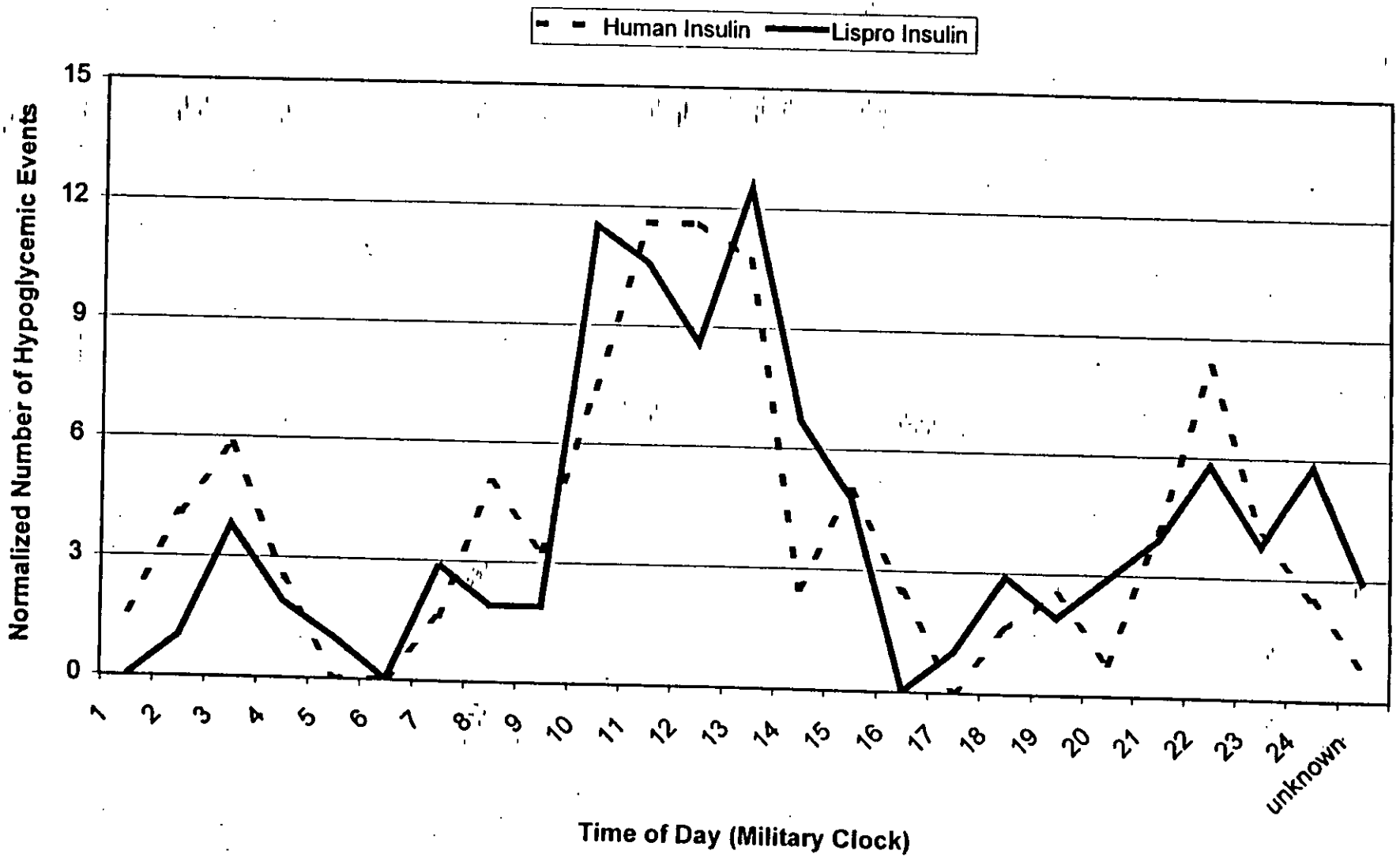

Fig. 2 Hypoglycemia by Time of Day (30/70+50/50 vs Low Mix+Mid Mix; IODM)

