NDA 20-563

JUN 14 1996

Lilly Research Laboratories
Attention: Timothy R. Franson, M.D.
Executive Director, North American Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Franson:

Please refer to your March 13, 1995, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Humalog [insulin lispro (rDNA origin) injection], 100 units/mL.

We acknowledge receipt of your amendments dated March 15, May 9, June 5, 6, 7, 8, 9, and 12, July 13 and 21, August 18, September 6, 7, 13, 15, 20, and 22, October 5, 10, 11, 23, 25, 26, 27, and 30, November 3, 6, and 13, and December 8, 11,13, 14, 18, 19, and 22, 1995; and February 6 and 14, April 1, 3, and 22, May 14, 22, 24, and 28(2), and June 14, 1996. We note that your December 18, 1995, major amendment extended the user fee goal date to June 14, 1996.

This new drug application provides for the treatment of diabetes mellitus in patients requiring insulin.

We have completed the review of this application including the submitted draft labeling [including a physician package insert because this drug is approved for prescription use only] and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft carton and vial labeling submitted on April 22, 1996, and the draft physician package insert and draft patient package insert submitted June 14, 1996. Accordingly, the application is approved.

The final printed labeling (FPL) must be identical to the labeling submitted on April 22 and June 14, 1996. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 16 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING for approved NDA 20-563." Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

The range of of labeled claim for insulin assay of the drug product is approved for an interim period until sufficient historical analytical batch data and stability data are obtained. In accordance with a telephone conversation between Dr. Stephen Moore of the FDA and Dr. Greg Davis of Lilly on June 11, 1996, Lilly will meet with the FDA in approximately 1 year to review this data and determine

whether the assay range can be tightened to , to be consistent with other marketed insulin products.

We remind you of your commitments to conduct Phase 4 studies as specified in your submissions dated:

May 14, 1996

1.

2.

May 24, 1996

1.

2

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May 28, 1996

For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "**Phase 4 Commitments**."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print.

Please send one copy to the Division of Metabolic and Endocrine Drug Products, HFD-510, and two copies of both the promotional material and the package inserts directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-40
5600 Fishers Lane
Rockville, MD 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Ms. Julie Rhee, at 301-443-3510.

Sincerely yours,

J Bilstad 6/14/96

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Original NDA 20-563
HFD-510/Div. Files
HFD-2/MLumpkin
HFD-21 (w draft labeling)
HFD-40 (w draft labeling)
HFD-80 (w draft labeling)
HFD-85/MHolovac (+exclusivity checklist)
HFD-102 (w draft labeling)
HFD-333/SSpungen
HFD-510/BKoller/RMisbin/AFleming/SMoore/WBerlin/DHertig/AJordan
HFD-511/JRhee/EGalliers
HFD-715/DMarticello/ENevius
HFD-805/PCooney
HFD-820/YChiu
HFD-870/MFossler/HYAhn
HFD-613 (w draft labeling)
HFD-735 (w draft labeling)
HF-2/MedWatch (w draft labeling)
DISTRICT OFFICE
HFD-222

Drafted 5/21,24,26/96/JWeber/lispro.app
Edited: JShort/LRipper
final: JShort (emg) 6/14/96

APPROVAL w/ Ph. 4 commitments (AP) - NDA 20-563

6/14/96

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

Name	Discipline	Signature	Date	
Q WEBER	CSO		5/20/96	
M. FOSSLER	CLIN. PHARM/BIOPHARM		5/21/96	
H. Ahn	OCPB		5/21/96	
A. Dem	Med. Officer		5/22	
R Misono	Med Offcr		5/24/96	
C A Keller	Medical Officer	C A Keller (Label is Unlabel)	5/24/96	
E. Galliers	CPMS	Ell Galliers	5-26-96	See separate notes to CSO.
D. Hertig	Pcl Reviewer		5/28/96	
A. Jordan	Pcl Tm Ldr		5/28/96	
W. Berlin	Chem Reviewer		5/29/96	
S. Moore	Chem Tm Ldr. II	Stephen Moore	5/29/96	
S Sobel	Division Director		5/30/96	

ODE I/II ORIGINAL NDA/NDA EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA # 20-563 Drug Humalog (lispro) Insulin

Applicant Eli Lilly and Co CSO JWeber phone 443-3510

Arrange package in the following order

		Check or Comment
1	ACTION LETTER with supervisory signatures	AP X AE ___ NA ___
2	ACTION PACKAGE TRACKING FORM	Chem/Ther Types 1 - 5
3	Completed copy of this CHECKLIST in package	
4	LABELING (package insert and labels) (If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch include current Rx Package insert and HFD-210 review of OTC labeling)	Draft X Final ___ Revised Draft ___
5	SUMMARY BASIS OF APPROVAL (Copy of previous version with ODE's comment as well as disk. FPL and sign-off sheet must accompany revised or final version. If no SBA, include memo stating what reviews will be used as SBA equivalent.)	SBA N/A Revised SBA N/A SBA Equivalent N/A
6	PATENT INFORMATION Y	EXCLUSIVITY CHECKLIST Y
7	DEBARMENT CERTIFICATION (Copy of applicant's certification for all NDA's submitted on or after June 1	Y
8	*DIVISION DIRECTOR'S MEMO* (If more than 1 review for any 1 discipline, separate reviews with a sheet of colored paper. Any conflicts between reviews must have resolution documented)	Y
	GROUP LEADER'S MEMO	Y
	PEDIATRIC PAGE	Y
	MEDICAL REVIEW	Y
	SAFETY UPDATE REVIEW	Y
	STATISTICAL REVIEW	Y
	BIOPHARMACEUTICS REVIEW	Y
	PHARMACOLOGY REVIEW (Include pertinent IND reviews.)	Y
	Statistical Review of Carcinogenicity Study(ies)	N/A
	CHEMISTRY REVIEW	Y
	Date EER Completed 11/27/95 + 5/22/96 (attach signed form or CIRTS printout) EER needed Y ___ requested ___	OK Y or OK ___ No, Completed ___
	Have the methods been validated?	Yes (attach) ___ NO X
	Environmental Assessment Review	Y
	MICROBIOLOGY REVIEW	Y
	Has the monograph been approved?	OK ___ NO Y
9	Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES	
	If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status	Not required as specified by DSI
10	CORRESPONDENCE and MEMOS OF TELECONS	Y
11	MINUTES OF MEETING	
	Date of End-of-Phase II Meeting N/A	5/6/92 (Gn'l)
	Date of pre-NDA Meeting ___	2/1/94 + 5/5/94 (CMC) 2/8/94 (Stats+Bpha)
12	ADVISORY COMMITTEE MEETING MINUTES or, if not available, 48 Hour Info Alert or pertinent section of transcript 3-29-96	Minutes N Info Alert N Transcript Yes No mtg ___
13	*FEDERAL REGISTER NOTICES, OTC or DESI DOCUMENTS*	N/A
14	If approval letter has ADVERTISING MATERIAL been reviewed? If no and this is an AP with draft labeling letter, has advertising material already been requested?	Yes ___ No X Yes, documentation attached ___ No, included in AP ltr ___
15	Have all disciplines completed their reviews?	Yes X No ___
	If no, what review(s) is are still pending?	___
16	Integrated Summary of Safety	Y
17	NDA Summary (especially Medical/Statistical)	Y

CERTIFICATION

NDA Application: 20-563

Drug Name: Humalog™, [insulin lispro (rDNA origin)

Pursuant to provisions of 21 USC 335a(k)(1), Eli Lilly and Company, through Timothy R. Franson, M.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: _____
Timothy R. Franson, M.D.

Title: Executive Director
North American Regulatory Affairs

Date: March 9 1995

May 30, 1996
Division Director's Memo
To the file: NDA 20-563 Humalog [insulin lispro (rDNA) origin] injection
From: Solomon Sobel M.D,Director, Division of Metabolism and Endocrine Drug Products 5/30/96
Subject: Approval of NDA

The issues which require some clarification include the prescription (non OTC) status of lispro, the clinical utility of this insulin analog, the significance of the pharmacokinetic profile with its resultant lower post prandial glucose levels and the need for various Phase 4 studies.

The Advisory Committee unanimously recommended that lispro be made available only through prescription and not have the OTC status accorded other insulins.There is an already existing exception under CFR 429.11 (h) (1) for insulins containing 500 units per milliter. This exception, of course, reflects the safety issue of inadvertent administration of a very high dose of insulin.
In the case of lispro there is, likewise, a safety issue of inadvertently inducing hypoglycemia because of the more rapid pharmacodynamic effect and potentially a lack of enterally absorbed glucose at that time.
. Other safety issues discussed during the advisory committee meeting included the potential of more rapid intracellular inflow of potassium which might be induced by lispro beyond that of other available insulins given subcutaneously.
In regard to other regulations affecting insulins, lispro should be treated conventionally. It is subject to the current certification requirements for insulins. It would not be reasonable to interpret the definition of the term insulin as given under CFR 429.3 (g) "the active principle of **pancreas** which affects ther metabolism of carbohydrate in the animal body" as excluding the recombinant lispro whose amino acid sequence is not found in any animal specie.

In respect to clinical utility our Indications and Usage section states simply that "Humalog is an insulin analog..... which is indicated in the treatment of patients who require insulin to achieve or maintain normal glucose homeostasis."
The advantage of the rapid absorption of lispro seems to be primarily logistical,i.e., that the insulin can be taken closer to meal time.
There is a demonstrated lower post prandial level of blood glucose at one and two hours but the clinical benefit of this is not clear. There is no benefit as measured by the effect on glycosylated hemoglobin levels. (This is in contradistinction to agents such as acarbose which blunt the post prandial glucose

response but which also effect a lowering of glycosylated hemoglobin).
The lessening of nocturnal hypoglycemic events reflects the shorter duration of action of lispro and the resultant higher levels of blood sugar during the night (most clearly from midnight to 6 am.)

We have requested a number of phase 4 clinical studies. These are mostly reflective of recommendations made during the advisory committee discussions.
We have also requested phase 4 commitments in respect to

Conclusion:
The Division recommends approval of lispro.
The drug will require a prescription. Insulin certification requirements will be those that apply to other insulins.
Various phase 4 commitments have been made and are outlined in in the approval letter.

Solomon Sobel

cc: NDA Arch.
HFD-510
HFD-510/EKoller, RMisbin, AFleming, JWeber

Group Leader's Note

NDA 20-563
Humalog™ (lispro insulin)

May 26, 1996 **Lilly Research Laboratories**

Humalog is the first insulin analog to be presented for marketing. While there is abundant experience with nonhuman insulins and formulations of animal and human insulin designed to alter the time-action profile, this is the first insulin molecule that behaves kinetically differently from human insulin because of its modification in amino acid sequence. The clinical consequences of treatment with this modified insulin require further resolution. We have enough evidence to suspect that there might be some differences in outcomes of patients treated with Humalog compared with conventional insulin. For his reason alone, we consider Humalog a special case among insulin drug products. It is different enough from all previous insulin products that physician product labeling is warranted. However, a reasonable perspective should be maintained about this drug product. Humalog's amino acid sequence is closer to that of human insulin than beef insulin. Though the modification is in a critical location with respect to self affinity of Humalog molecules, it is outside regions that interact directly with insulin or IGF receptors. Thus, it is unlikely that this molecule will interact with these receptors to induce adverse effects on insulin-mediated diabetic complications. Humalog does, nonetheless, have some real and theoretical advantages and problems. It is important to distinguish what is known from what remains a concern. This review is organized according to three categories of various degrees of certainty.

I. What is well-established about Humalog?

Humalog has a significantly more rapid onset and offset of hypoglycemic action than regular insulin when given subcutaneously. This has been clearly shown in normal subjects. There are less PK-PD data from patients, in whom anti-insulin antibodies might be expected to reduce the difference in performance of Humalog and regular insulin (Humulin). Those data also show that Humalog performs differently from Humulin. Results of the phase III studies also confirm the significant time course difference in a less formal fashion.

Humalog's more rapid onset of action undeniably represents a convenience for some patients. A pediatrician mother recently contacted me about continuing Humalog use in her four year old girl who had participated in a Lilly-sponsored study. She said that Humalog had made a miraculous difference in her ability to control her daughter's diabetes. Obviously, a single testimonial of this sort does not prove much, but it does help to establish that Humalog's time-action profile is not just different but this difference results in a substantial benefit for one or more patients. No attempt was made by the sponsor to quantitate the benefit of convenience to the patient. Ultimately, this may be Humalog's sole substantial benefit

II. What is strongly suspected about Humalog therapy?

Glycemic Control

In the phase III studies, Humalog therapy resulted in comparable glycemic control to that achieved with regular insulin, but there was a very small difference favoring Humulin in HbA1c reflected glycemic control. This difference is of no clinical significance for an individual patient, but it may reflect a slight down side for use of the drug in the aggregate. At the very least, physicians and physician cannot expect Humalog to reduce their efforts to achieve good glycemic control. It appears reasonable to assume that comparable or even improved control with Humalog, compared to Humulin, can be obtained over many years of therapy, but this remains to be shown.

Hypoglycemia

It is plausible to expect Humalog therapy to reduce frequency and severity of hypoglycemia, but this was not convincingly shown in the controlled studies. A small difference favoring Humalog in episodes of night time hypoglycemia was found in the phase III studies, but this could simply be the result of a slight loss in glycemic control as reflected by higher fasting glucose averages associated with Humalog therapy. It is also reasonable to expect that severe day time hypoglycemia, particularly related to increased physical activity, will be reduced by Humalog therapy. This was not shown in the phase III studies, but they were not powered to demonstrate this effect.

Insulin Allergies

The very small increase in a variety of allergic-related reports seen with Humalog therapy compared to that with Humulin therapy is a cause for concern. Obviously, a change in the primary structure of insulin could easily result in a more allergenic molecule. Of greater concern is several reports of immediate, even anaphylactic-like reactions seen with Humalog in the absence of such reports from Humulin-treated patients. The frequency of such events appears to be acceptable when compared to experience with animal insulins. On the other hand, immediate-type allergic reactions are very rare with human insulin. Non-immediate allergic reactions represent more of a nuisance than a serious concern. The low level of these reactions in Humalog treated patients nonetheless appeared to be significantly different from those treated with Humulin. While clinically insignificant, this may again point to increased allergenicity inherent to the analog.

III. What are lesser and/or theoretical concerns about Humalog therapy?

Decline of Response to Humalog with Time

The phase III studies showed a small, but significant increase over six months in the doses of basal insulin used by those on Humalog compared with those on Humulin. It is not clear why

a treatment effect was observed on the basal and not the rapid acting insulin doses. The signal here is weak and may turn out to be a chance occurrence. Alternatively, this could result from a sensitizing effect of Humalog on insulin antibody production. No clear relationship between changes in insulin doses and antibodies was seen, but this does not exclude that mechanism.

Rapid metabolic effects

It is conceivable that the rapid glucose lowering effect of Humalog could lead to transient intracellular influx of potassium and thereby promote cardiac arrhythmias. There is absolutely no pre-clinical or clinical evidence of Humalog having such cardiac effects. Furthermore, there is little reason to suspect that this would occur given the insulin kinetics and glucodynamics following subcutaneous administration of Humalog. Humalog when given sc comes very close to mimicking the physiologic profile of postprandial insulin release and glucose response. It is true that diabetics typically have a wider excursion from peak to nadir glucose levels than non diabetics. This greater absolute influx of glucose and possibly potassium could conceivably be arrhythmigenic. However, the time course of sc Humalog on glucose levels is considerably longer than that seen during iv insulin injection, where the hypokalemic effect is known to occur and is even exploited to treat life threatening hyperkalemia. Again, Humalog performance in this respect appears much closer to physiology than to the iv pharmacologic effect.

Effect of mixing Humalog with other insulins

Humulog might lose its rapid acting feature when it is mixed and incubated with protamine insulin (NPH) for a prolonged period. This does not appear to be a problem when such insulin mixtures are promptly administered. It was shown that there was no Humalog association with protamine for up to 30 hours *in vitro*, but this does not exclude such an interaction *in vivo*. This is unlikely to be more than a trivial effect under most circumstances, but a study will be done to examine this effect under more extreme situations.

Integrating clinical and regulatory perspectives

Humalog appears to offer sufficient overall benefits (perhaps nothing more than convenience) to justify the apparent incremental risk of substituting therapy with this new insulin molecule for regular insulin therapy. There are two pieces of information necessary and sufficient for approval of this drug product. The first is of Humalog's glucodynamic profile. The second is its safety profile during clinical use compared with that of conventional insulin therapy under conditions that result in comparable glycemic control. This information has been adequately provided in the NDA. Humalog's safety profile appears equivalent to that of Humulin with the possible exceptions discussed above and in the proposed labeling. A very large patient exposure has been accumulated, but the duration of controlled exposure is limited to six months. The open-label design has obvious draw backs, but I believe that it was the more practical way to achieve the large exposure needed to have some chance of detecting less frequent but important events.

Comments about the physician labeling

Lilly's current draft (sent by FAX 5/24/96) of the proposed physician labeling represents the result of four major rounds of negotiations with the company. Our primary reviewers have done an excellent job of insisting on retaining a number of important points. In my estimate, the sponsor has come a great distance in accepting virtually all these points. We have not yielded in any substantial way, but have been open to editorial approaches palatable to the sponsor that preserved the sense and the potential impact of each point. I believe that this draft labeling is acceptable. Our primary reviewers would like to see yet one more addition made to the labeling as is described in the attached Email messages. As I say in my note, it is not an unreasonable proposal, but it will be seen as unreasonable by the company at this point in the process given the extensive changes to which they have already agreed. The company's point of view would not be important if this were information that should be included. I believe that the benefit of their proposed statement is debatable. Therefore I recommend that we accept the sponsor's latest proposed labeling.

Our colleagues, Anne Reb and Ken Feather, in DDMAC has closely reviewed the proposed physician labeling, and has clearly documented their concerns about how this could be used to make unwarranted advertising claims (see attachment). These concerns are appropriate, but I am hopeful they will not be issues after Lilly submits its advertising material. If they become issues, we in DMEDP will strongly support DDMAC's efforts. On the other hand, I do not think we can justify tightening up the labeling further as a means of preventing any possibility of the sponsor inappropriately advertising their product.