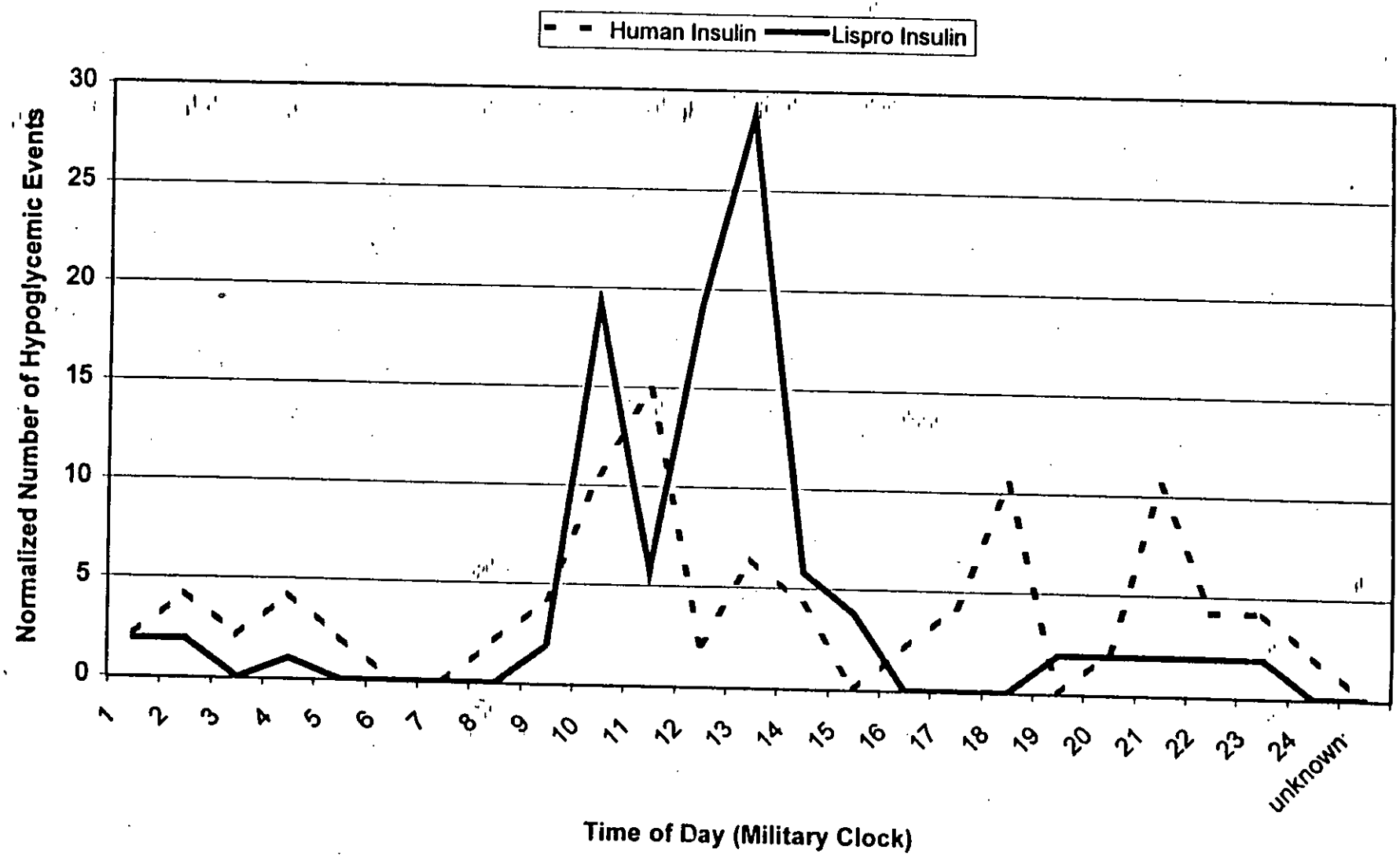

Fig. 3 Hypoglycemia by Time of Day (30/70 vs Low Mix; IODN)

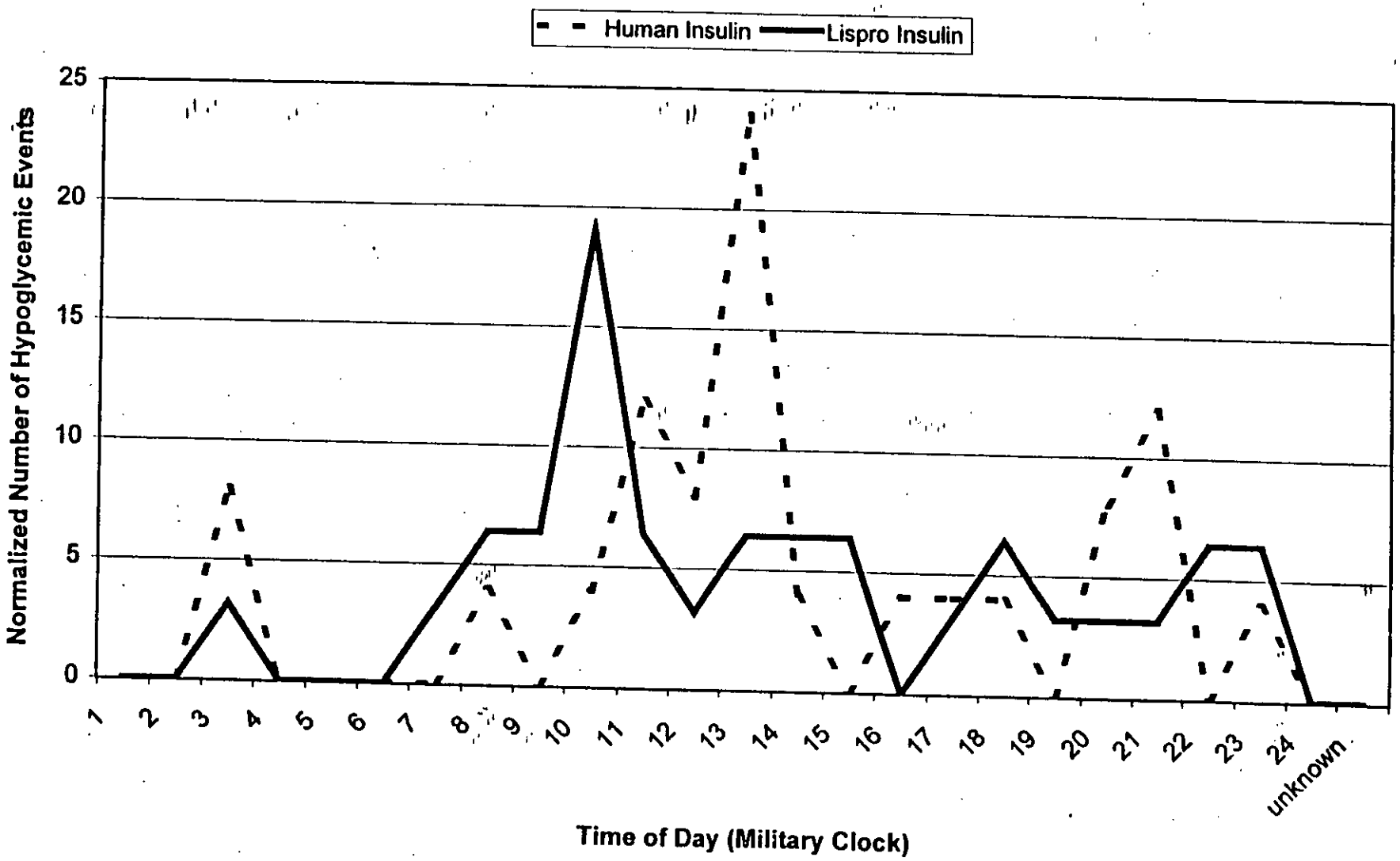

Fig. 4 Cross-reacting Antibodies: Changes in Individual Patients over Time (Exposed to Lispro during the 12 Month Controlled Trial and the 12 Month Extension; IODI)

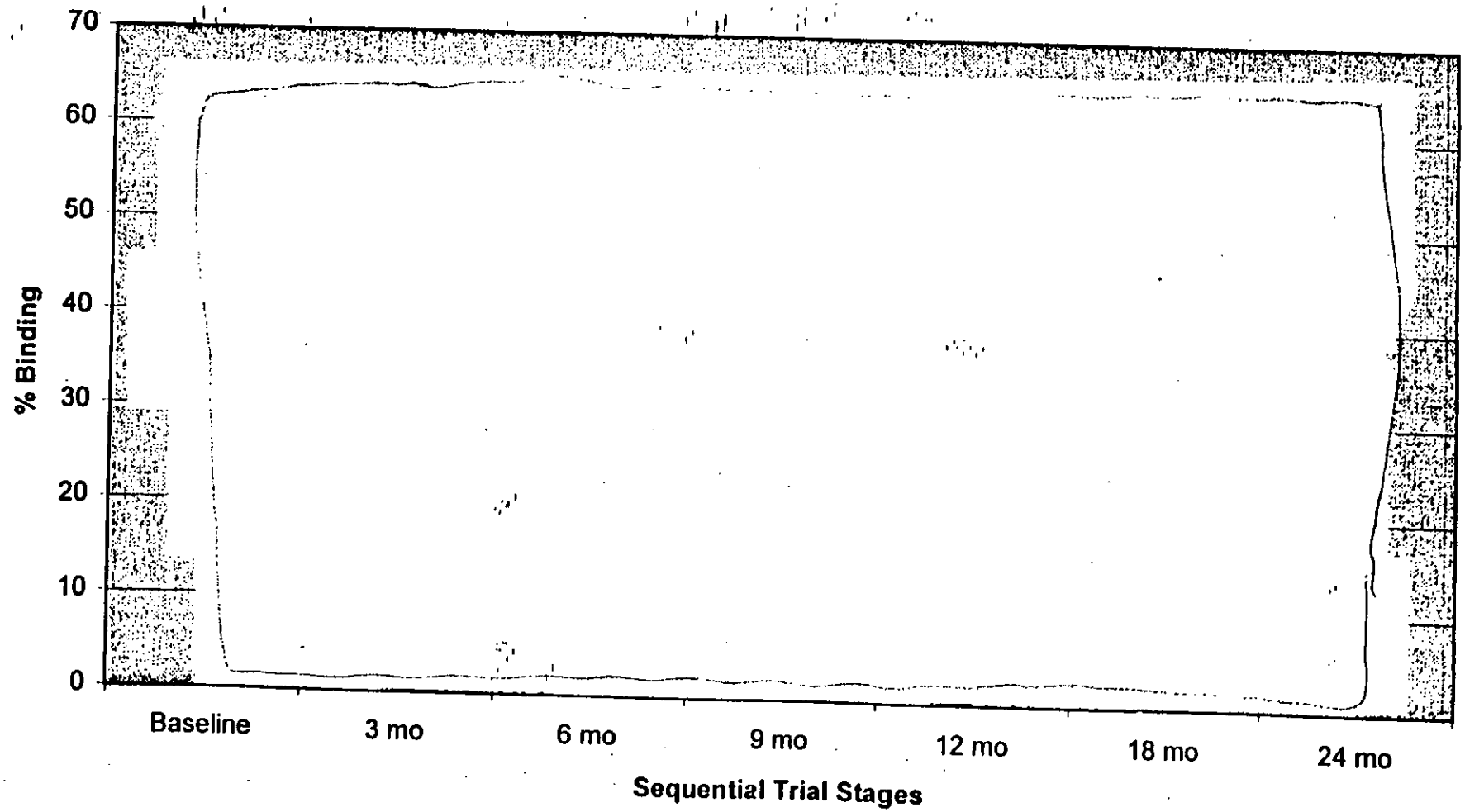

Fig. 5 Cross-reacting Antibodies: Changes in Individual Patients over Time (Exposure to Lispro Mixtures during the Second 3 Months of the Controlled Trial and during the 18 Month Extension; IODK)