Our primary reviewers have brought back another issue, their feeling that we should caution about the use of Humalog in patients with _____ I am not persuaded by their concern. There is

However, it is the gastric dysfunction that is the issue and not the drug itself. Because there is a vast range of _____ among patients with this diagnosis, how could a physician do anything other than individualize therapy with Humalog as she/he already must do with Humulin? I am puzzled by the notion that physicians and patients who already struggle with the consequences of _____ everyday have to be re-educated to monitor glycemic response to insulin therapy of any kind. Humalog's physician labeling cannot be a comprehensive guide to insulin therapy. I am also unsure of the kind of study that should be done in this patient population or whether one is needed at all.

Summary and Recommendations:

Humalog has been adequately demonstrated to be safe and effective as a rapidly acting insulin together with a long acting insulin product in patients requiring chronic insulin therapy. Humalog is

significantly more rapid acting than regular insulin when given subcutaneously, and this is likely to be beneficial to patients. There are some lingering concerns about allergenicity, rapid metabolic effects, and long term tachyphylaxis, but these represent small, acceptable risks that are appropriately discussed in the physician labeling. The NDA should be approved contingent on the sponsor's commitment to complete the phase 4 studies listed in the draft letter of approval. The sponsor's latest version of proposed labeling is acceptable.

5/28/96

Alexander Fleming, M.D.

with 5 pages of attachments

cc:
HFD-510
/Div. Files/ NDA 20-563
/M. Fossler, E. Koller, R. Misbin, S. Sobel, G. Troendle, J. Weber

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-563 Trade (generic) names Invirase

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

X 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to ~~expect early widespread~~ pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

X (1) Studies are ongoing. Refer to Brief Review 5/7/96
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

____ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

5/7/96
Signature of Preparer

5/7/96
Date

Refer to Brief Review

cc: Orig NDA
HFD-__/Div File
NDA Action Package

5-24-96

NDA # 20.563 MEMORANDUM TO THE FILE

The sponsor has proposed by FAX several phase 4 studies:

The sponsor did not propose studies to assess the use of Humalog in:

g) pregnancy
h) autonomic neuropathy
i) gastroparesis/abberrant gastric emptying
j) select subpopulations with cardiac disease +/- use of drugs that increase the risk of dysrhythmia
k) exercise
l) smoking
m) increased subcutaneous thickness/obesity

The sponsor-proposed studies were briefly discussed by Drs. Misbin and Koller with Dr. Sobel 4/22/96. Studies e) and f) were not thought to be as important as the other studies and completeness of the list would need to be considered. It was agreed that Dr. Koller would write a Memoradum for the File RE: the above proposals and that Dr. Misbin would request a formal submission of the FAXed proposals. Later that afternoon Dr. Sobel indicated that he agreed that studies examining were also important. He was taking additional time to consider other appropriate studies. A copy of the Advisory Committee Transcipts, flagged with the study requests by members, was provided to Dr. Sobel.

The potential addition of studies regarding h), i), and j) was discussed by Drs. Koller and Misbin with Dr. Winn by phone 5/23/96.

Elizabeth Koller, M.D.
Prepared 5/22/96 Updated 5/24/96

FAX enclosed
CC: Weber/Sobel/Koller/Misbin/Fleming

The following table includes those studies that are to be conducted with Humalog® (insulin lispro).

Study Title	Comments

1. Medical Officer Review: New Drug Application
1.1. Administrative Summary
1.1.1. NDA: #20,563 MAY 22 1996

1.1.2. Review: #1

1.1.3. Submissions
1.1.3.1. Paper submission: 3/13/95

1.1.3.2. CANDA submission: 3/15/95 (6 compact disks)
(Information for indexing provided to DISD 8/96).
CANDA resubmission: 12/14/95 (because of validation problems

1.1.3.3. Major Amendment: 12/18/95
69 volumes-1 General information
2 F3Z-SB-IOAT
3-34 F3Z-MC-IOAY
35-39 F3Z-MC-IOBN
40-69 Extension studies: IOAK, IOAM, IOAN, and IOAO

1.1.3.4. Supplemental Submissions:
-6/5/95 Microbiology information
-6/6/95 1 volume with an incomplete response to questions RE: IOAA posed by the Division in a 3/6/95 letter from DMEDP
-6/7/95 1 volume with a response to questions RE: IOAC posed by the Division in a 1/19/95 letter from DMEDP
Hypoglycemia versus level of glucose control
Retinopathy data
-6/8/95 1 volume with a response to questions RE: IOAD posed by the Division in a 3/6/95 letter from DMEDP
Renal data
-6/12/95 1 volume with an incomplete response to questions RE: IOAF posed by the Division in a 3/6/95 letter from DMEDP
-7/13/95 4 volumes of a safety update
-7/21/95 Chemistry, manufacturing, and control Data
-8/18/95 Confirmation of questions raised by DMEDP 7/27 and 8/10/95.
-9/6/95 3 volumes with responses to questions posed by DMEDP
Attachment A Investigators in Canada who used standardized meals during the trials
Attachment B Rashes.
Attachment C Pruritis.
Attachment D Dysmenorrhea.
Attachment E Number of hypoglycemic episodes-uncorrected by time interval-sorted by glucose level.
Attachment F Creatinine.
Attachment G Insulin determination assay.
Attachment A1 F3Z-LC-IMAD Synopsis without raw data, F3Z-SB-IOAT Berger clamp data synopsis without raw data, F3Z-EW-E001 Injection site PK data, F3Z-LC-IMAB Effect of addition of zinc-individual patient data
Attachment A2 F3Z-LC-IMAC Dose-ranging studies-individual PK data, F3Z-MC-IOAA/AK-renal data from 2 patients discontinued (renal/drug use), EKG readings
Attachment A3 Neuropathy and hypoglycemia

Attachment A4 Neuropathy and hypoglycemia
Attachment A5 Prior insulin use in IOAF
Attachment A6 Anti-insulin antibody assay validation
Attachment A7 Miscellaneous responses
-9/7/95 Determination of patients in the U.S in extension trials avaialable for retinopathic evaluation
-9/13/95 Response to request for validation of glucose excursion Clinical report F3Z-SB-IOAT (Berger)
-10/10/95 EKG data
-10/11/95 Protocols for sites to be investigated
-10/23/95 Study IMAD, Meal data from 4 patients
-10/25/95 Antibody data, Hypoglycemia by time
-10/26/95 Background information on select patients
-10/27/95 Allergic reaction information, Counter-regulatory responses in normal subjects
-10/30/95 Definition of baseline
-11/6/95 Stability data
-12/8/95 EKG Information, Quality of Life
-12/11/95 24 volumes of case report forms for select patients from (F3Z) EW-E002, MC-IOAA, MC-IOAB, MC-IOAC, MC-IOAD, MC-IOAE, MC-IOAF, MC-IOAG, MC-IOAH, and MC-IOAN
-12/14/95 CANDA resubmission
-12/19/95 Physician labeling-draft #1
-2/14/96 Transposition of statistical data-correction
-4/1/95 Draft labels #2
-4/3/95 Draft label diskette
-4/22/96 Revised draft labels

1.1.4. Review completed: 5/19/96

1.2. Drug Name
1.2.1. Generic name: Insulin Lispro

1.2.2. Proposed trade name: Humalog

1.3 Sponsor: Eli Lilly Laboratories

1.4 Pharmacologic category: insulin analogue

1.5 Proposed indications:
For treatment of patients with IDDM or NIDDM, who require insulin therapy by subcutaneous injection.

1.6 Dosage form and route of administration:
1.6.1 Dosage forms: vials for injection and cartridges for use in specified injection pens.

1.6.2 Route of administration: subcutaneous injection

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:

IND# final study reports
F3Z-MC-IOAA completed 11/13/94
F3Z-MC-IOAB completed 9/13/94
F3Z-MC-IOAC completed 11/25/94
F3Z-MC-IOAD completed 11/25/94
F3Z-MC-IOAE completed 2/3/95
F3Z-MC-IOAF completed 1/19/95
Advisory Committee Document
Cardiology consult

1.10. Materials reviewed:
-Volumes: 1, 1A, 4, 8, 21-30, 34, 45-53, 58-59, 63-80, 85-119, 125-128, 130-132, 191-192, 203, 212, 214, 242, 246, 268-270, 333, 370-373, and 387.
-CANDA
-Supplemental submissions as described above
-Major Amendment; Volumes 1-69

1.11. Table of Contents

2. Introduction

In current U100 insulin preparations, the insulin molecule tends to aggregate as a hexamer. Dissociation must occur before insulin can be absorbed into the blood. Conversely, the IGF-I monomer demonstrates a decreased propensity for aggregation. Although the two compounds share large regions of structural, homology, there are non-homologous regions. The sponsor exploited what was known about these non-homolous areas to engineer a change from proline to lyseine and lyseine to proline at positions 28 and 29 respectively of the B chain of insulin. Early studies confirmed that the modified insulin tended to lower glucose earlier than human regular insulin. Because this effect was seen only with subcutaneous administration, and not with intravenous adminstration, and because its bioavailablity was not altered by route of administration, it has been determined that lispro's novel pharmacokinetic properties are directly related to the altered rate of absorption. Rapid absorption permits administration closer to mealtime and somewhat reduces the need for advanced planning of food intake. It was also hoped that this somewhat more physiologic profile result in improved glucose control and that the shorter duration of action would result in less hypoglycemia.

There are, however, potential problems with the use of a new, rapidly-acting insulin product:
1) Lispro, as a new molecular entity, may have undesirable properties independent of its glucose lowering capabilities.
2) A short acting insulin might give rise to delayed, postprandial hyperglycemia.
3) A rapidly acting insulin might not be tolerated by diabetics with cardiovascular or neuropathic complications.
4) An insulin product that improved the glucose excursion, an unvalidated measure of efficacy, at the expense of HgbA1c could be deleterious to the goals of diabetes management, ie., reduction of the risks for chronic complications.

The sponsor submitted 10 clinical trials for review (8 IOAA-IOAH 3/95 and 2 IOAY and IOBN 12/95). Despite the number of trials, there were problems in the collection of important pharmacologic data and in the conduct of the trials. These problems limit conclusions about both safety and efficacy data.

3. Objectives

The sponsor sought to optimize the glucose control that can be obtained with lispro. Nine studies employed multiple shots of rapid acting insulins given in conjunction with 20% or more of daily calories. To assess glucose control, the sponsor utilized measurements of HgbA1c, fasting glucose, postprandial glucose, and the glucose excursion, (serum glucose at 1 or 2 hours postprandially minus the fasting glucose value). The excursion was designated the major outcome parameter, but remains unvalidated.

4. Pentium chip use

The sponsor has indicated that an IBM 3090 was used for any mathematical calculations.

5. CANDA Submission
The Sponsor developed their own CANDA software. The CANDA was submitted 3/15/95, but did not become fully operational until late August, 1995. Multiple requests for indexing variables were made by K. Edmunds (DSID). There were a significant number of problems with the CANDA, which were, in part, outlined to the Sponsor in a DMEDP letter. These problems included the inability to identify through the ACCESS pathway groups of patients defined by two or more criteria. Case report forms were not electronically encoded as such. Information on individual cases could be obtained only after entry into multiple data bases. Data entry was not uniformly codified. For example, death was coded as an outcome by some investigators and as an adverse event by others so, unless one knew which data bases to search a priori, data assessment could be incomplete. There was a similar problem for the codification of data on retinal events. (Refer to comments by Dr. Chambers in the Advisory Committee transcipts.)

6. Notable chemistry issues
The sponsor has provided documentation that all reagents of bovine origin have been obtained from herds free of bovine spongiform encephalopathy. (Volume 8)

7. Notable pre-clinical studies
7.1 Growth Promotion
Although promotion of growth is one of insulin's metabolic activities, IGF-I is more potent as a growth promotor. Changes in the insulin molecule which could potentially increase IGF-I activity need to be considered for several reasons:
1) IGF-I has been implicated as a mediator for some of the long-term complications of diabetes, e.g., retinopathy and nephropathy.
2) The clinical features associated with the hyperinsulinemia of severe insulin resistance and Syndrome X have been attributed by some investigators with the interaction with the IGF-I receptor.
3) The increased cardiac mass seen with acromegaly may not be well tolerated by diabetic patients.

In <u>in vitro</u> studies utilizing human mammary epithelial cells, another insulin analogue Asp B10 demonstrated more growth stimulation and binding to IGF-I receptors than lispro. Growth stimulation was similar for lispro and human insulin. Binding to the IGF-I receptor, however, was 30% greater for lispro than for unmodified human insulin. Thymidine uptake into human aortic smooth muscle cells was also somewhat greater for lispro than human insulin. (Volumes 21-22)

The clinical significance of changes of this magnitude is uncertain. Cumulative exposure may magnify small changes seen with <u>in vitro</u> assays, and insulin requirements often necessitate administration for decades.

7.2 Electrocardiographic changes
Prolongation of the QRS complex and the QTc interval are the type of changes that have been associated with subsequent dysrhythmias and sudden death in human subjects. Studies in dogs have shown such electrocardiographic changes. They are transient and resolve several hours after subcutaneous administration of lispro. Similar changes are seen with both lispro and human insulin when administered to beagles intravenously. (1994 Annual report)

Presumably these changes are related to the influx of glucose into the cell and/or the eflux of potassium from the cell. The rapidity of absorption may cause the modified insulin act more like intravenous insulin, (which is usually administered in a monitored setting). Although such changes were apparently tolerated without incident by the healthy dogs in the study, subsets of diabetic patients may be less tolerant of rapid changes in serum glucose or potassium, e.g., Patients using diuretics are more prone to hypokalemia, which can potentiate the risk for dysrhythmia, e.g., Digoxin also becomes more toxic in the setting of hypokalemia. (Refer to FDA Cardiology Consultation.)

Patients with class 3 or 4 cardiac disease were excluded from the clinical trials, and subjects were never assessed with postdosing electrocardiograms.

8. Notable pharmacokinetic-pharmacodynamic issues
8.1 Absorption: serum levels
In pharmacokinetic studies, the sponsor is expected to demonstrate absorption of drug. In this case specifically, the sponsor has claimed that the engineered changes in their insulin molecule will increase the rate of absorption. This has been adequately demonstrated in normal volunteers. In patients with diabetes, however, insulin values cannot be measured directly because most patients with any significant exogenous insulin exposure have anti-insulin antibodies on the serum. These must be removed to reduce interference with Such extraction was not performed on samples for insulin levels in the majority of the Sponsor's studies including the population PK collections in the clinical trials. Adequate data for the pharmacokinetic profile in diabetics were provided in Study IOAT, but is limited to ten patients. (9/13/95 Submission)

8.2 Absorption: inter/intra-patient variability
The glucodynamic response (insulin levels are unknown) of Humalog was somewhat less variable than that seen with Humulin R when evaluated in 8, young, IDDM patients (IOAJ: cross-over design). The degree of variability may be different in other populations, e.g., obese subjects. This would limit clinical relevance.

8.3. Variables influencing absorption
8.3.1. Injection site effect
A more potent maximal effect on glucose lowering was seen with subcutaneous injection to the abdominal region than with injections to the femoral or deltoid regions, and the maximal

effect was seen sooner with lispro than with regular human insulin. Studies were conducted only in normal subjects. (Volume 80) Lipodystrophy and/or lipohypertrophy may occur in diabetic patients and are among the variables that might influence absorption. (Young, RJ. Diabetic lipohypertrophy delays insulin absorption. Diabetes care. 1984;7:479.)

8.3.2. Effect of weight
The early pharmacokinetic-pharmacokinetic studies utilized normal weighted volunteers (body mass index not to exceed 25). There were, however, several subjects who were outliers with respect to both weight and testing results. The limited data suggested that obesity and/or subcutaneous fat thickness reduced the rate of absorption. This hypothesis was not formally tested by the sponsor although it is known that many diabetics are overweight.

8.3.3. Effect of smoking
Smoking is thought to have an effect on insulin activity. In part, this may be related to vasoconstriction of the blood vessels involved in absorption. This hypothesis was not formally tested by the sponsor. (Koivisto, VA. Various influences on insulin absorption. Neth J med 1985;28(Suppl):25.)

8.3.4. Effect of drug concentration
Changing the concentration of the insulin suspension may facilitate the onset of insulin action. More dilute solutions (U10,U40) are absorbed more quickly than more concentrated forms (U100,U500). (Galloway, JA; Chapter 7. Chemistry and clinical use of insulin. In Galloway JA et al., eds. Diabetes Mellitus. 9th ed. Indianapolis: Lilly Research Laboratories; 1988:106-33. Chanteleau, E et al.; Absorption of subcutaneously administerd regular human and porcine insulin in different concentrations. Diabetes Metab (Paris). 1985;11:106. Published data from Chatelau and Heinemann suggest that the half maximal glucose infusion rate for U40 Actrapid exceeded that of U100 and approached that of another rapid acting insulin analogue (Diabetes Research and Clinical Practice. 1993 21:201-2).

8.3.5. Effect of mixing with other insulins
8.3.5.1. The more rapid absorption of Lispro is attenuated by mixing with NPH, but not by ultralente. (Study IOAI-Volume 79) (Refer to Biopharm Report)

8.3.5.2. The short acting properties of regular insulin may be attenuated by mixing with ultralente. (Schlictkrull J, Pingel M, Hedig LG, Brang J, Jorgensen KH; Insulin prearation with prolonged effect. In Handbook of Experimental Pharmacology: Insulin II. Hasselblatt E, Burchhausen FV, ed. Berlin, Heidelberg, New York Springer 1975:729-77) Whether this interaction contributes to some of the differences in outcomes seen with studies in which ultralente was used exclusively as the longer-acting insulin versus NPH is unknown.