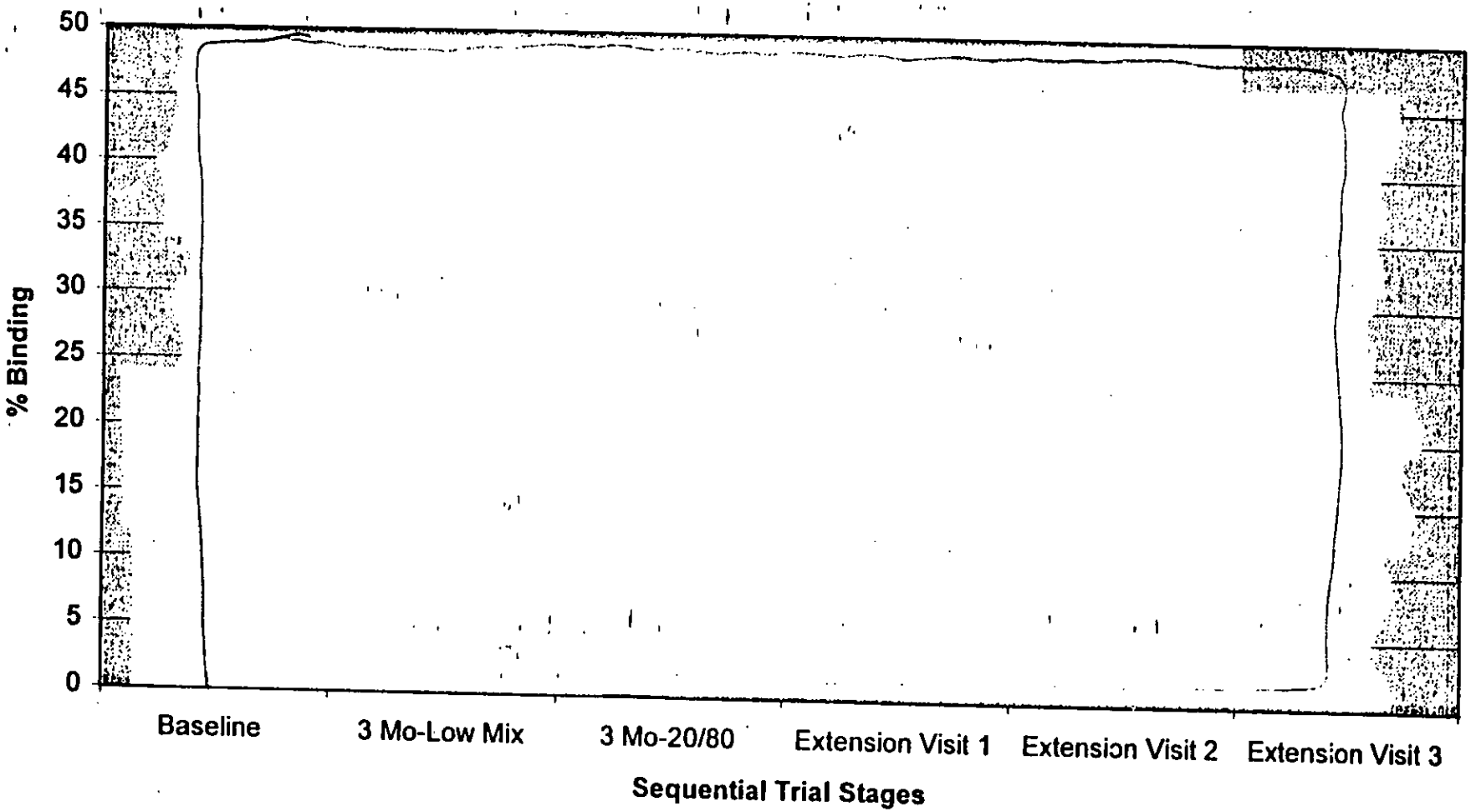

Fig. 6 Cross-reacting Antibodies: Changes in Individual Patients over Time (Exposure to Lispro Mixtures during the Second 3 Months of the Controlled Trial and during the 18 Month Extension; IODK)

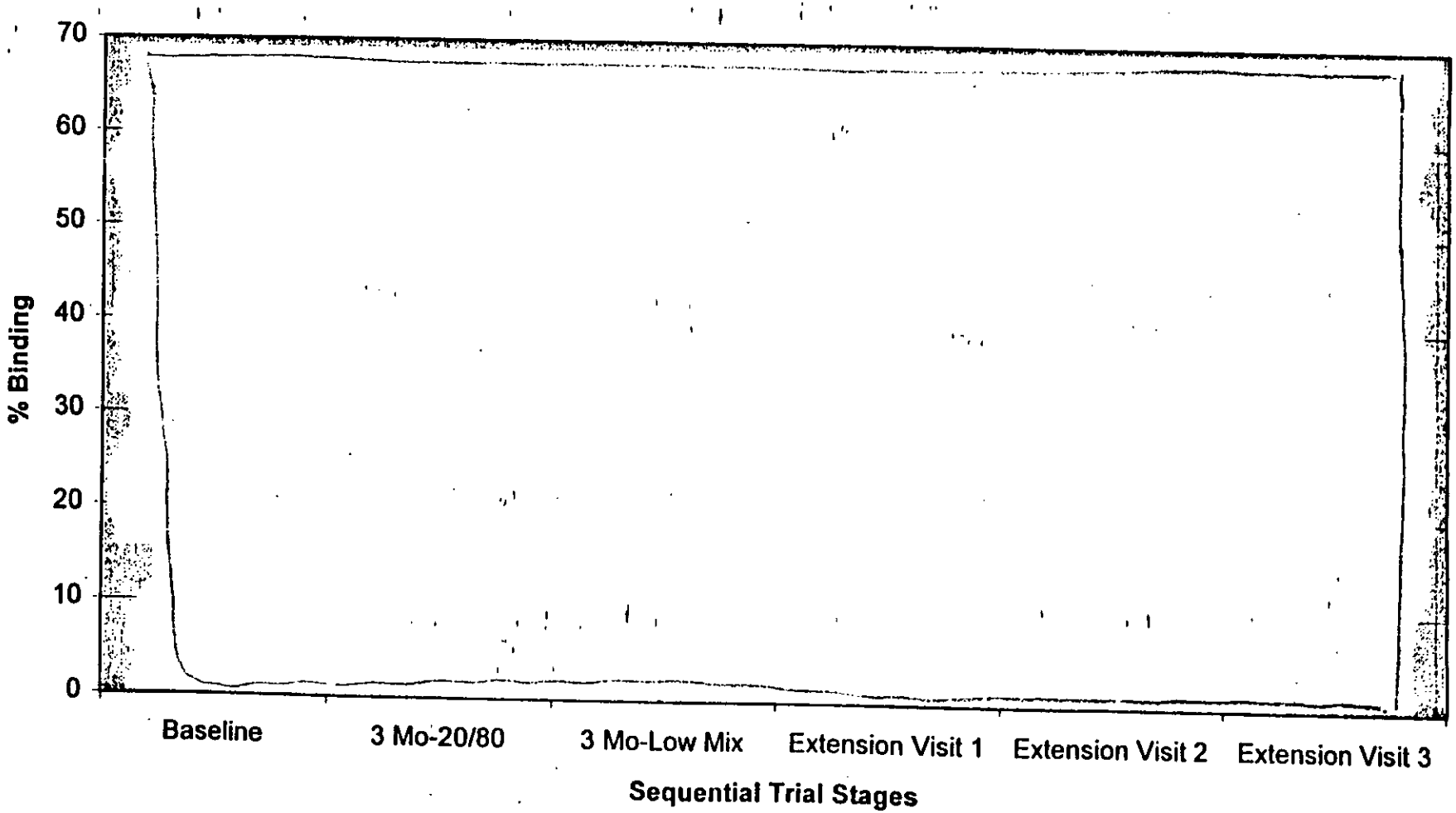

Fig. 7 Cross-reacting Antibodies: Changes in Individual Patients over Time (Exposure to Lispro Mixtures during the First 3 Months of the Controlled Trial and during the Uncontrolled 18 Month Extension; IODL)