9. Study design
9.1. General

Table 1

DESIGN FEATURES OF CLINICAL STUDIES

Study	Diabetes Type	Study Type	Dosing Rapid Insulin	Tx Arm Duration	Blinding	Uniform Meal	Basal Insulin *	Glucose Labs****
IOAA	1	parallel	with meals	12 mo	no	no	U	lab
IOAB	2	parallel	with meals	12 mo	no	no	U	lab
IOAC	1	parallel	with meals	12 mo	no	no	N	lab
IOAD	2	parallel	with meals	12 mo	no	no	N	lab
IOAE	1(new to insulin)	parallel	with meals	12 mo	no	no	N/U	lab
IOAF	2(new to insulin)	parallel	with meals	12 mo	no	no	N/U	lab
IOAG	1	x-over	with meals	3 mo	no	no	N/U	lab
IOAH	2	x-over	with meals	3 mo	no	no	N/U	lab
IOAY**	1 and 2	x-over	BID	2 mo	no	no	N	means of 4 days meter readings/visit
IOBN***	1	x-over	with meals *****	3 mo	yes	no	N qHS	means of 4 days of meter readings/visit

U=Ultralente, N=NPH Tx=Treatment

* In studies where both types of longer acting insulins were used there was no randomization for the type of longer acting insulin It was an uncontrolled variable

** Some patients used preparations with a fixed ratio of Humulin R to a longer acting insulin There was no comparable fixed ratio preparation for Humalog

*** HgbA1 and/or HgbA1 samples were collected

**** "Lab" indicates that glucose values were determined by laboratory assays and not self monitoring by meter

***** Both Humulin R and Humalog were given immediately prior to meals In other studies, Humulin R was given 30-45 minutes prior to meals

9.2. Patient selection criteria

9.2.1. Exclusionary criteria:

Class 3 or 4 cardiac disease or severe vascular disease (peripheral or central)
renal transplantation or dialysis
serum creatinine greater than 2 mg/dl in IOAA-IOAD or 3 mg/dl in IOAE-IOAH
cancer or life expectancy less than three years
significant hepatic disease including SGOT levels greater than twice the upper normal limit.
allergy to insulin or its excipients
insulin by pump infusion
insulin doses greater than 2 U/kg/day
body weight greater than 35 kg/meter squared
pregnancy (or risk of) and lactation
non-compliance or situations which will interfere with proper completion of control
recent participation in trials with another investigational pharmaceutical agent
history of significant hypoglycemic unawareness and hypoglycemia
(more than two hospitalizations in the preceding year)
adrenal insufficiency
hemoglobinopathies or anemias

9.2.2. Additional exclusionary criteria for F3Z-MC-IOAE and IOAF

prior exposure to animal insulins
insulin use longer than two months

9.2.3. Additional exclusionary criteria for F3Z-MC-IOAY
HgbA1c >2x the upper limit of normal
has not used insulin BID for at least 2 months
creatinine <3 mg

9.2.4. Additional exclusionary criteria for F3Z-MC-IOBN
HgbA1c > than 1.5 times the upper normal value
NIDDM
not performing QID insulin administration
unable to perform home glucose monitoring
take less than 50% of their insulin 15 minutes prior to meals
creatinine <3 mg

9.3. Number of patients

The number of patients who were randomized to and who dropped out of each treatment and each treatment arm is described in Table 2. Drop-out rates were similar. The reasons for drop-out tended to be similar.

Table 2 Number of Patients in Study

Study	# Randomized				# Drop-outs				% Drop-out			
	L	H	L/H	H/L	L	H	L/H	H/L	L	H	L/H	H/L
IOAA	81	74			7	7			8.6	9.4		
IOAB	72	73			2	2			2.8	2.7		
IOAC	81	88			6	5			7.4	5.7		
IOAD	73	77			5	6			6.8	7.8		
IOAE	50	43			5	5			10.0	11.6		
IOAF*	186	189			30	28			16.1	14.8		
IOAG	1008		508	500	22	26	21	27	2.2	2.6	4.1	5.4
IOAH	722		354	368	20	16	21	15	2.8	2.2	5.9	4.1
IOAY	707		353	354	6**	23	16	13	0.8	3.2	1.7	6.5
-IDDM	379		195	184								
-NIDDM	328		158	170								
IOBN	93		41	52	3***	3	5	1	3.2	3.2	12.2	1.9

L=lispro
H=regular human insulin

* ~10% of patients were ineligible for entry; reanalysis of data did not change results
** 2 patients were dropped for hypoglycemia
*** 2 patients were dropped for lack of efficacy

9.4. Characteristics of study population

9.4.1 Intended patient population for each of the trials.
The target population for each clinical trial is described in Table 3.

Table 3 Characteristics of the Intended Patient Population

Study	Diabetes Type	Insulin Use	Age(yrs)
F3Z-MC-IOAA	IDDM	>2 months on insulin	12-70
F3Z-MC-IOAC	IDDM	>2 months on insulin	12-70
F3Z-MC-IOAE	IDDM	<2 months on insulin	12-70
F3Z-MC-IOAG	IDDM	>2 months on insulin	12-70
F3Z-MC-IOBN	IDDM	very well controlled comfortable with intensive therapy	18-75
F3Z-MC-IOAY	IDDM	> 2 months on BID therapy HgbA1c </=2x upper normal	18-70

9.4.2. Characteristics of the patients enrolled.
9.4.2.1. Age
Of the 2834 patients enrolled, 118 (4.2%) were under the age of 18. No patients were under age 12 (by entry criteria). 338 (12%) were aged 65 years or more.

9.4.2.2. Gender
1265 (45%) of enrollees were female and 1569 (55%) were male. (N.B. Gender may be of some importance. In studies F3Z-MC-IOAA through IOAD, lower glucose excursion values were seen in women treated with Lispro.)

9.4.2.3. Race
90% of enrollees were classified as Caucasian, 4.5% as African, 3.4% as other, and 2.5% as Hispanic.

9.4.2.4. Location
48% of enrollees were from North America, 40% from Europe, 8% from South Africa, and the remander from the Pacific Rim.

9.4.2.5. Body mass index
Although IDDM patients constituted 51% of the enrolled patients, over 60% of the enrollees were obese (BMI >/=25).

9.4.2.6. Duration of diabetes
64% of patients IDDM were known to have had diabetes for less than 10 years. 18% of enrollees were known to have had diabetes for 20 or more years. Patients were not, however, assessed for the complications of diabetes except by serum creatinine. Those with problematic hypoglycemia (perhaps secondary to autonomic neuropathy) were excluded from the trials. Those with elevated serum creatinines or renal complications were excluded.

9.5. Number of Patients Per Investigator
An investigator is more likely to recognize associations between a drug and adverse if the investigator has treated a sufficient number of patients with the drug for a sufficient duration. In addition, investigator impact cannot be properly assessed when an investigator has treated fewer than ten patients in each treatment arm. The average number of patients per investigator was low. (The ability to evaluate investigator effect is markedly limited when there are less than ten patients per treatment arm per investigator.)

Table 4 Number of Patients Per Investigator

Study	#Pts/Investigator	Study	#Pts/Investigator
F3Z-MC-ICAA	11.1	F3Z-MC-IOAB	11.1
F3Z-MC-IOAC	9.9	F3Z-MC-IOAD	11.5
F3Z-MC-IOAE	4.4	F3Z-MC-IOAF	8.7
F3Z-MC-IOAG	9.7	F3Z-MC-IOAH	9.8
F3Z-MC-IOAY	9.4	F3Z-MC-IOBN	9.3

9.6 Blinding
Blinding is an important feature of study design. The ideal study would have utilized a blinding with dosing of insulin and a placebo-at the optimal time of action for each insulin species. This design is somewhat more cumbersome, but could have reduced some of the confounding present in the trials. If an open-label design is utilized, significant care must be taken to avoid test parameters that are subjective and to maintain high expectations for both treatment groups.

Of the clinical trials submitted, only F3Z-MC-IOBN (n=93 IDDM patients) was a blinded study. Insulin doses were given only at a single preprandial time (which tended to favor Humalog for postprandial outcomes). Patients were expected to administer their insulin at the proper time and to do their own glucose monitoring for seven point glucose profiles. This presented the potential for even these blinded patients to determine/suspect their treatment status.

The postprandial glucose values obtained in F3Z-MC-IOAA through IOAH are an example of test parameters with elements of subjectivity. Patients were given the test insulins at time appropriate to their distinct pharmacokinetic properties in an open label fashion, but ingested test meals that were not standardized for the trial. (Breakfasts were to remain the same for a given patient during the trials.) The use of a cross-over design may mitigate, albeit incompletely, the absence of standardization for the meals.

Collection of the data on hypoglycemia is another example of a test parameter with elements of subjectivity. Patients were encouraged to report any episodes of suspected hypoglycemia even without documentation of glucose. Vasodilatory episodes and other

events-particularly in the presence of autonomic neuropathy-can also be perceived as hypoglycemia. The investigator brochure indicated that a reduced frequency for hypoglycemia was a likely benefit of treatment with the new insulin analogue. If this was conveyed to patients, there was the potential for under-reporting in the lispro treatment group. (Alternatively, investigators may have been more aggressive with therapy if they believed the hypoglycemia risk to be lower.)

Study duration may also be more important in an unblinded clinical trial. There is reduced novelty with extended use of a drug so compliance and behavior patterns altered by expectation may become more realistic. Studies F3Z-MC-IOAG, IOAH, IOAY, and IOBN all had treatment arms limited to two or three months in duration.

9.7. Study drug-formulation

Humalog has the empirical formula C257H383N65077S6. The primary structure is identical to that of human insulin except for the reversal of the amino acids in positions 28 (proline-->lyseine) and 29 (lyseine-->proline) of the B chain.

Each milliliter of the commercial formula contains insulin lispro (100 units), glycerin (16 mg), cresol (3.15 mg), phenol (trace), zinc ion (0.0197 mg from zinc oxide), water to volume buffered with dibasic sodium phosphate (1.88 mg) to a pH of 7-7.8.

The initial formulations lacked the presevative zinc. Although zinc can increase self-aggregation, it had only a limited effect on the more rapid absorption rate seen with the molecular changes. (Volume 70) (Data from humans, pigs, and dogs were not concordant.)

9.8 Dose-Route-Regimen

9.8.1. Subcutaneous administration

The pivotal clinical trials were all conducted using subcutaneous administration.

9.8.2. Intravenous administration

Although intravenous adminstration was used in early PK-PD studies, only a limited number of patients were assessed in these studies. Moreover, the data (F3Z-LC-IMAC) suggest that the PK-PD profiles of regular human insulin and insulin lispro are identical when this route of administration is used. This is consistent with the hypothesis that the more rapid onset of action is due to more rapid absorption. (Volume 49)

9.8.3 Pump adminstration

Subcutaneous administration does not include the utilizaton of pumps (whether internal or external). For approval in pumps, the sponsor must submit acceptable data assessing a number of in vitro parameters including buffering capacity as outlined in the Agency's draft guidelines from 1986.

9.8.4 Use of longer acting insulin concomitantly
The trials were structured so that the rapid acting insulin was used in conjunction with a longer acting insulin. In the clinical trials in which either ultralente or NPH could be used as the longer acting insulin, the unblinded investigator determined without randomization which longer acting insulin would be used. The majority of patients used NPH as a basal insulin. (In F3Z-MC IOAE and IOAF, 9/462 were using lispro+NPH and 12/462 were using Humulin R+NPH at visit 2. In F3Z-MC-IOAG and IOAH, 1362/1697 were using lispro+NPH and 1384/1765 were using Humulin R+NPH at visit 2. The remainder were using ultralente or no longer-acting insulin.) Longer acting insulins could be given once or twice a day.

9.8.5. Mixing insulins
The C-max for lispro occurred later and was lower and the R-max occurred later when lispro was mixed with NPH. Because this interaction does not occur with ultralente, it is presumed that protamine is responsible. The Sponsor has not provided information correlating protamine content with the degree of attenuation of the rate of glucose lowering. It is also not known whether the duration of mixing affects the extent of attenuation. The Sponsor was not able to provide information on the number of subjects who mixed insulins and what specific mixing regimens were used at various times during the trials. This confounds interpretation of data regarding the timing of hypoglycemia and postprandial glucose measurements.

9.8.6. Regimens and titration
Investigators were instructed to adjust doses of insulin to minimize glucose values at 1 and 2 hours postprandially and at the time of fasting. Hypoglycemia was also to be kept to a minimum. A lead-in period was often utilized to make major changes before the start of the treatment period. Because of the known pharmacokinetics and the postprandial target sampling times favoring Humalog, excessive dosing of regular human insulin and the subsequent hyperglycemia could be expected to result. To achieve lower fasting levels, particularly with Humalog, doses of basal insulins could be adjusted. This was not always clearly permitted by protocol. If only the rapid acting insulin was permitted to be adjusted, lower fasting glucose levels might be achieved only at the expense of hypoglycemia occurring earlier in the evening. This would be expected particularly for Humalog with its known shorter duration of activity.

Patients in IOAY who were on fixed ratios of Humulin R and a longer acting insulin were allowed to remain on these fixed ratios. There was no comparable fixed ratio treatment for Humalog. Fixed ratios limit the the ability of the physician to fine tune glucose control.

9.8.7. Site of injection
The site of injection will influence the rate of absorption. (Kovisto, VA; Alterations in insulin absorption and in blood

glucose control associated with various insulin injection sites in diabetic patients. Annals Int Med 1980;92:59.) Absorption is more rapid from an abdominal site than from a deltoid or thigh site unless the extremity is exercised, massaged, or heated. (Kovisto, VA; Various influences on insulin absorption. Neth J Med 1985;28(Suppl):25. Interpretation of the postprandial measurements in F3Z-MC-IOAY and IOBN is complicated by the uncontrolled site of injection. Because postprandial glucose values were derived from home glucose monitoring, subjects were not asked to limit their exercise for glucose sampling.

Table 5 Injection Sites

Study	rapid acting insulin	basal insulin
IOAA	abdomen	abdomen
IOAB	abdomen	abdomen
IOAC	abdomen	abdomen
IOAD	abdomen	abdomen
IOAE	abdomen	not designated
IOAF	abdomen	not designated
IOAG	abdomen	not designated
IOAH	abdomen	not designated
IOAY	not designated	not designated
IOBN	not designated	not designated
	kept similar although rotated during the trial	kept similar although rotated during the trial

9.7.8. Time of injection
In studies, F3Z-MC-IOAA through IOAH and F3Z-MC-IOAY, unblinded subjects were asked to inject Humulin R 30-45 minutes and Humalog </=15 minutes prior to meals. In study F3Z-MC-IOBN, blinded subjects were asked to inject Humulin R and Humalog </=15 minutes before the meal. The postprandial data are confounded by the administration of both insulins at a time point prior to meals (</=15 min) that favors the more rapidly absorbed compound.

9.9. Duration of Therapy
9.9.1. Controlled trials
F3Z-MC-IOAA through IOAF are parallel design studies in which patients were treated with Humulin R or Humalog for ~12 months after randomization.

F3Z-MC-IOAG, IOAH, and IOBN are studies in which patients were randomized to treatment with Humulin or Humalog for 3 months and then crossed-over to the alternative treatment.

F3Z-MC-IOAY is a study in which patients were randomized to treatment with Humulin or Humalog for 2 months and then crossed-over to the alternative treatment.

9.9.2. Uncontrolled extension trials
Patients who had used lispro and had completed their trial were allowed enter an uncontrolled extension trial: IOAK, IOAM, IOAN,

or IOAO. The initial maximal length of the extension trials was 2 years. Extensions to the extension trials were added.

9.10. Concomitant medications

9.10.1. Other insulin products

Refer to 9.7.5. Dose-Route-Regimen (Mixing Lispro with NPH insulin and 8.3.5. Biopharmaceutical Issues (Mixing regular insulin with ultralente).

9.10.2. Beta blockers

Beta blockers are known to mask the signs of hypoglycemia. There were no specific studies to address the issue of hypoglycemic unawareness and lispro. The clinical trial data on hypoglycemic unawareness is limited by the Sponsor's definition(s) of hypoglycemia. It was unclear from the data provided whether a patient with a glucose value of e.g. 60 mg/dl and who did not experience symptoms had hypoglycemic unawareness or whether the patient had an appropriate glucose level for his overall level of glycemic control.

9.10.3. Drugs altering potassium status; drugs dependent on the kalemic state

There were no electrophysiologic studies in patients at risk for the EKG changes described previously. No integrated analysis of electrocardiographic changes and kalemic status in patients with sudden death or using drugs that could aggravate the potential for dysrhythmia was provided. (In the CANDA, information that could partially address this issue was scattered throughout the database. Patients using digoxin-like preparations were listed under at least seven categories (digitoxin, Digotab, digoxine, digoxin, Digoxin- lanoxin, and ?Digitrin. Patients using a diuretic were listed under at least seven categories (Dyazide, hydrochlorothyazide, hydrochlorothyazide with (unspecified), furosamid, furosamide, lasix, Lasix Retard, ?Fusid, and ?Hydrodiuril). Patients using potassium supplements were listed under at least five categories (K-dur, K-lor, K-lyte, Kalium Retard, K Tab, ?Kaluril, or ?

9.11. Safety variables

9.11.1. Physical Assessment

Physical exams were performed during screening. Vital signs and weights were assessed at each visit. No additional physical examination was routinely scheduled. No exit physical was routinely performed. Routine diabetes care was to be provided, but was not defined by the sponsor. Ophthalmologic assessment including retinal examination was not obtained at baseline or exit from the controlled trials. Routine assessment of the common autonomic and sensory neuropathic problems associated with diabetes was not done.

9.11.2. Laboratory Assessment

The trials were designed to collect routine clinical chemistry tests including BUN, creatinine, and creatine kinase, routine hematologic tests, and routine urinalysis including spot protein

assessment. 24 hour urine collections for creatinine and protein were not obtained. Subjects with elevated urine protein levels or changes in serum creatinine did not receive any subsequent systematic evaluation. Antibodies specific to human insulin and the insulin analog were assessed at baseline, exit, and at some intervening visits. Similarly, samples for antibodies cross-reactant to both types of insulin and for antibodies reactant to E. coli peptides were obtained on a similar schedule. Antibody assessment during the extension studies was frequently limited to the antibodies specific to a particular insulin although changes were likely to be seen with the cross-reactant antibodies.

9.11.3. Electrocardiographic Assessment
Electrocardiograms were obtained during the screening period. For subjects in some foreign countries, most notably Canada and Australia, additional electrocardiographic studies were obtained during the trials. These electrocardioagrams were not scheduled to assess any transient changes post dosing that might be expected from the canine data.