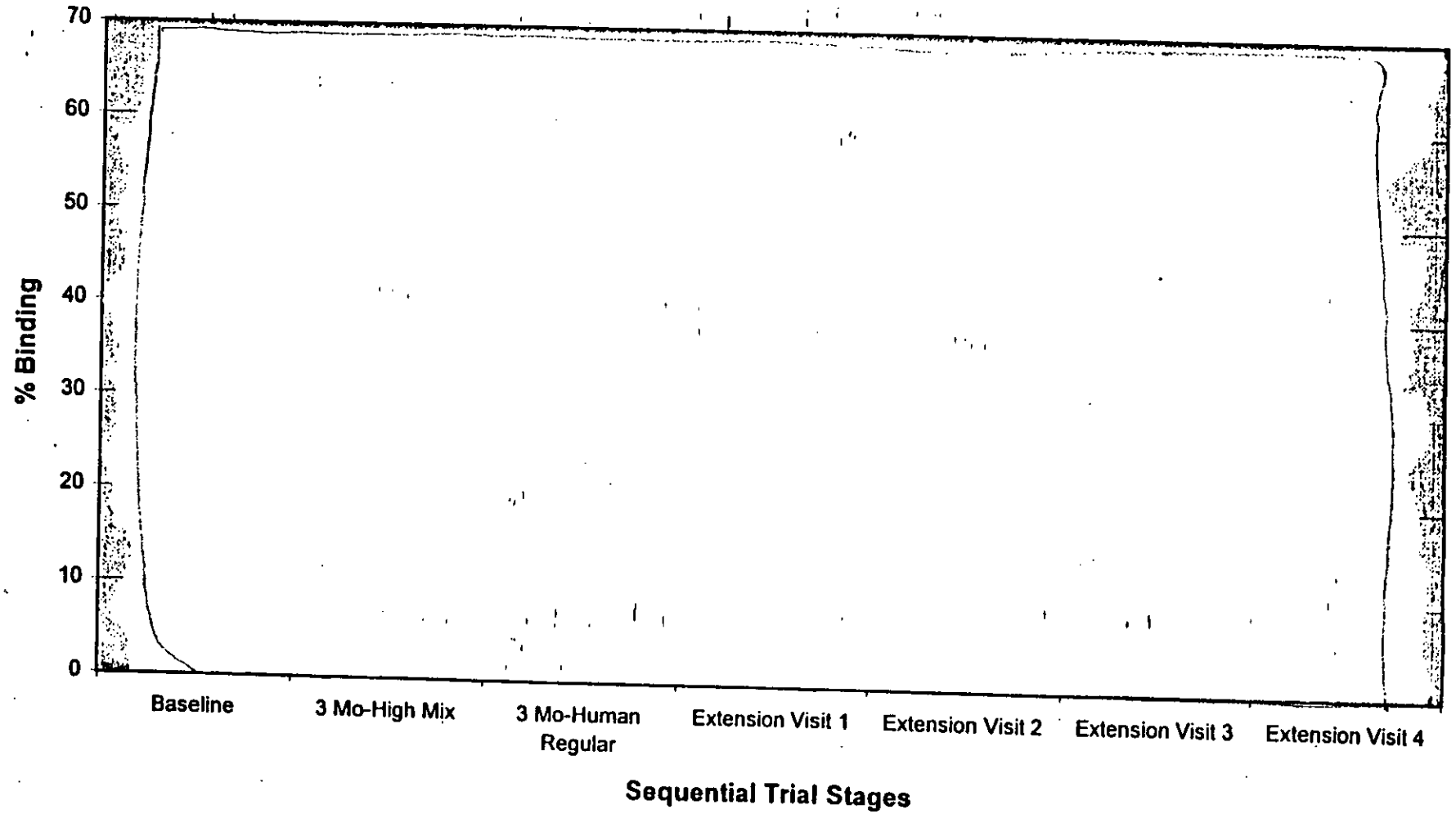

Fig. 8 Cross-reacting Antibodies: Changes in Individual Patients over Time (Exposure to Lispro Mixtures during the First 3 Months of the Controlled Trial and during the Uncontrolled 18 Month Extension; IODL)(Outliers Excluded)