9.12. Efficacy variables

9.12.1 Efficiacy variables for the clinical trials

F3Z-MC-IOAA through IOAD
- HgbA1c (performed at a central lab)
- Fasting glucose
- Postprandial glucose
- Lipids: cholesterol, triglycerides, LDL, HDL
- Daily insulin dose
- Frequency and incidence of hypoglycemic episodes (blood glucose <36 mg/dl)

F3Z-MC-IOAE through IOAH
- HgbA1c (performed at a central lab)
- Fasting glucose
- Postprandial glucose 1 and 2 hour (Glucose excursion 1 and 2 hour)
- Lipids: cholesterol, triglycerides, LDL, HDL
- Daily insulin dose
- Frequency and incidence of hypoglycemic episodes (blood glucose <63 mg/dl)

F3Z-MC-IOAY
- HgbA1c (by at a central lab)
- Fasting and pre-meal glucose (home monitoring)
- Postprandial glucose (2 hour) (home monitoring)
- Bedtime glucose (home monitoring)
- (Glucose excursion (2 hour) not clearly designated as a parameter)
- Frequency and incidence of hypoglycemic episodes (blood glucose <63 mg/dl)
- Daily insulin dose

F3Z-MC-IOBN
- HgbA1c or HgbA1 (performed at both a central and local lab)

Fasting and pre-meal glucose (home monitoring)
Postprandial glucose (2 hour) (home monitoring)
Bedtime glucose (optional) (home monitoring)
(Glucose excursion (2 hour) not clearly designated as a parameter)
Frequency and incidence of hypoglycemic episodes
(blood glucose <45 mg/dl)
Daily insulin dose
Weight
Number of snacks

9.12.2. The sponsor was advised in a meeting with the Division 5/6/92 that the glucose excursion even if statistically significant would not be acceptable as an endpoint unless validation was provided.

9.13. Procedures
The sponsor obtained postprandial glucose measurements. In studies F3Z-MC-IOAA through IOAH, blood samples were analyzed in a laboratory. In studies F3Z-MC-IOAY and IOBN, patients were responsible for collecting their own values through self-monitoring. The meal ingested by the unblinded subjects was not standardized for the study population. Patients were to ingest their own routine breakfasts at the study sites. The sponsor was not able to provide information on the caloric content or the composition of the meals ingested. Complete food diaries for one year for three patients were submitted, an attenuated food diary was submitted for a fourth patient. (10/23/95 Submission)

9.14. Protocol Amendments
F3Z-MC-IOAA-IOAD(b)(2) required Canadian investigators to collect additional antibody, chemistry, hematologic samples, additional EKGs, and a complete history and physical at the final visit. Patients were also to be discontinued if insulin needs increased by 100% or antibody levels increased by 3 standard deviations above baseline values.

F3Z-MC-IOAC(b)(3) permitted in Canada the addition of 3 test meals (ADA, high carbohydrate, high fat) for additional visits between visit 8 and 9 and the three 500 Calorie test meals after visit 9. Humulin R and Lispro were to be used in a 50/50 mixrure ratio.

F3Z-MC-IOAG and IOAH(1) required Australian investigators to collect additional EKGs during the trial and at exit.
F3Z-MC-IOAG and IOAH(2) required investigators in the United Kingdom to exclude women of child-bearing potential.

F3Z-MC-IOAG(3) permitted investigators at the University of Rome to hospitalize subjects for their first dose.

F3Z-MC-IOAH(3) permitted Dr. de Leiva to collect additional additional samples for apo A1, apo B-100, apo(a)(Lp(a)), hepatic lipase activity, and endothelial liprotein lipase activity.

F3Z-MC-IOAG(4) permitted Dr. de Leiva to collect additional additional samples for apo A1, apo B-100, apo(a)(Lp(a)), hepatic lipase activity, and endothelial liprotein lipase activity.

F3Z-MC-IOAY(1) introduced an interim analysis where previously none specifically had been planned. Dr. D. Yue was the designee as the final report coordinating investigator, and Dr. J. Anderson was the designee to sign the final report for the investigators.

9.15. Statistical Analysis

9.15.1. Interim analysis

Interim analyses were conducted on several of the studies, but the sponsor has not provided information on what statistical adjustments were made.

9.15.2. Use of active controls

The use of an active control can be problematic particularly in an open label trial. Equivalence can be more easily (and erroneously) shown if if attention is not given to optimizing the control group. In the submitted clinical trials, this was not a major problem. The HgbA1c values tended not to change or to decrease slightly from baseline regardless of treatment arm. (Spilker, B; Chapter 94 "Interpretating data from active medicine control groups" from Guide to clinical trials; 1991, Raven Press, New York.)

Confidence intervals may be more appropriate statistical measures when an active control is used. (Rosner, B; Chapter 7 in Fundamental of Biostatistics; 1986, PWS Publishers, Boston.)

9.15.3. Effect of the individual investigator

Investigator impact cannot be properly assessed when an investigator has treated fewer than ten patients in each treatment arm. (Refer to Section 9.5.)

9.15.4. Carry-over effect

There was a carry-over effect seen for the first month in F3Z-MC-IOAG and IOAH.

10. Efficacy

10.1. Efficacy Variables

10.1.1. Primary Efficacy Variables

10.1.1.1. Glucose Parameters

Integrated glucose control is best indicated by HgbA1c. It is the standard that is accepted by the FDA and by the academic community. The Diabetes Control and Complications Trial (DCCT) has shown that lower HgbA1c values with human insulin therapy are associated with fewer chronic complications in IDDM patients. Whether this data can be extrapolated to modified insulins or other hypoglycemic compounds which may have other growth potentiating and metabolic properties is unknown.

HgbA1c requires three months for full equilibration. Approximately 60% of equilibration is achieved by one month. Equilibration was probably not reached in most of the shorter studies (F3Z-MC-IOAG, IOAH, IOAY, and IOBN) because of their duration and because the studies permitted continual modification of the insulin doses. Nonetheless, HgbA1c is the most appropriate outcome variable, and the clinical trials did provide some useful data.

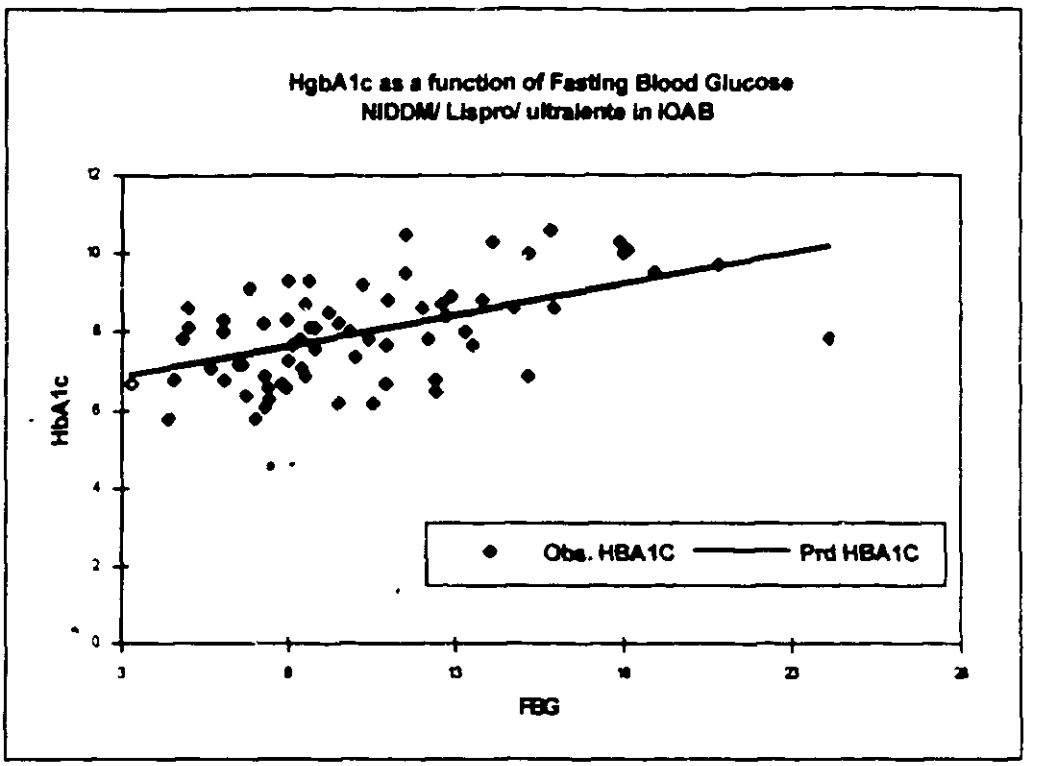
The interpretation of postprandial values, however, is extremely limited. Plasma (serum) glucose values after a designated, oral, liquid glucose load (50, 75, or 100 gm) can be used to diagnose diabetes. Mixed meal testing can be used to measure endogenous insulin release through the assessment of C-peptide. Glucose values serve only as a gross indicator that food has been absorbed. A postive response indicates that endogenous insulin is present. A negative test, however, is less informative. Reversible glucose toxicity of the islet cells may be present. Insulin release may be delayed regardless of glucose values. Such mismatch is frequently seen in NIDDM. Gastric emptying is quite variant even among normal subjects and is a major confounding variable with mixed meal testing. No normal values for postprandial glucose have been established even with the use of standardized meals. Standardized meals were not used in these trials, and only one small trial F3Z-MC-IOBN was blinded. Measurements of glucose at a single timepoint, with the possible exception of fasting values, do little to help the clinician estimate the extent and duration of glucose exposure. Serial glucose measurements (while fasted and at one, two, three, and four post oral challenge) could be used to determine the total area under the glucose curve (AUGC) and to estimate this glucose exposure. The available data did not include the late postprandial measurements, but was plotted against Hgb1c. The relationship is shown in figure 1, panels A and B.

The Sponsor has also defined a new parameter, the glucose excursion, as the blood or plasma(serum) glucose value at one or two hours postprandial value minus the fasting glucose value. This parameter does not account for potential differences in the fasting glucose for the two treatment groups and that postprandial glucose values taken later, eg, three and four hours postprandial would more likely favor human insulin because of lispro's short duration of activity. HgbA1c is generally accepted as the integrated measure of mean glucose exposure and correlates well with the occurrence of diabetic complications for adults. Measurements of postprandial glucose and the glucose excursion have not been validated and appear to have a limited correlation with HgbA1c at best as is demonstrated in figure 2.

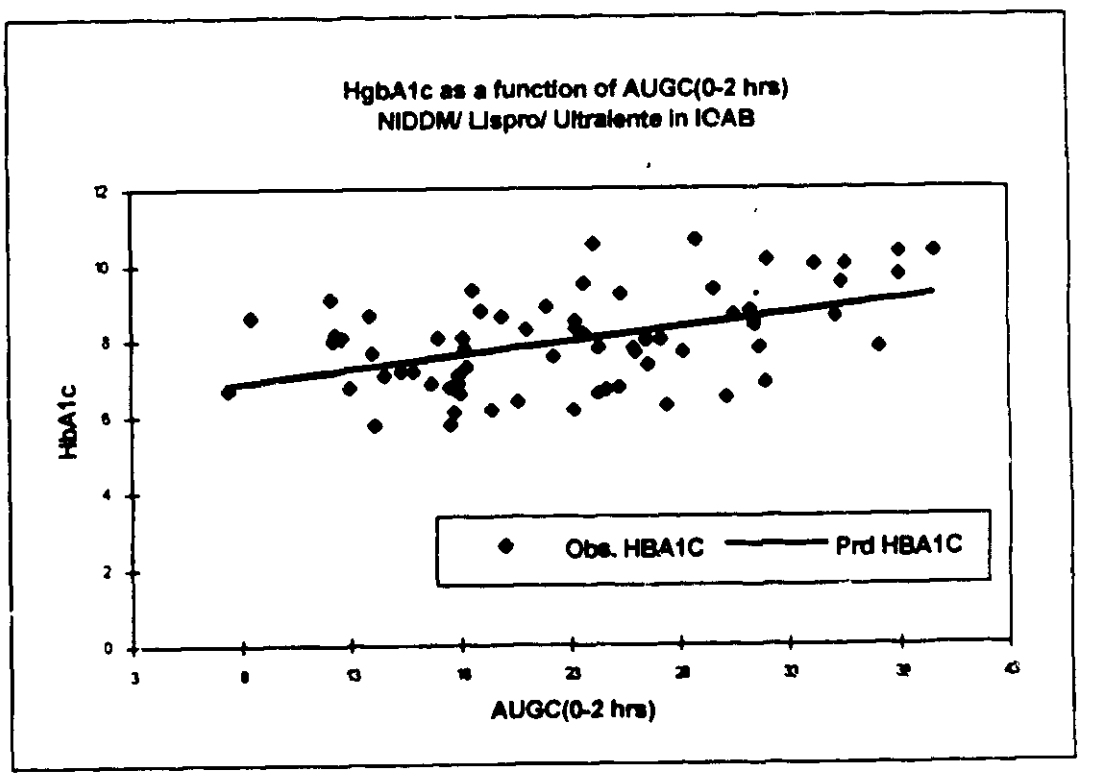
The numeric value of the postprandial glucose and the glucose excursion can also be manipulated by the timing of insulin administration. If the human insulin were given one hour preprandially, its glucose lowering profile would more closely approximate that seen with administration of lispro fifteen minutes or less before a meal. In studies F3Z-MC-IOAA through

Figure 1 Measures of Glucose Exposure: Relationship to HgbA1c

Panel A



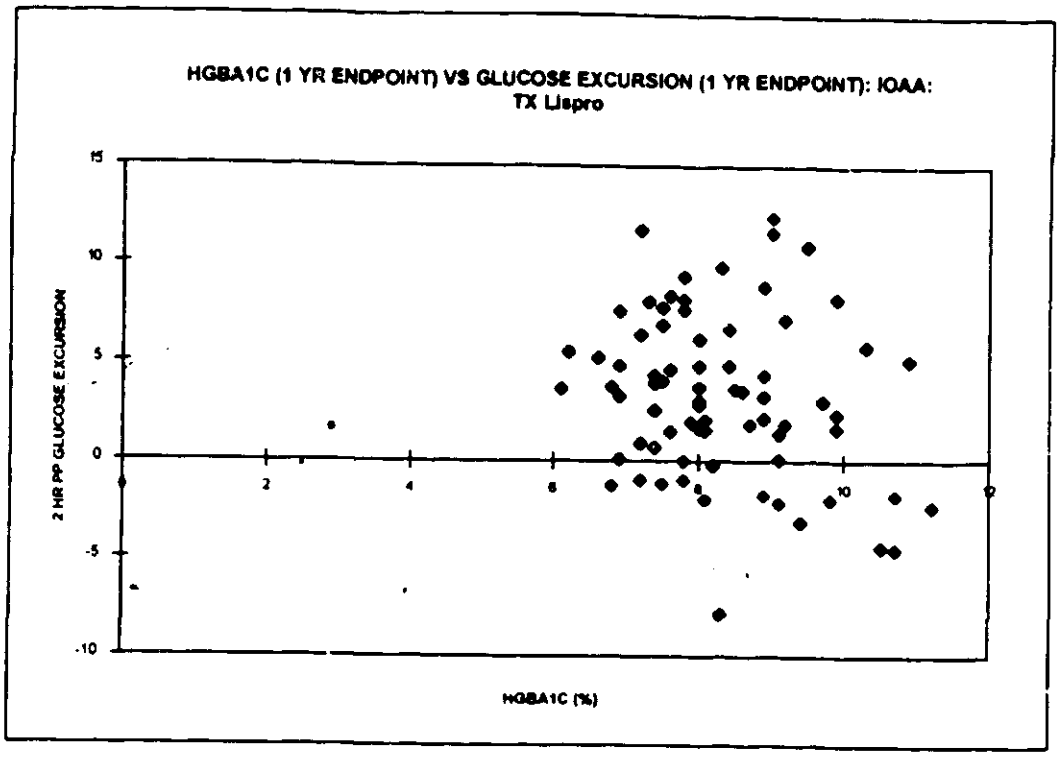
Panel B



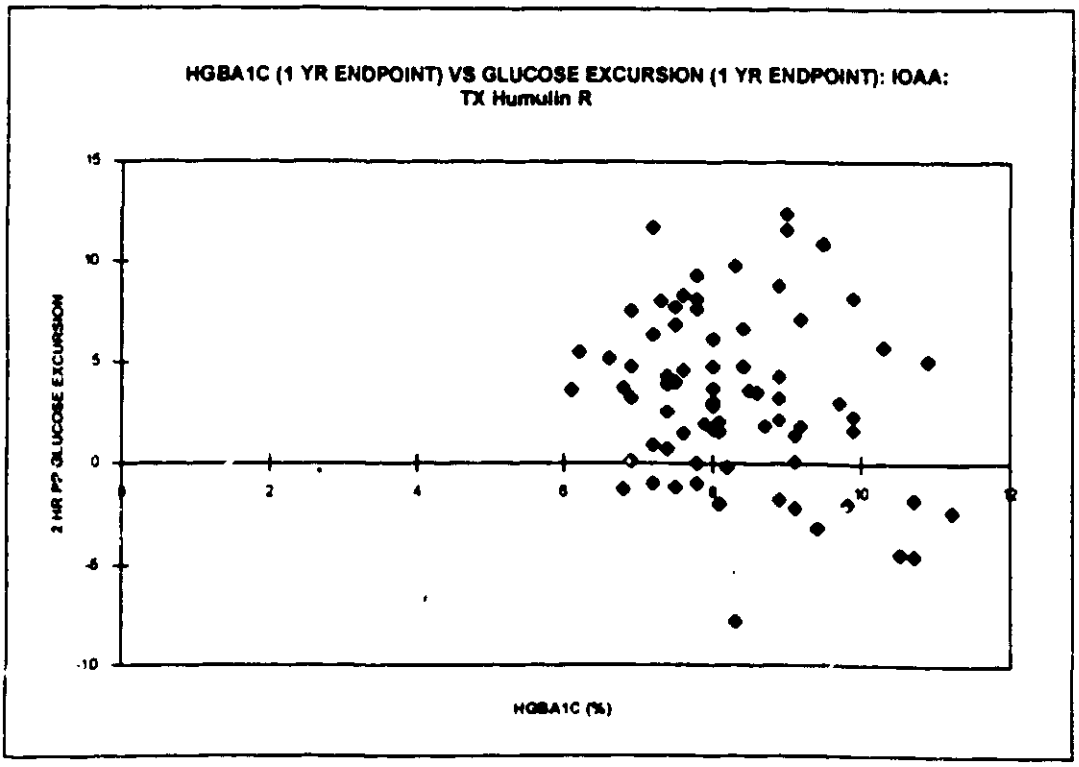
Obs=Observations Prd=Predicted

Figure 2 Glucose Parameters: Relationship to HgbA1c

Panel A



Panel B



IOAH, subjects using human insulin were given their insulin 30-45 minutes prior to breakfast. In F3Z-MC-IOBN, subjects using human insulin were instructed to take insulin within fifteen minutes of a meal and to conduct self-monitoring. This timing of administration favors Humalog if early postprandial glucose values are to be assessed. In the protocol for F3Z-MC-IOAY, it is not clear that subjects using human insulin were given any specific time for administration. (Their efficiacy data was also derived from home-monitoring data.) No trials employed double dummy administration of insulin at times optimal to each drug.