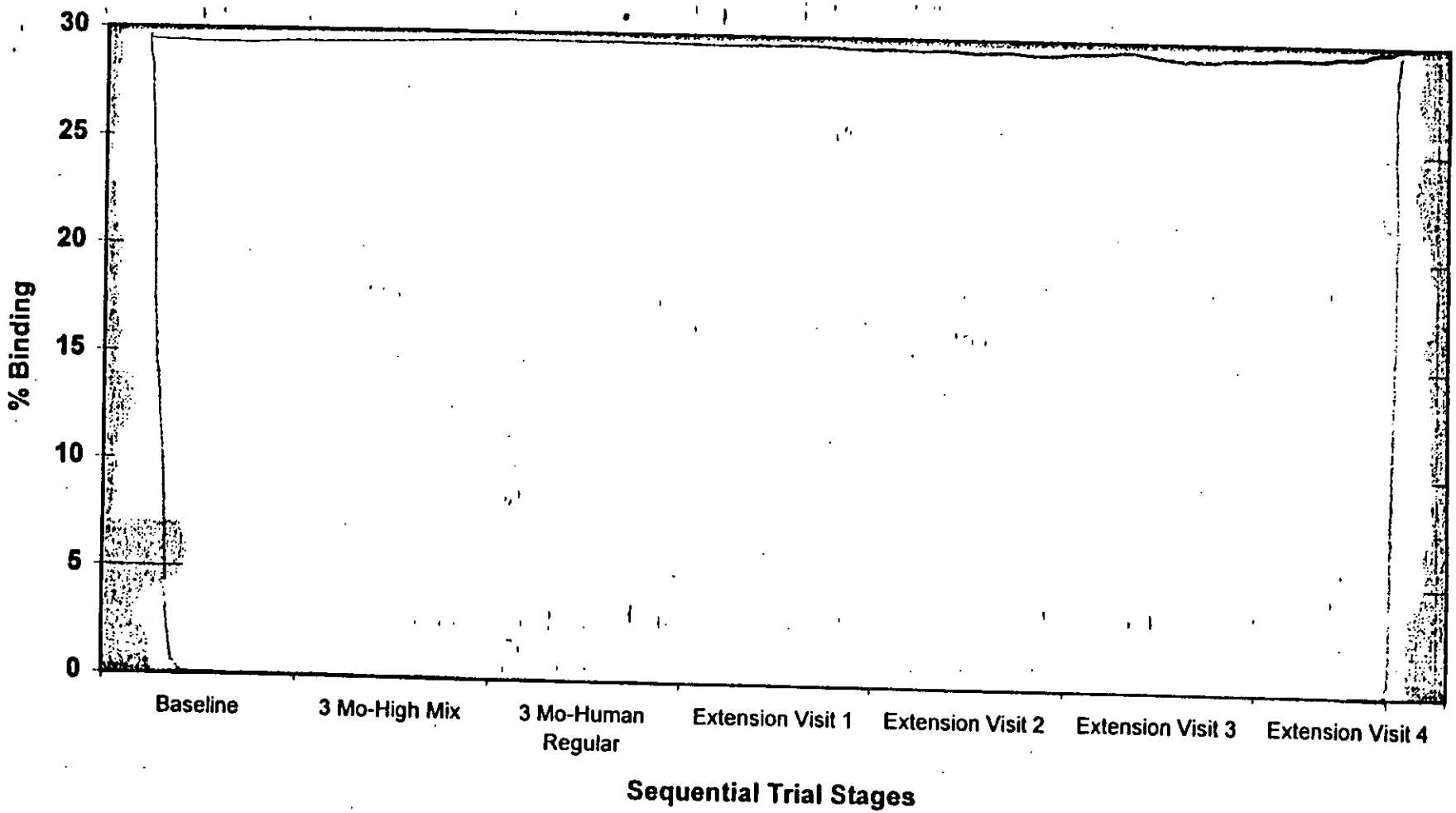

Fig. 9 Cross-reacting Antibodies: Changes in Individual Patients over Time (Exposure to Lispro Mixtures during the Second 3 Months of the Controlled Trial and during the Uncontrolled 18 Month Extension; IODL)

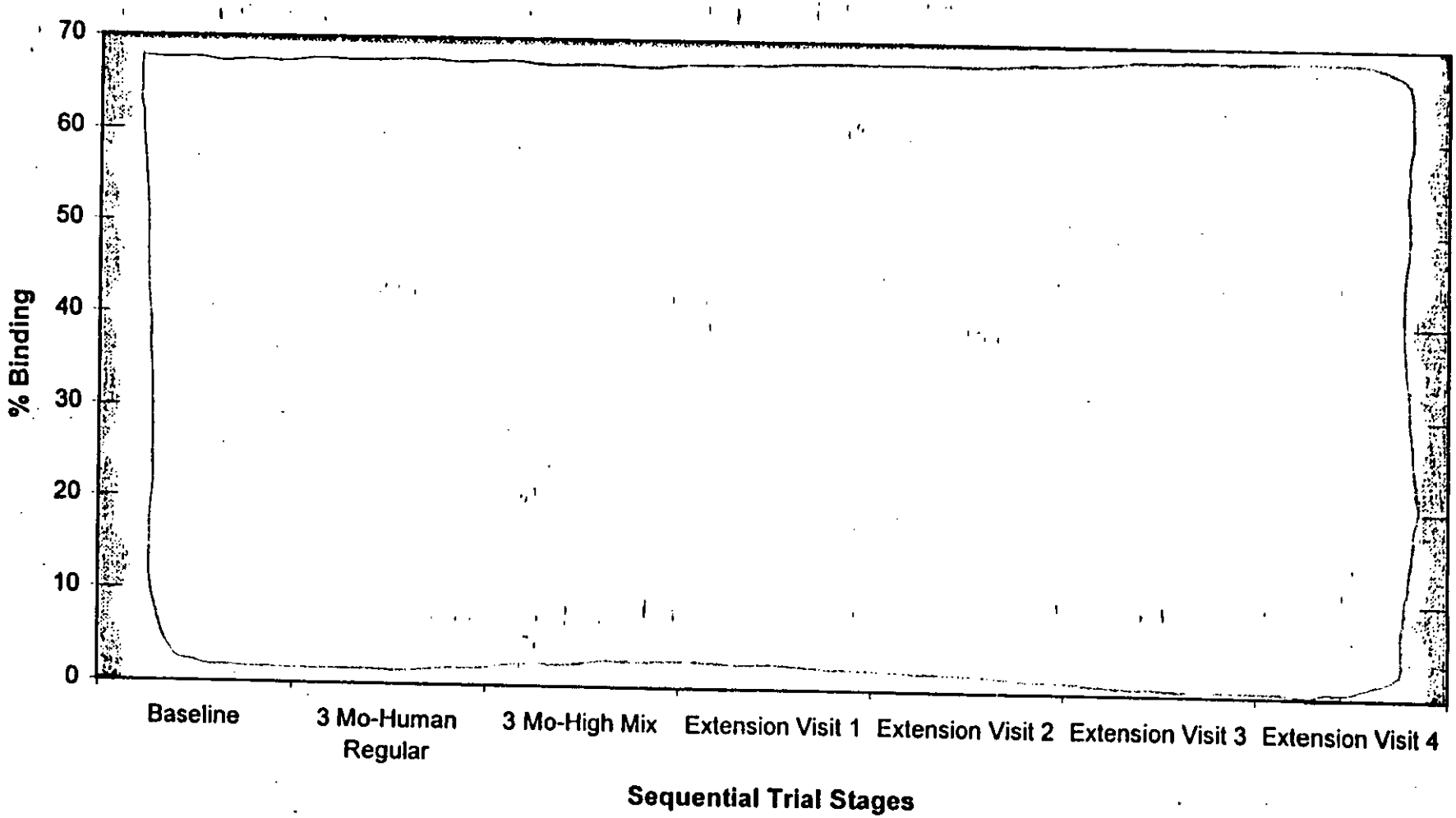

Fig. 10 Cross-reacting Antibodies: Changes in Individual Patients over Time (Exposure to Lispro Mixtures during the Second 3 Months of the Controlled Trial and during the Uncontrolled 18 Month Extension; IODL) (Outliers Excluded)