HgbA1c values for the two treatment groups were similar. (Refer to table 6. HgbA1c values are expressed in %; Diamat methology used.) In a major pivotal study, F3Z-MC-IOAG (n=1008 IDDM patients, 3 month treatment--> cross-over), the p-value was 0.089 in favor of Humulin R. When 95% confidence intervals were calculated, the difference was statistically significant at endpoint.

The fasting glucose values consistently tended to be lower for the Humulin R treatment group. (Refer to table 7. Glucose values are expressed in mmol/L.) Although bedtime sampling was done only in IOAY and IOBN (and was optional for the latter), the data tend to suggest that diabetic subjects using Humulin R retired at night with a lower blood glucose and awoke with a lower blood glucose. (Refer to figure 3.) Although no glucose sampling was performed routinely during these hours in any of the trials, it is likely that glucose values remained lower for the Humulin R treated group in the late postprandial period and throughout the "sleep interval".

Figure 3

GLUCOSE PROFILES DURING THE DAY: STUDY IOBN
(IDDM patients used rapid acting insulins 10 minutes ac meals)

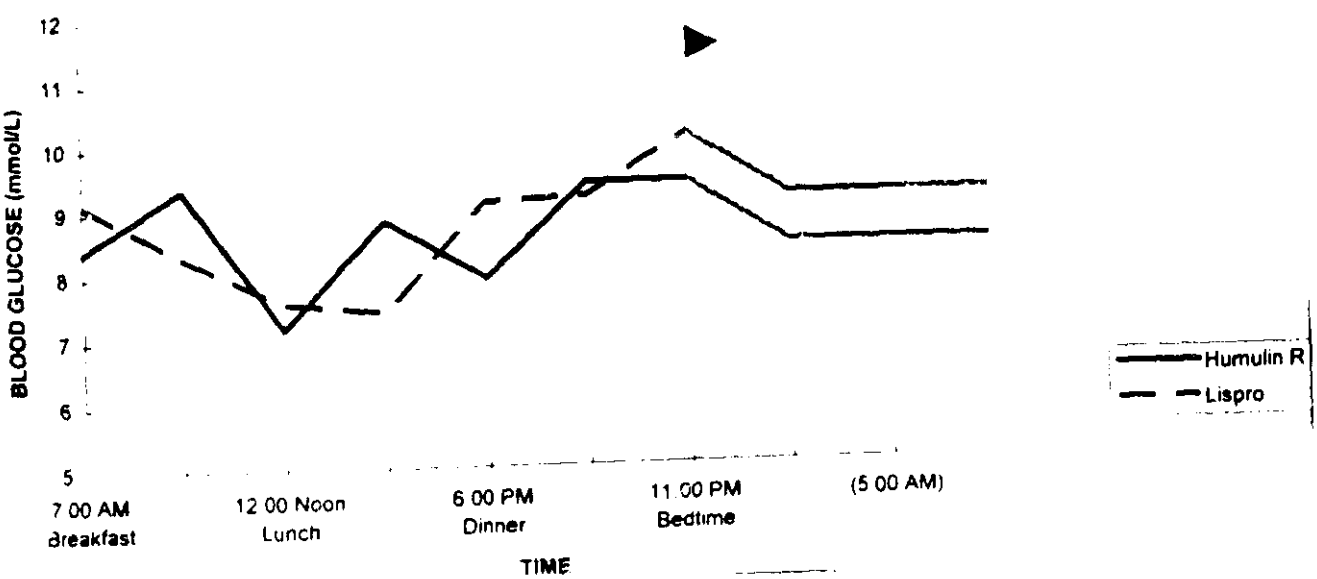


Table 6 Efficacy variable: HgbA1c (%) (Diamat methodology)

HgbA1c	Humulin R			Lispro			
Baseline	Mean	SD	n	Mean	SD	n	p-value
IOAA	8.32	1.67	78	8.17	1.41	75	0.11
IOAC	8.14	1.62	88	8.28	1.58	81	0.79
IOAE 2wk	8.84	2.19	46	9.17	2.2	50	0.46
IOAG	8.45	1.71	987	8.45	1.71	987	NA
IOAB	8.79	1.76	71	8.69	1.53	70	0.83
IOAD	8.99	1.56	76	8.78	1.4	73	0.1
IOAF 2wk	9.55	1.82	178	9.5	1.91	173	0.57
IOAH	8.88	1.67	713	8.88	1.67	713	NA
IOBN	7.52	1.09	93	7.52	1.09	93	NA
IOAY iddm	8.02	1.5	370	8.02	1.5	370	NA
IOAY niddm	8.13	1.32	321	8.13	1.32	321	NA
3 mo							
IOAA	8.29	1.53	75	7.99	1.45	75	0.04*
IOAC	8.04	1.42	87	7.78	1.26	78	0.14
IOAE	6.96	1.07	44	6.97	1.44	48	0.97
IOAG	8.17	1.44	959	8.25	1.5	964	0.09
IOAB	8.34	1.48	65	8.01	1.26	60	0.77
IOAD	8.28	1.46	71	8.03	1.2	67	0.22
IOAF	8.09	1.5	171	8.16	1.44	166	0.28
IOAH	8.16	1.35	689	8.16	1.31	689	0.67
IOBN	7.51	1.11	87	7.43	1.12	88	0.92
2 mo							
IOAY iddm	7.86	1.46	363	7.79	1.36	365	0.66
IOAY niddm	8.08	1.42	312	8.1	1.35	316	0.65
endpoint							
IOAA	8.38	1.37	84	8.14	1.3	81	0.03*
IOAC	8.22	1.44	88	8.08	1.43	80	0.25
IOAE	7.84	2.35	46	7.77	2.24	50	0.96
IOAG	8.17	1.46	991	8.24	1.49	984	0.09
IOAB	8.2	1.64	72	8	1.21	72	0.69
IOAD	8.5	1.73	77	8.38	1.52	71	0.52
IOAF	8.08	1.54	182	8.32	1.57	179	0.06
IOAH	8.18	1.38	705	8.18	1.3	710	0.68
IOBN	7.51	1.11	89	7.44	1.11	90	0.81
IOAY iddm	7.86	1.46	363	7.79	1.36	365	0.66
IOAY niddm	8.08	1.42	314	8.1	1.35	317	0.65
12 mo							
IOAA	8.4	1.39	79	8.09	1.33	75	0.03*
IOAC	8.2	1.43	84	8.08	1.46	76	0.35
IOAE	7.88	2.4	43	7.8	2.34	45	0.91
IOAG	X			X			
IOAB	8.21	1.65	71	7.98	1.22	70	0.66
IOAD	8.48	1.78	70	8.34	1.55	67	0.54
IOAF	8.07	1.53	159	8.23	1.53	155	0.51
IOAH	X			X			
IOBN	X			X			
IOAY iddm	X			X			
IOAY niddm	X			X			

Table 7 Efficacy variable: Fasting glucose (mmol/L)

Fasting Glucose	Humulin R			Lispro			
Baseline	Mean	SD	n	Mean	SD	n	p-value
IOAA	11.49	5.93	86	12.29	5.49	81	0.38
IOAC	11.26	4.68	87	11.06	496	79	0.66
IOAE 2 wk	7.87	2.32	46	8.47	3.52	49	0.48
IOAG	12.36	5.45	988	12.36	5.45	988	NA
IOAB	11.57	5.09	73	11.53	3.96	72	0.88
IOAD	11.5	4.29	77	11.74	4.36	72	0.97
IOAF 2 wk	11.82	4.12	180	11.61	3.73	176	0.54
IOAH	11.47	4.04	712	11.47	4.04	712	NA
IOBN	8.5	2.83	93	8.5	2.83	93	NA
IOAY iddm	8.14	2.65	379	8.14	2.65	379	NA
IOAY niddm	8.42	2.35	324	8.42	2.35	324	NA
3 mo							
IOAA	11.11	5.46	80	12.22	5.47	79	0.13
IOAC	10.93	4.8	87	9.76	3.95	78	0.09
IOAE	8.01	3.41	44	7.72	3.18	48	0.3
IOAG	**11.31**	4.96	953	**11.66**	5.08	959	0.2
IOAB	11.42	4.47	66	10.52	4.41	64	0.97
IOAD	11.43	4.37	74	11.41	4.29	70	0.96
IOAF	9.67	3.04	174	9.6	2.9	167	0.74
IOAH	**10.13**	3.61	683	**10.61**	3.71	690	0.004*
IOBN	**8.46**	3.13	85	**9.04**	3.43	89	0.03*
2 mo							
IOAY iddm	**8.26**	2.54	367	**8.67**	2.6	367	0.28
IOAY niddm	**8.46**	2.16	312	**8.79**	2.32	315	0.52
endpoint							
IOAA	**10.73**	5.08	86	**11.17**	4.91	81	0.5
IOAC	**9.9**	4.32	88	**11.06**	4.99	80	0.2
IOAE	**9.51**	4.32	46	**9.99**	4.39	50	0.48
IOAG	**11.34**	4.96	990	**11.64**	5.09	984	0.27
IOAB	**10.11**	3.66	72	**10.37**	4.16	72	0.53
IOAD	**10.29**	3.71	77	**10.55**	3.79	73	0.54
IOAF	**10**	3.13	182	**10**	3.44	179	0.98
IOAH	**10.17**	3.67	705	**10.67**	3.77	710	002*
IOBN	**8.39**	3.09	89	**9.13**	3.53	90	0.02*
IOAY iddm	**8.28**	2.55	368	**8.67**	2.6	367	0.28
IOAY niddm	**8.45**	2.17	313	**8.79**	2.31	316	0.52
12 mo							
IOAA	**10.82**	4.95	78	**11.42**	5	73	0.46
IOAC	**10.07**	4.27	82	**10.93**	4.99	76	0.38
IOAE	**9.7**	4.38	43	**10.09**	4.47	45	0.47
IOAG	X			X			
IOAB	**10.19**	3.63	71	**10.3**	4.2	70	0.66
IOAD	**10.24**	3.74	70	**10.49**	3.78	67	0.64
IOAF	**9.99**	2.99	159	**9.81**	3.23	154	0.87
IOBN	X			X			
IOAH	X			X			
IOAY iddm	X			X			
IOAY niddm	X			X			

The one hour postprandial glucose values for the two treatment groups differed by less than 1 mmol/L (or <18 mg/dl). These differences were statistically significant only in the larger, shorter, cross-over studies. (Refer to table 8.)

Table 8

	Endpoint (mmol/L)		End-of Study	
STUDY	Lispro	Humulin R	Lispro	Humulin R
F3Z-MC-IOAA	12.63+/-5.37	13.53+/-4.99	13.16+/-5.33	13.85+/-4.91
F3Z-MC-IOAB	12.44+/-4.11	13.22+/-4.57	12.36+/-4.12	13.24+/-4.60
F3Z-MC-IOAC	14.05+/-5.44	13.52+/-4.91	13.86+/-5.45	13.56+/-4.92
F3Z-MC-IOAD	13.72+/-4.29	13.75+/-3.96	13.56+/-4.31	13.46+/-3.97
F3Z-MC-IOAE	12.73+/-5.81	13.14+/-5.77	12.63+/-5.88	13.22+/-5.89
F3Z-MC-IOAF	13.28+/-4.08	13.49+/-3.73	13.44+/-3.97	13.46+/-3.38
F3Z-MC-IOAG	12.91+/-5.43	13.89+/-5.37*	12.94+/-5.41	13.87+/-5.35*
F3Z-MC-IOAH	13.23+/-4.43	13.89+/-4.18*	13.19+/-4.38	13.88+/-4.16*

The two hour postprandial glucose values were statistically lower in the Humalog treatment groups of the shorter, cross-over studies (F3Z-MC-IOAG n=1008, IOAH n=722, IOAY n=707, and IOBN n=93) and not in the longer, parallel studies (F3Z-MC-IOAA n=156, IOAB n=145, IOAC n=169, IOAD n=150, IOAE n=93, and IOAF n=375). (Refer to table 9. Glucose values are expressed in mmol/L.) The absolute differences between the two hour postprandial values for the two treatment groups were approximately 1 mmol/L or 18 mg/dl. (Refer to table 9, column headed differences). These postprandial glucose values were were approximately 10% lower with Humalog treatment. The clinical significance of this amount of lowering in the face of two hour postprandial values that always exceeded 140 mg/dl and frequently exceeded 200 mg/dl is uncertain. Moreover, in IOBN, in which two hour postprandial and preprandial (or approximately four hour postprandial) glucose values were obtained, the glucose values were alternately lower for Humalog and Humulin R throughout the day (Refer to figure 3.) Likewise in IOAY, glucose values not uniformly lower for any one insulin treatment and the absolute differences between the glucose values were small. (Refer to table 10.)

Table 10 Serial glucose measures in IDDM patients (F3Z-MC-IOAY)

	Blood Glucose (mmol/L)	
Time	Humulin R	Humalog
Fasting	8.26	8.67
2 hr p Breakfast	9.74	8.58
AC Lunch	6.71	6.42
2 hr p Lunch	9.87	10.07
AC Supper	8.95	9.29
2 hr p Supper	9.59	8.60
Bedtime	8.58	8.22

Table 9 Efficacy variable: 2 hour postprandial glucose (mmol/L)

Postprandial Glucose-2 hr	Humulin R			Lispro			
Baseline	Mean	SD	n	Mean	SD	n	p-value
IOAA	13.81	5.98	83	13.31	5.72	78	0.77
IOAC	13.87	5.71	87	13.77	6.31	80	0.87
IOAE 2 wk	10.12	5.17	45	9	4.24	50	0.3
IOAG	12.96	5.83	989	12.96	5.83	989	NA
IOAB	14.76	5.73	71	14.08	4.68	69	0.34
IOAD	14.32	4.34	76	14.03	5.05	72	0.66
IOAF 2 wk	15.26	5.67	178	13.58	5.26	172	0.004
IOAH	13.92	4.74	711	13.92	4.74	711	NA
IOBN	9.5	2.95	93	9.5	2.95	93	NA
IOAY iddm	9.74	3.48	377	9.74	3.48	377	NA
IOAY niddm	10.59	3.14	317	10.59	3.14	317	NA
3 mo							
IOAA	11.98	4.91	80	10.92	5.9	79	0.2
IOAC	13.06	5.44	87	10.57	5.31	77	006*
IOAE	10.05	5.41	44	9.54	4.8	47	0.46
IOAG	**12.89**	5.77	949	**11.2**	5.31	954	<0.001*
IOAB	14.5	5.45	67	11.45	4.24	64	< 001*
IOAD	13.57	4.75	73	12.43	4.69	69	0.36
IOAF	12.28	4.14	174	11.35	4.22	166	0.19
IOAH	**13.13**	4.47	680	**12.04**	4.57	687	001*
IOBN	**9.31**	2.99	85	**8.22**	2.85	89	0.009*
2 mo							
IOAY iddm	**9.74**	3.12	362	**8.58**	3.05	360	<0.001*
IOAY niddm	**10.36**	2.93	312	**9.47**	3.04	313	<0.001*
endpoint							
IOAA	**13.29**	5.2	85	**11.32**	5.2	81	0.05
IOAC	**12.76**	5.03	88	**13.06**	5.83	80	0.74
IOAE	**12.39**	6.43	45	**11.44**	6.07	50	0.68
IOAG	**12.47**	5.77	987	**11.16**	5.3	979	<0.001*
IOAB	**12.69**	4.82	72	**11.41**	4.38	72	0.1
IOAD	**13.19**	4.24	77	**12.32**	4.3	71	0.29
IOAF	**12.95**	4.22	179	**12.31**	4.6	175	0.3
IOAH	**13.14**	4.48	703	**12.08**	4.62	709	0.001*
IOBN	**9.32**	2.96	88	**8.28**	2.9	90	0.006*
IOAY iddm	**9.75**	3.11	363	**8.58**	3.05	360	<0.001*
IOAY niddm	**10.36**	2.93	313	**9.46**	3.04	314	<0.001*
12 mo							
IOAA	**14**	4.84	75	**11.98**	5.08	71	0.02*
IOAC	**12.76**	5.09	84	**12.76**	5.75	76	0.9
IOAE	**12.49**	6.57	43	**11.42**	6.3	45	0.67
IOAG	X			X			
IOAB	**12.72**	4.85	71	**11.33**	4.34	69	0.1
IOAD	**13.01**	4.39	70	**12.2**	4.23	67	0.29
IOAF	**12.85**	3.76	161	**12.48**	4.6	154	0.53
IOAH	X			X			
IOBN	X			X			
IOAY iddm	X			X			
IOAY niddm	X			X			

The glucose excursion at one hour postprandium was statistically significant in four studies. (Refer to table 11.)

Table 11 Glucose excursion at one hour postprandium

	Endpoint (mmol/L)		End-of Study	
STUDY	Lispro	Humulin R	Lispro	Humulin R
F3Z-MC-IOAA	1.50+/-3.83	3.25+/-3.14*	1.67+/-3.97	3.30+/-3.25*
F3Z-MC-IOAB	2.07+/-3.00	3.01+/-3.20*	2.07+/-3.01	3.05+/-3.21*
F3Z-MC-IOAC	3.01+/-3.85	3.63+/-3.95	2.92+/-3.92	3.56+/-3.95
F3Z-MC-IOAD	3.12+/-3.24	3.39+/-2.53	2.94+/-3.18	3.23+/-2.46
F3Z-MC-IOAE	2.59+/-3.69	3.53+/-3.08	2.54+/-3.79	3.52+/-3.14
F3Z-MC-IOAF	3.37+/-2.82	3.38+/-2.42	3.64+/-2.74	3.46+/-2.39
F3Z-MC-IOAG	1.24+/-4.00	2.53+/-3.83*	1.27+/-3.95	2.57+/-3.56*
F3Z-MC-IOAH	2.59+/-3.08	3.74+/-2.38*	2.58+/-3.10	3.75+/-2.83*

The glucose excursion at two hours postprandium was statistically significant by p-value and 95% confidence interval at both endpoint and end-of-study for F3Z-MC-IOAA, IOAB, IOAD, IOAG, IOAH, IOAY, and IOBN, but not F3Z-MC-IOAC, IOAE, and IOAF. (Refer to table 12. Glucose values are expressed in mmol/L.) The difference in the values for the two hour glucose excursions for the two treatment groups at endpoint ranged from 0.45 mmol/L (~8 mg/dl) to 2.85 mmol/l (~52 mg/dl) with most of the values between 1.45 and 2.03 mmol/L (~26 and 36 mg/dl).