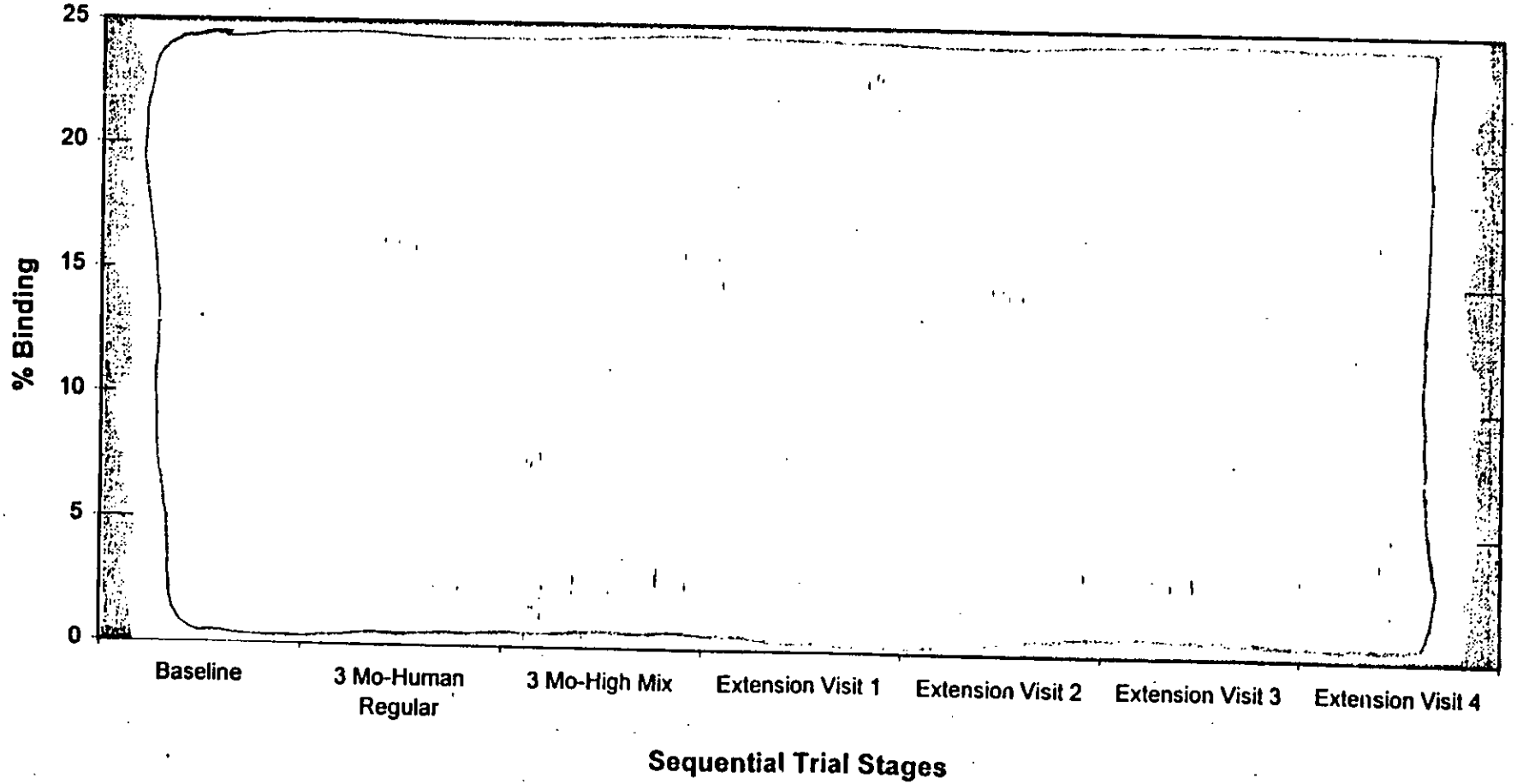

Fig. 11 Total Daily Insulin Doses: Changes in Individual Patients over Time (Exposed to Lispro during the 12 Month Controlled Trial and during the 12 Month Extension; IODI)