It is unclear whether the differences between the two treatment groups and the putative advantages of Humalog (as measured by the glucose excursions and early, postprandial glucose values) will persist with chronic therapy. (Refer to figure 4.) When the maximal differences between the treatment groups during the first three months are compared to the values at twelve months, the differences appear to diminish in magnitude for subjects who completed the trials. (Refer to figure 5 and table 13.)

Figure 4

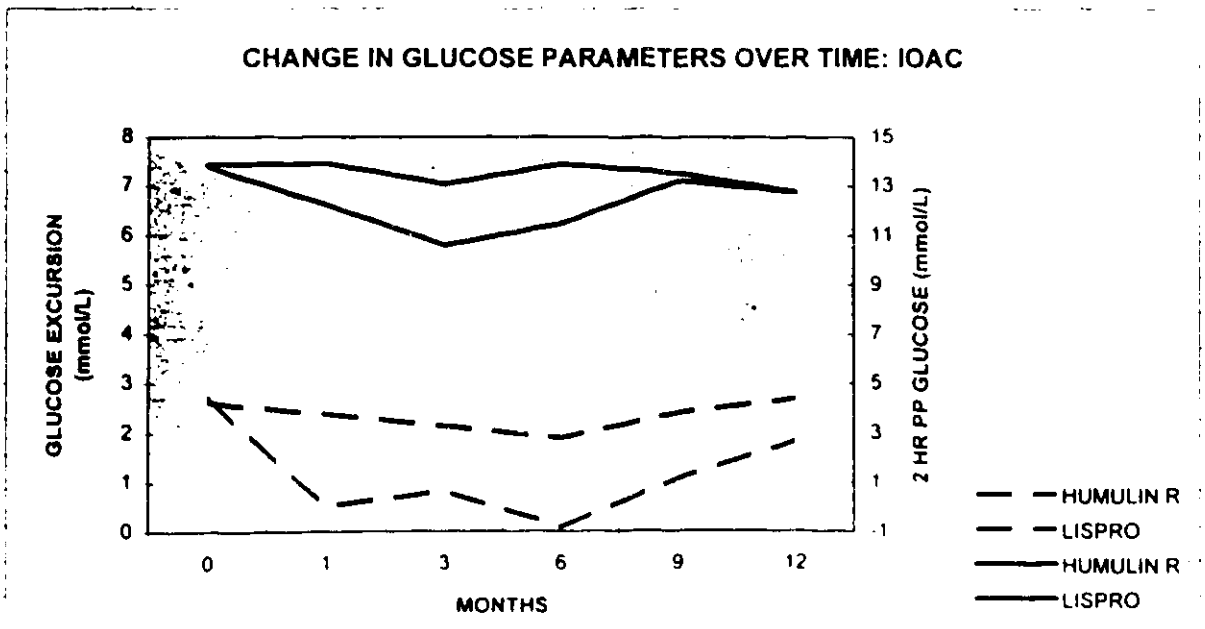


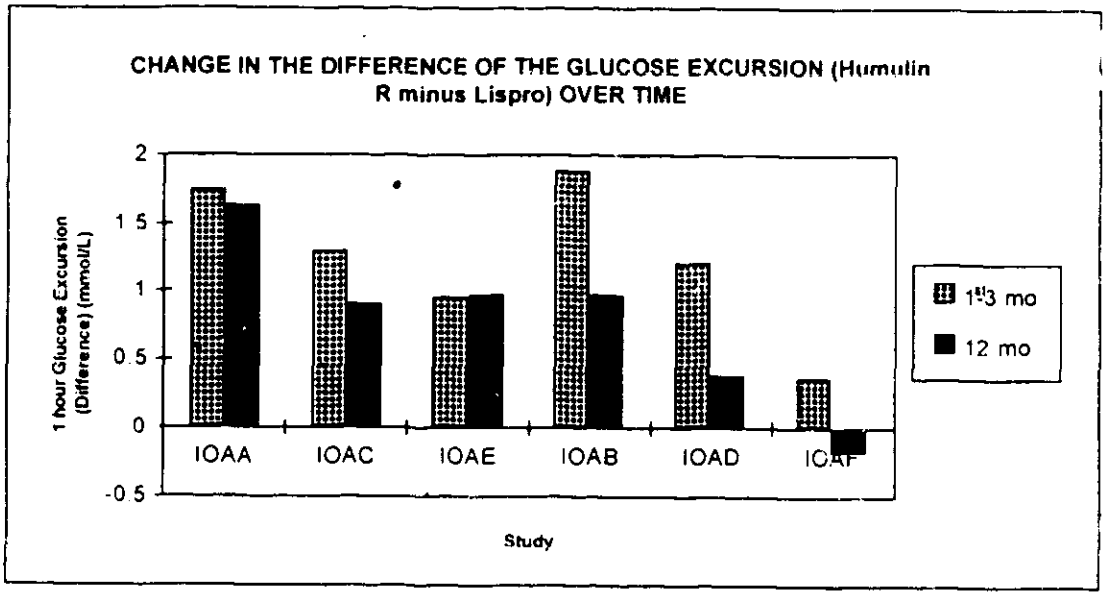
Table 12 Efficacy variable:
Glucose excursion at 2 hour postprandium (mmol/L)

Glucose Excursion-2 hr	Humulin R			Lispro			
Baseline	Mean	SD	n	Mean	SD	n	p-value
IOAA	2.33	5.32	83	0.92	5.08	77	0.15
IOAC	2.69	4.15	86	2.89	5.43	78	0.4
IOAE 2 wk	2.24	3.95	45	0.38	4.14	49	0.07
IOAG	0.61	5.22	985	0.61	5.22	985	NA
IOAB	3.33	3.46	70	2.52	3.72	69	0.11
IOAD	2.71	3.45	76	2.36	3.22	71	0.73
IOAF 2 wk	3.35	3.46	177	2.07	3.96	171	0.006
IOAH	2.46	3.69	709	2.46	3.69	709	NA
IOBN	0.98	3.64	93	0.98	3.64	93	NA
IOAY iddm	1.6	3.24	377	1.6	3.24	377	NA
IOAY niddm	2.16	2.61	317	2.16	2.61	317	NA
3 mo							
IOAA	1.58	5.06	78	-0.51	4.31	75	0.02*
IOAC	2.13	4.45	87	0.88	4.31	77	0.12
IOAE	2.04	3.51	44	1.82	3.38	47	0.97
IOAG	1.58	5.07	941	-0.51	4.83	949	<0.001*
IOAB	3.04	4.32	66	0.93	3.7	64	<0.001*
IOAD	2.15	3.42	72	1.39	3.51	67	0.17
IOAF	2.61	2.96	174	1.75	3.36	166	0.04*
IOAH	2.98	3.72	678	1.41	3.66	683	<0.001*
IOBN	0.83	3.31	85	-0.86	2.99	89	<0.001*
2 mo							
IOAY iddm	1.55	2.96	362	-0.1	3.05	360	<0.001*
IOAY niddm	1.9	2.42	311	0.67	2.66	313	<0.001*
endpoint							
IOAA	2.92	4.28	85	0.07	4.87	81	0.001*
IOAC	2.75	4.64	88	1.99	5.08	80	0.46
IOAE	2.78	4.37	45	1.31	4.29	50	0.21
IOAG	1.52	5.05	987	-0.51	4.88	979	<0.001*
IOAB	2.49	3.94	72	1.04	3.66	72	0.02*
IOAD	2.84	3.25	77	1.74	3.76	71	0.03*
IOAF	2.83	2.94	179	2.38	3.64	175	0.3
IOAH	2.97	3.73	703	1.04	3.67	709	<0.001*
IOBN	0.89	3.3	89	-0.89	2.98	90	<0.001*
IOAY iddm	1.54	2.96	363	-0.1	3.05	360	<0.001*
IOAY niddm	1.91	2.42	312	0.67	2.66	314	<0.001*
12 mo							
IOAA	3.11	4.33	75	0.54	4.73	69	0.005*
IOAC	2.72	4.63	82	1.83	5.16	76	0.52
IOAE	2.79	4.47	43	1.33	4.47	45	0.2
IOAG	X						
IOAB	2.53	3.95	71	1.06	3.63	69	0.02*
IOAD	2.83	3.29	69	1.58	3.66	66	0.02*
IOAF	2.82	2.97	159	2.7	3.55	153	0.7
IOAH	X				X		
IOBN	X				X		
IOAY iddm	X				X		
IOAY niddm	X				X		

Figure 5 Change in glucose parameters over time

The longitudinal data in F3Z-MC-IOAC suggested that the differences between the insulins as measured by the postprandial efficacy parameters tended decrease with time. Maximal differences for the two insulins during the first 3 months were compared to differences at the 12 months. The 3 month values for patients in IOAG and IOAH were comparable to those found during the first three months of the parallel studies. (Data not shown.)

Panel A 1 hour glucose excursion



Panel B 2 hour glucose excursion

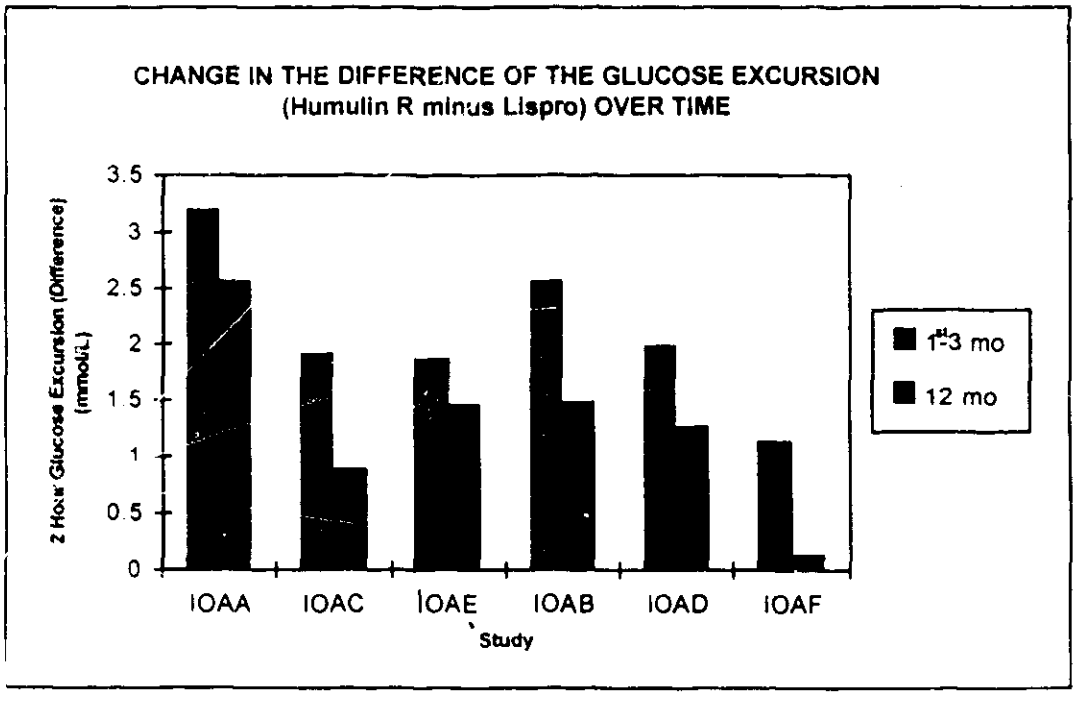
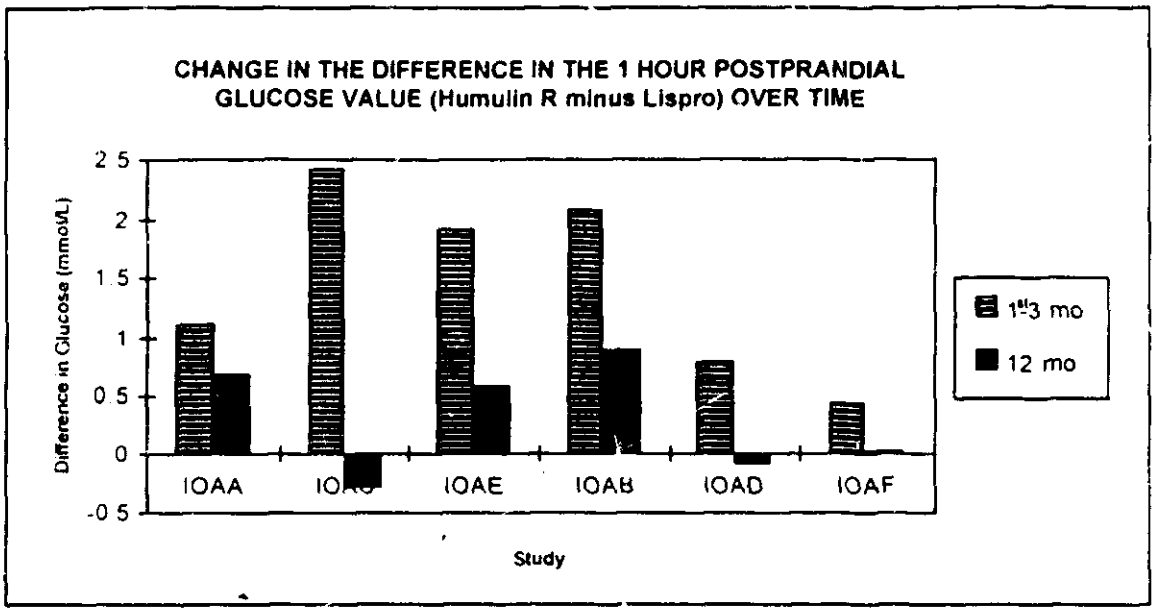


Figure 5 (Cont.) Change in glucose parameters over time

Panel C 1 hour postprandial glucose



Panel D 2 hour postprandial glucose

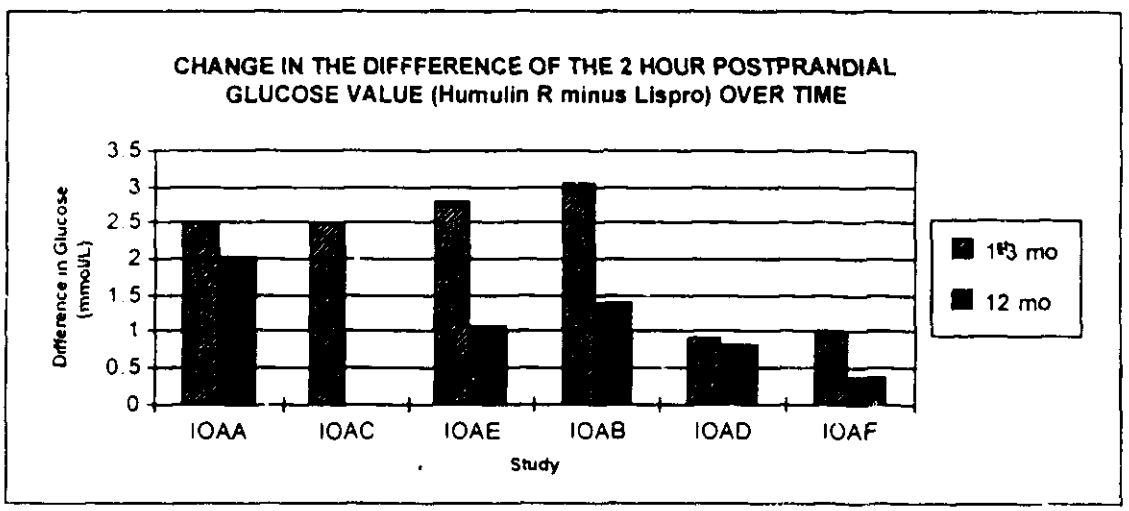


Table 13 Change in glucose excursion over time

CHANGE IN GLUCOSE EXCURSION OVER TIME									
Diabetes	Study	Visit #	2 Hour Glucose Excursion (1-3 mo)			Visit #	2 Hour Glucose Excursion (12 mo)		
Type			HumulinR	Lispro	p value		HumulinR	Lispro	p value
IDDM	IOAA	4	1.86	-1.33	<0.001	12	3.11	0.54	0.005
		6	0.88	-1.3	0.002				
	IOAC	4	2.35	0.45	0.044	12	2.72	1.83	0.521
		6	2.13	0.88	0.122				
	IOAE	4	2.37	0.51	0.026	12	2.79	1.33	0.195
		6	2.04	1.82	0.974				
NIDDM	IOAB	4	2.91	0.35	<0.001	12	2.53	1.06	0.021
		6	3.04	0.93	<0.001				
	IOAD	6	2.32	0.34	0.938	12	2.83	1.58	0.19
		7	2.15	1.39	0.166				
	IOAF	4	2.88	1.76	0.001	12	2.82	2.7	0.702
		6	2.61	1.75	0.038				

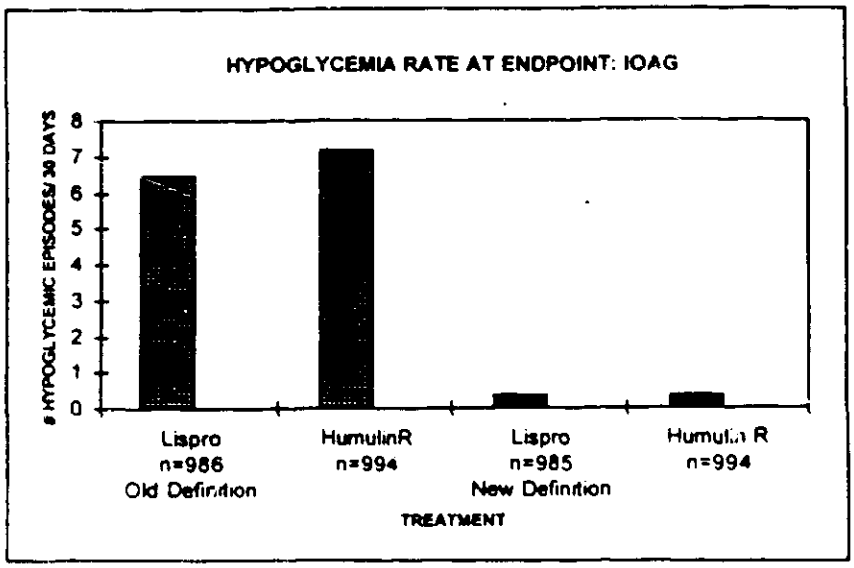
Glucose excursion=fasting glucose-2 hour postprandial glucose value
Glucose excursion expressed in mmol/L
Visit 4=1.5 mo for IOAE and IOAF and 1 mo for other studies
Visit 6=3.0 mo for all studies

The largest studies were also the shortest. To try to answer this question would require a longer period of observation. Although many patients entered long-term extension trials, the entry was not randomized, any data collection was uncontrolled (except for comparisons to self), and the extensions were not structured to collect efficacy data. The pathophysiology underlying such a phenomenon, if truly present, is unknown.

10.1.1.2. Hypoglycemia rates

Hypoglycemia rates, as presented by the Sponsor, were difficult to interprete because the sponsor used several different glucose levels to define hypoglycemia, and several of these thresholds would have been in the "normal range" after conversion from blood glucose (as measured in glucose meters) to serum glucose. In addition, subjects were permitted to report hypoglycemia if they felt hypoglycemic. (Review of individual patient data in the CANDA identified subjects with documented blood glucose levels of 7 mmol/L were recorded as being hypoglycemic.) To assess events that were more clinically significant and to reduce elements of subjectivity in unblinded studies, hypoglycemia was redefined by the reviewer as a glucose reading less than or equal to 36 mg/dl or an episode requiring the intervention of another. This definition was not quite as restrictive that of the DCCT which required intervention by another, but reduced the hypoglycemia rate by a magnitude. Under the old definition, the hypoglycemia rate in F3Z-MC-IOAG was somewhat higher for Humulin R than for Lispro treated IDDM patients: 8.09 events/30 days versus 7.22 events/30 days (p-value </=0.001). Under the new definition, the number of events decreased approximately 20-fold. These corrected rates more closely approximated the rates found in the DCCT, and the apparent differences under the old definition disappeared. As expected, the rates of hypoglycemia in subjects with IDDM were approximately a magnitude larger than in subjects with NIDDM. This relationship was not altered by application of the new definition. (Refer to figure 6.)

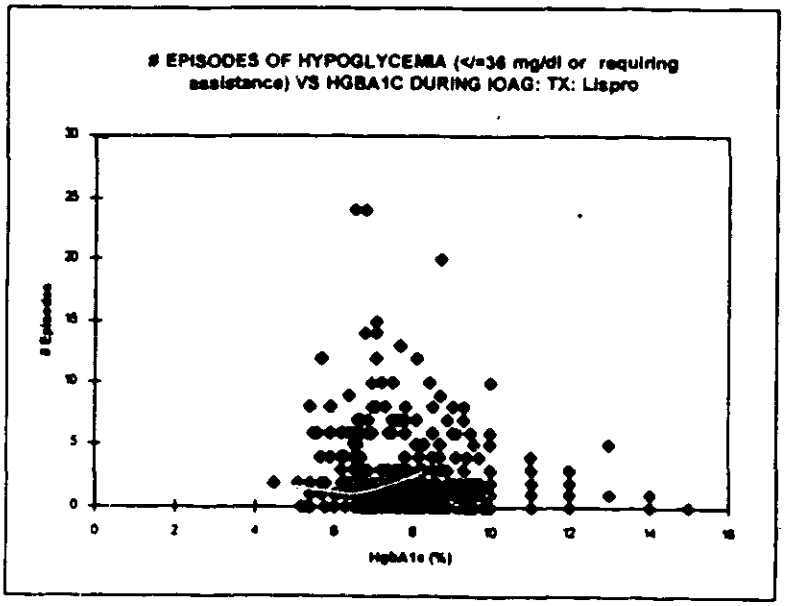
Figure 6 New Definition of Hypoglycemia



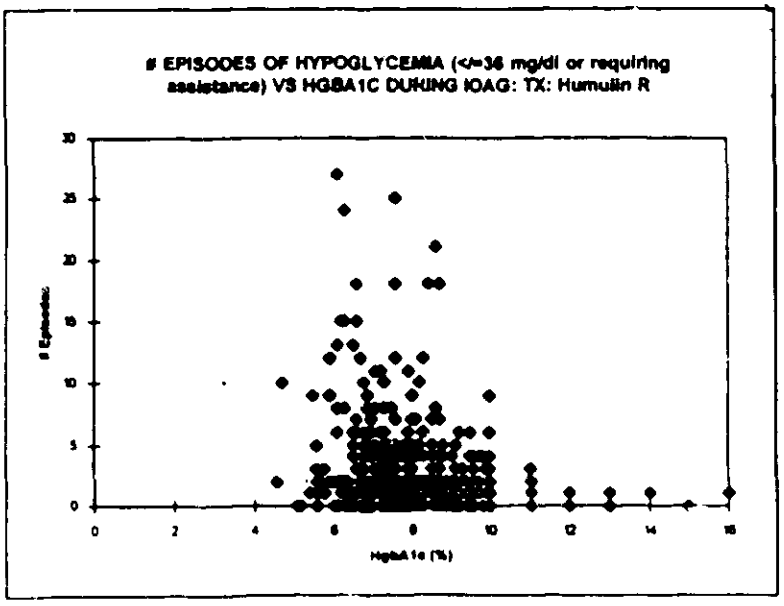
Hypoglycemia rates are also known (by clinical experience and by the DCCT) to be inversely related to the HgbA1c level. Adjustments for the relative level of glycemic control must be made to reduce confounding. The HgbA1c data should also reflect the time interval for which the hypoglycemia data was collected. For example, in F3Z-MC-IOAG, HgbA1c levels tended to be lower for Humulin R-treated patients than for Humalog-treated patients: 8.17% versus 8.24% (p-value=0.089; 95% confidence intervals were statistically significant). To assess hypoglycemia in the presence of multiple variables, the number of episodes of hypoglycemia versus the final HgbA1c was plotted for patients who completed F3Z-MC-IOAG and had at least one hypoglycemic episode. The data from the two insulin treatments are essentially superimposable. (Refer to figure 7.) (The r values were -0.17 and -0.20 for lispro and human insulin respectively. The scatter of the data was not conducive to regression analysis.)

Figure 7 Adjusting hypoglycemia by HgbA1c

Panel A



Panel B



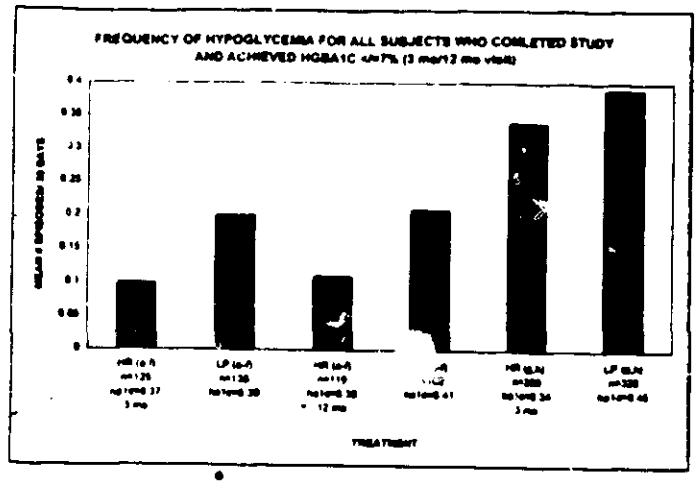
Because the goal of diabetes management is to optimize glucose control, hypoglycemia rates were also evaluated for subjects who achieved a HgbA1c </=7% at study end. The data showed that a smewhat greater number of the patients using Humulin R were able to reach this level of glycemic control and that there was a trend for a lower rate of hypoglycemia in the Humulin R treated group. This pattern was present regardless of the diabetes type and, in the 12 months studies, regardless of the basal insulin used. (Refer to figure 8, panels A,B, and C.)

The above data suggest that the frequency of clinically significant hypoglycemia is similar for the two treatment groups after adjustment for HgbA1c and when the HgbA1c results were comparable to those on conventional therapy in the DCCT.

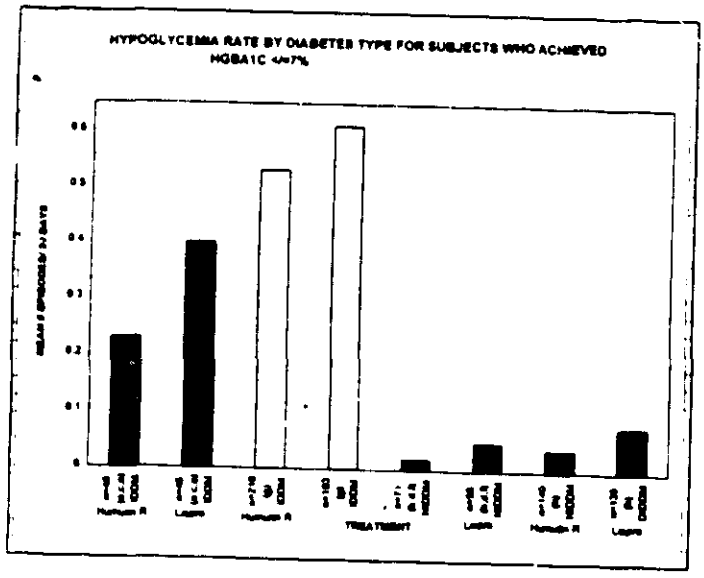
10.1.1.3. Timing of hypoglycemia
The pharmacokinetics suggest that the timing of hypoglycemia seen with Humalog might be different from that seen with Humulin R. This question was not addressed prospectively by the sponsor. All analyses are post hoc. The sponsor reported statistically significant differences in the frequency (unspecified time interval) of hypoglycemic episodes (hypoglycemia level undefined) between the hours of 12 midnight and 6 A.M in studies F3Z-MC-IOAA, IOAG, and IOAH. These differences favored Humalog. (Refer 10/25/95 submission, pp 97-104.) In an attempt to identify diurnal patterns of hypoglycemia, the medical reviewer evaluated the number of episodes of hypoglycemia during the interval prior to the final visit for the study (3 months or 12 months). To eliminate any confounding from differences attributable to HgbA1c, the absolute number of hypoglycemic episodes was normalized and then plotted as a percent number on a military clock. (Refer to figure 9, panels A, B, and C.) The number of episodes of at night tended to be relatively less than the numbers during other parts of the day. Episodes during the day did not fit clearly predictible patterns. The differences between the two treatment groups for the % number of episodes at night was less than 5% at any given time point. The clinical significance of such small differences is uncertain. The clinical importance of when hypoglycemic occurs is also open to judgement especially when the overall hypoglycemia rates appear to be similar. Hypoglycemia during the day is more likely to impact vocational activities and driving and may have consequences for persons other than the patient.

Exercise is one of the variables other than insulin that can influence the timing of hypoglycemia. There are very limited data based on a study in ten IDDM patients. The author reports that "in the analogue-treated patients the exercise-induced hypoglycaemia was 2.2-fold greater ($p<0.01$) during the early exercise, but 46% less ($p<.05$) during late exercise as compared to the treatment with human insulin (Tuominen JA, Karonen S-L, Melamies L, Bolli G, Koivisto VA; Exercise-induced hypoglycemia in IDDM patients treated with a short-acting insulin analogue. Diabetologia 1995 38:106).

Figure 8 Hypoglycemia in well controlled patients
Panel A



Panel B



Panel C

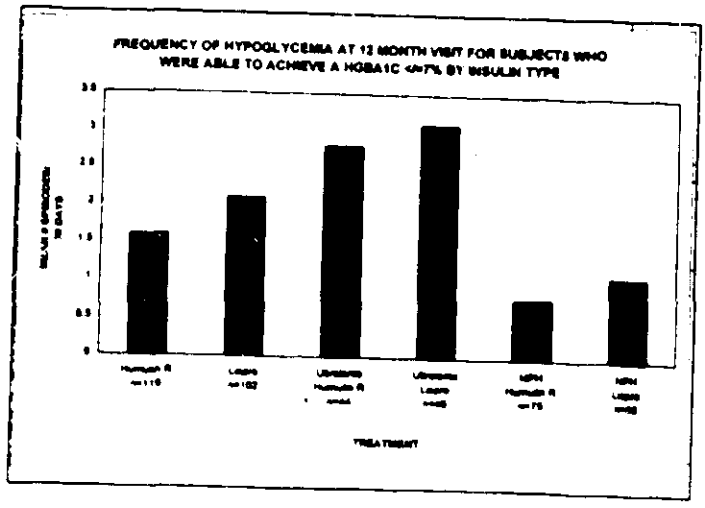
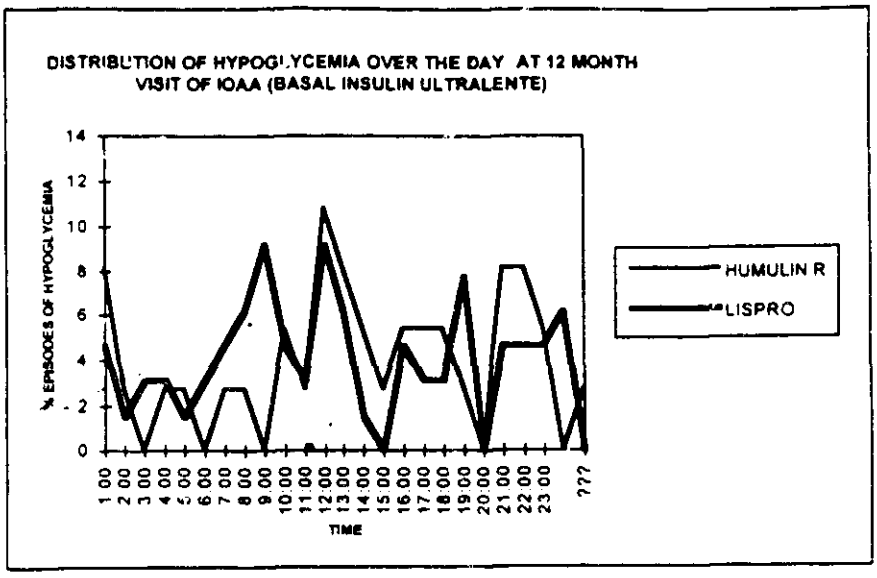
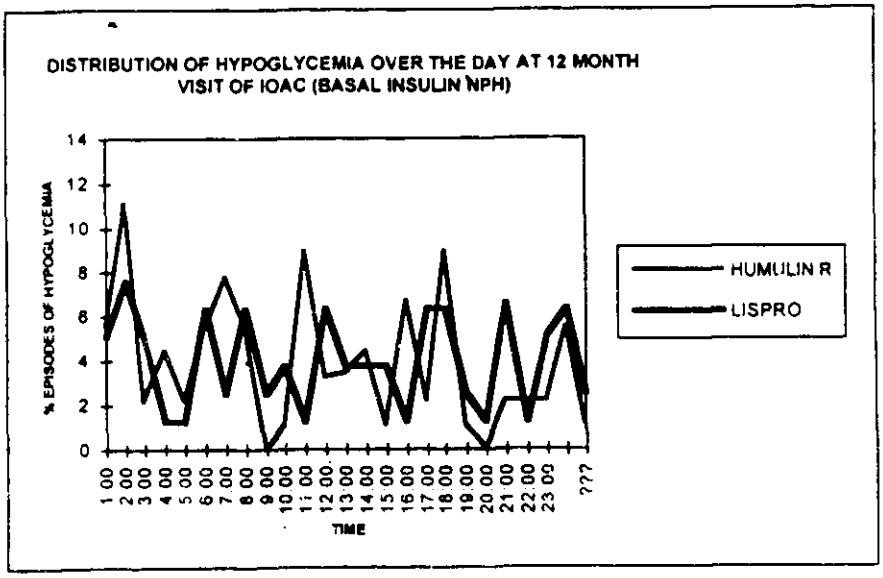


Figure 9 Relative distribution of hypoglycemia throughout day Hours expressed on a military clock. ??? designates events at an unknown time. Hypoglycemia: glucose </=36 mg/dl or requiring assistance.

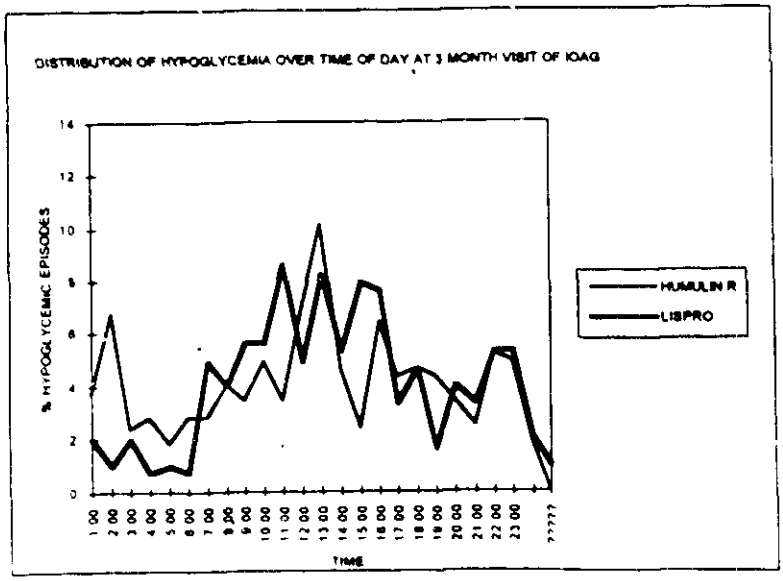
Panel A



Panel B

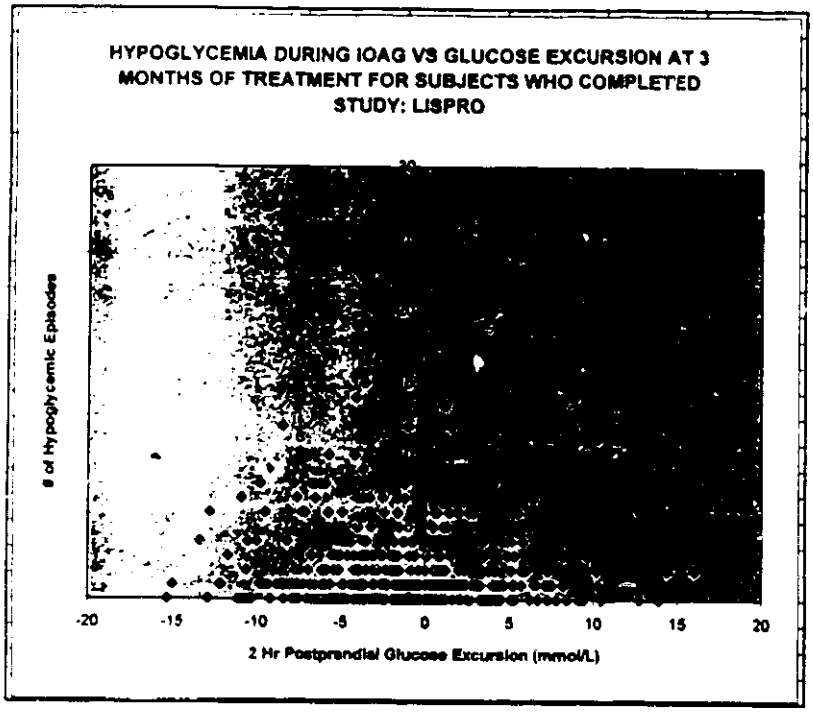


Panel C



10.1.1.4. Relation of hypoglycemia to glucose excursion. The magnitude of the glucose excursion does not appear to correlate with the number of hypoglycemic episodes. (Refer to figure 10.)