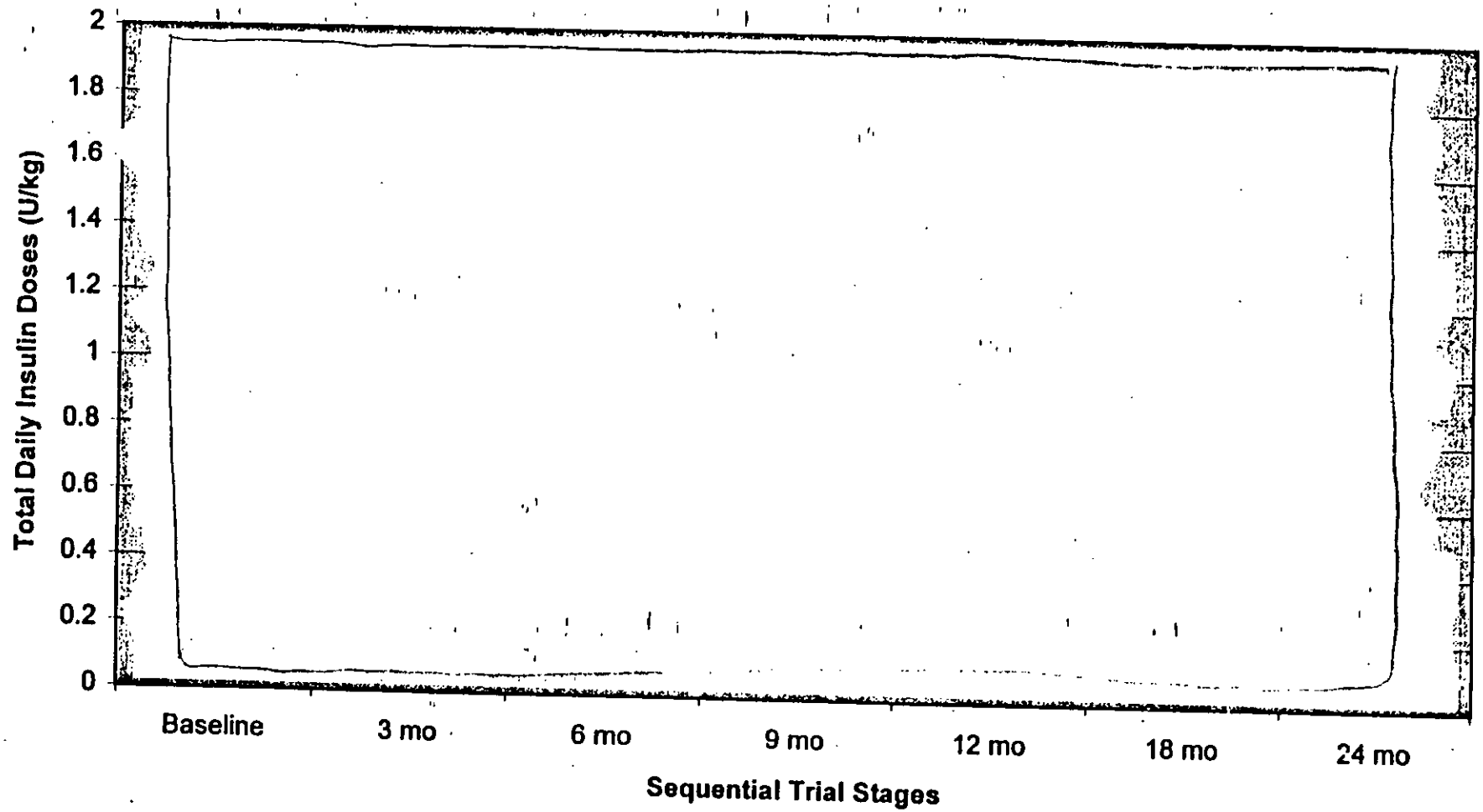

Fig. 12 Total Daily Insulin Doses: Changes in Individual Patients over Time (Exposure to Lispro Mixtures during the First 3 Months of the Controlled Trial and during the Uncontrolled 18 Month Extension; IODK)

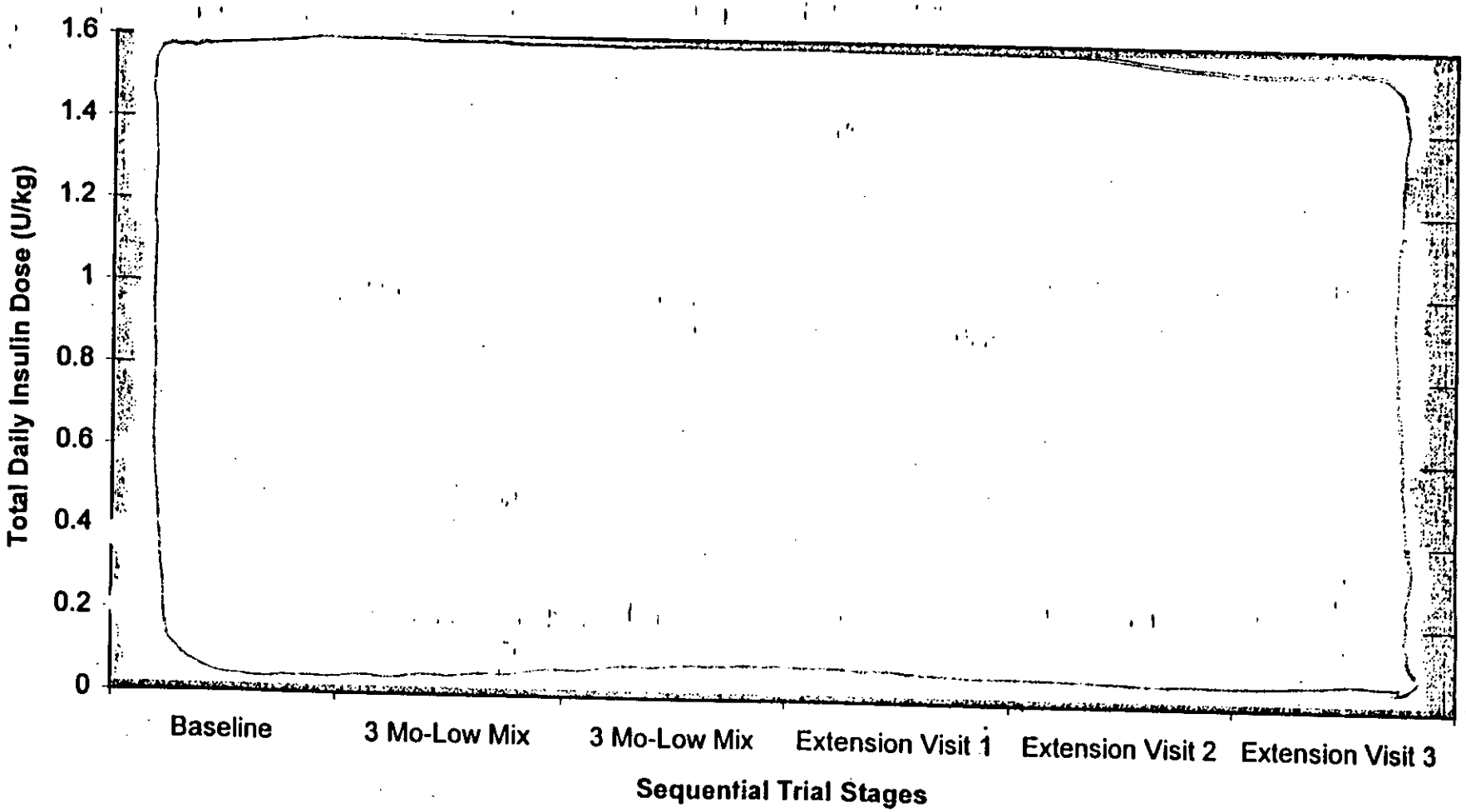

Fig. 13 Total Daily Insulin Doses: Changes in Individual Patients over Time (Exposure to Lispro Mixtures during the Second 3 Months of the Controlled Trial and during the Uncontrolled 18 Month Extension; IODK)