Figure 10



10.1.2 Secondary Efficacy Variables
10.1.2.1 Weight
The sponsor also has postulated that the rapid absoption of insulin could mimic the first phase insulin response and improve thermogenesis. The first phase insulin response which occurs within the first five minutes of islet cell stimulus is frequently impaired in diabetes. Decrement in the first phase insulin response have been associated with decrements in thermogenesis. The clinically relevant, integrated, and validated measurement of thermogenesis is weight and changes in weight.

Although patients tended to gain weight with the more insulin intensive therapy regimens in the trials, there were no significant differences either statistically or clinically in weight or weight gain between the two treatment groups. (Refer to Table 14.)

Table 14 Weight (kg) During Clinical Trials

	Human regular insulin			lispro insulin		
Study	Entry	12 mo	Endpoint	Entry	12 mo	Endpoint
F3Z-MC-IOAA	70.56	71.01	71.60	71.97	73.07	73.40
			p-value	0.663	0.372	0.489
F3Z-MC-IOAB	80.97	83.18	83.29	83.18	84.67	85.06
			p-value	0.801	0.451	0.684
F3Z-MC-IOAC	72.19	74.51	74.48	70.84	72.16	71.73
			p-value	0.339	0.247	0.137
F3Z-MC-IOAD	83.12	85.12	85.23	80.05	81.75	81.67
			p-value	0.154	0.216	0.171
F3Z-MC-IOAE	66.48	71.02	70.99	69.01	72.88	72.86
			p-value	0.154	0.225	0.221
F3Z-MC-IOAF	80.57	84.58	85.01	79.97	84.29	83.66
			p-value	0.758	0.345	0.554
	Entry	3 mo	Endpoint	Entry	3 mo	Endpoint
F3Z-MC-IOAG	71.20	71.90	71.80	71.20	71.50	71.50
			p-value		0.037	0.029
F3Z-MC-IOAH	80.20	81.20	81.20	80.20	81.00	80.90
			p-value		0.081	0.100
F3Z-MC-IOBN	76.64	77.62	77.15	76.64	77.19	77.03
			p-value		0.641	0.543
	Entry	2 mo	Endpoint	Entry	2 mo	Endpoint
F3Z-MC-IOAY	Information obtained per protocol but not reported					

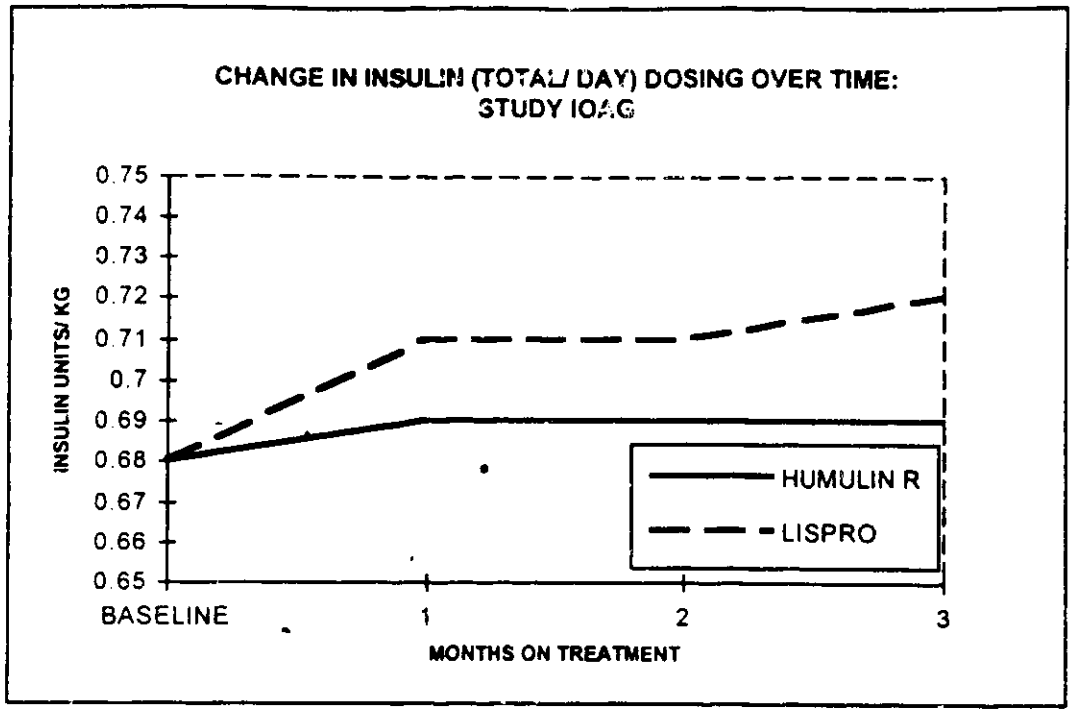
10.2.1.2 Insulin doses

Insulin doses tended to increase in both treatment groups during clinical trials. The differences between the the two groups were most apparent in the cross-over trials F3Z-MC-IOAG, IOAH, IOAY and IOBN. (Refer to figure 11 and table 15.) There was an approximately 5% higher dosing requirement for the total, rapid acting, or basal insulin dose in the Humalog treatment arms. (Although the HgbA1c values achieved by these doses were similar in most of these studies, the difference in HgbA1c favoring regular human insulin in F3Z-MC-IOAG approached statistical significance when p-values were calculated and attained statistical significance when confidence intervals were used.)

Table 15 Insulin doses

INSULIN DOSE (U/Kg) (CROSS-OVER STUDIES)																	
		IOAG n=1008			IOAH n=732			IOAY-ROOM n=179			IOAY-HOOM n=328			IOBN n=93		
INSULIN	TX GROUP	BASELINE	ENDPOINT	3 MONTHS	BASELINE	ENDPOINT	3 MONTHS	BASELINE	ENDPOINT	2 MONTHS	BASELINE	ENDPOINT	2 MONTHS	BASELINE	ENDPOINT	3 MONTHS
RAPID	HUMULIN R	0.36	0.36	0.36	0.3	0.34	0.34	0.18	0.18	0.18	0.17	0.18	0.18	0.43	0.43	0.44
	LISPRO	0.36	0.36	0.36	0.3	0.34	0.34	0.18	0.19	0.19	0.17	0.19	0.19	0.43	0.46	0.46
P-VALUE			0.907	0.865		0.784	0.888		0.138	0.141		0.171	0.171		0.065	0.066
BASAL	HUMULIN R	0.32	0.33	0.32	0.32	0.36	0.36	0.42	0.42	0.42	0.4	0.41	0.41	0.26	0.26	0.26
	LISPRO	0.32	0.36	0.36	0.32	0.36	0.37	0.42	0.46	0.46	0.4	0.42	0.42	0.26	0.27	0.27
P-VALUE			< 001	< 001		0.002	0.001		0.014	0.014		0.179	0.179		0.37	0.116
TOTAL	HUMULIN R	0.68	0.69	0.69	0.62	0.7	0.7	0.6	0.6	0.6	0.56	0.59	0.59	0.69	0.7	0.7
	LISPRO	0.68	0.71	0.72	0.62	0.7	0.7	0.6	0.63	0.63	0.56	0.61	0.61	0.69	0.72	0.72
P-VALUE			< 001	< 001		0.178	0.182		0.01	0.01		0.063	0.063		0.073	0.057

Figure 11



It is unclear what the cause of these increased dosing requirements is. Initial studies with the drug suggested that there might be small differences in potency. Subsequent studies did not identify these differences, and the sponsor has indicated that each unit of Humalog contained the same number of moles of Humalog as a unit of Humulin. It is also unclear whether antibody formation contributes to these differences.

These differences are small and are problably clinically insignificant unless the change in dosing requirements is a harbinger of additional dosing increases with extended therapy. A longer treatment phase than found in any of the cross-over studies could have helped to address this. Analysis of data from the uncontrolled extension trials could also help address this issue if changes in HgbA1c are also considered.

10.2.1.3. Lipids
Lipid parameters (HDL, triglycerides and total cholesterol) were not statistically or clinically different between the two treatment groups in studies F3Z-MC-IOAA through IOAH.

10.2. Overall outcome
The clinical trials suggest the levels of glycemic control as measured by HgbA1c were similar between the two treatment groups. After redefining hypoglycemia and adjusting for HgbA1c, hypoglycemia rates appeared to be similar for the two treatment groups. Fasting blood glucose values tended to be higher in the Humalog treated patients. The 2 hour postprandial values and glucose

excursions in F3Z-MC-IOAG and IOAH were statistically lower in the Humalog treatment groups. These outcome variables remain unvalidated by the sponsor. Interpretation is further complicated by the lack of standardized meals and unblinded nature of the trials. There were no significant treatment associated differences in any of the lipid parameters or weight. There were small, but persistant differences for insulin dosing (higher for Humalog) in the four cross-over studies (2-3 month treatment arms). These differences (1-2 U/day) are probably clinically insignificant unless they increase significantly over time.

11. Safety results

11.1 Extent of exposure

Using very conservative estimates, there have been over 875 patient-years of experience with lispro in the setting of controlled clinical trials with treatment arms 2, 3, and 12 months in length.

11.2. Overview of adverse events

There are several expected and several putative adverse events:

a) Hypoglycemia as detailed under Efficacy Outcomes, sections 10.1.1. and 10.1.2.
   Hypoglycemia and autonomic neuropathy as detailed under Special Populations, section 12.5.
b) Antigenicity resulting in increased frequency of allergic reactions.
   Antigenicity resulting in increased anti-insulin antibody formation.
c) Syncope, dizziness, hypotension as detailed under Special Populations-autonomic neuropathy, section 12.5.
d) Acceleration of retinopathy, nephropathy, and/or atherosclerosis secondary to potential IGF-like qualities of the drug.
e) Dysrhythmias secondary to transient QTc changes +/- concomitant risk factors.

11.3. Serious adverse events

11.3.1. Death

There were seven deaths overall (lispro: four; human insulin: three) in the controlled segments of the clinical trials. The total number of deaths was small and probably reflects the direct and indirect exclusion criteria. Sudden death type events occurred in two patients (072-0573, 812-8141) using lispro and no patients using regular human insulin. There were twelve additional deaths, including four from sudden death type events (602-6025, 808-8181, 905-9105, 907-9342) during the uncontrolled extension studies. (Volume 3-12/18/95 submission and Executive Summary)

No definitive conclusions can be drawn because:

a) The numbers are small.
b) Patients most at risk for severe dysrhythmias because of their underlying disease, their use of drugs dependent on the kalemic state, e.g, and/or their use of drugs that altered the kalemic state, e.g., diuretics tended to be excluded from the trials.

c) Electrocardiograms were not routinely obtained after initiation of therapy (except in Australia and Canada) during the clinical trials.
d) The above EKGs were not definitively obtained during the time interval during which electrocardiographic changes might have been expected to occur.
e) There have been no special, cardiologic assessments in at-risk populations.
f) The kalemic status of the patients who died was often unknown.

(Refer to FDA Cardiology Consult.)

11.3.2. Allergy
Lispro is a foreign protein being administered parenterally on an intermittent basis so an antigenic response would not be entirely unexpected. The first case of a probable allergic reaction occurred during early PK-PD studies (F3Z-EW-E002). A normal volunteer developed urticaria and extensive edema immediately after receiving a single, intravenous dose of lispro. Subsequently there was greater reporting of pruritus often in the setting of rash. The computer data base was searched for cases of rash and/or pruritus that was not explained by other causes and persisted for at least one week. Cases that were present during both treatment arms of cross-over studies were excluded. Of the eighteen cases of such pruritus, sixteen patients were using lispro while two were using human regular insulin. In study F3Z-MC-IOAF alone, pruritus was identified in 8/175 patients using lispro versus 1/179 patients using human regular insulin. The p-value of the Chi-square evaluation was 0.017. An additional eight patients were reported to have discontinued lispro between 4/2/94 and 7/5/95 because of events described as "allergic reaction", anaphylactoid reaction", "uticaria", and rash. The group included one patient with subcutaneous insulin resistance and participants in trials other than F3Z-MC-IOAA through IOAH. From the data presented, there is no basis to reject the hypothesis that lispro is associated with a greater risk for allergic reaction..

11.3.3. Retinopathy
In the integrated safety summary, the sponsor reported statistically significant differences in the number of events listed under the COSTART category "retinal disorder". This difference was to the disadvantage of lispro. Subsequent analysis via the CANDA revealed that retinal events associated diabetes could be listed in multiple categories and that events listed under retinal disorder were not always appropriately classified. (Refer to Appendix on retinal disorder.) (Refer to the comments by Dr. W. Chambers during the Advisory Committee Meeting 2/29/96.)

In addition, the number of reports for diabetic retinopathy overall appears to be small-suggesting that there was under-reporting. Indeed, it is not clear that this was a required element of the entry physical, and there was no exit physical. There was also discordance for relationship between patients with

renal disease and patients with retinopathy. This also suggests that there was a reporting error.

Although it is unlikely that rate of progression of retinopathy could be accelerated to a degree that it could be detected in the shorter studies, no definitive conclusions regarding the induction or acceleration of diabetic retinopathy becasue of the problems with the study design and the data collection-categorization.

1.3.4. Syncopal type reactions
In study F3Z-MC-IOAF (n=377), there were ten events that could be categorized under syncope, vasovagal reaction, postural hypotension, and postural hypotension. Eight of these events occurred in patients using lispro; two in patients using regular human insulin. In addition, there were thirty three observations of dizziness or light-headedness. Twenty of these events occurred in patients using lispro; thirteen in patients using regular human insulin.

Whether this trend was present in the subsequent larger trials is uncertain because of the scattered categorization of the data. Whether these phenomenon are related to electrophysiologic events and/or the episodes of sudden death is unknown.

1.3.5. Diabetic ketoacidosis
This was a rare event in both treatment groups.

11.4. Laboratory evaluations
11.4.1. Hematologic parameters
There were no clear changes in the hematologic parameters when the studies were considered collectively.

11.4.2. Clinical chemistry parameters
There were no clear changes in the majority of clinical chemistry parameters assessed.

Select individuals experienced elevations in creatine phosphokinase. It is unclear whether these individuals inadvertantly injected intramuscularly or were reacting to drug-excipient from the data provided. Cresol, a preservative, has been implicated as the cause for elevated CPK, generalized myalgias, and localized injection site reactions (Bach MA, Blum DM, Rose SR, Charnas LR; Myalgia and elevated creatinine kinase activity associated with subcutaneous injections of diluent. J Pediatrics 1992 24(4):650).

There were no clear changes in the serum creatinine for subjects on either drug. Given the duration of the studies, the selected patient population, and the relative insensitivity of the serum creatinine (versus creatinine clearance), one would be unlikely to detect changes in the serum creatinine unless the toxicity was extraordinary. Refer to Appendix tracking renal changes in year

long studies in patients with serum creatinine values > than 1.5 mg/dl.)

11.4.3. Urinalysis
Patients were evaluated with spot urines, which have limited utility. Abnormalities in the spot urines did not correlate well with serum creatinine levels. (Refer to table 16.) In addition, one of the patients with retinopathy were among the patients with abnormalities in both serum creatinine and spot urine protein. (This is a somewhat discordant and unexpected finding-suggesting that evaluation and reporting of retinopathy is incomplete. Several patients with the most abberrant renal studies including 851-8525, 906-9092, 203-256, and 904-9150 did not have routine, follow-up laboratory studies.

Table 16 Abnormal Renal Studies

Diabetic patients* from studies	IOAA-IOAD		IOAE-IOAF	
	Humulin R	Lispro	Humulin R	Lispro
Abnormal urine protein				
# at Baseline	67	60	29	15
# (of above) with a value at Completion	56	57	22	14
# at Completion	60	56	22	20
Change in urine protein				
>/=1 unit	29(11)	20(10)	26(3)	16(2)
>/=2 units	5(1)	2(1)	5(2)	2(1)
Abnormal urine protein+ serum creatinine				
# at Baseline	5	5	5	1
# at Completion	6	6	8	4

* numbers in parenthesis are IDDM patients

Given the duration of the studies, the selected patient population, and the relative insensitivity of the spot urine (versus 24 hr collection), one would be unlikely to detect changes in proteinuria unless the toxicity was extraordinary.

11.4.4. Antibodies
Antibodies that cross-reacted to both human insulin and lispro were the type of antibodies that showed increases during the clinical trials F3Z-MC-IOAA through IOAH. The increases were most predominant in studies IOAE and IOAF, which evaluated patients with only limited or no prior exposure to endogenous insulin. Analysis of patients in IOAE suggested that patients with higher % binding required higher insulin doses. This appeared to be true regardless of the type of insulin used. The association between insulin doses and % binding, however, was less clear for IOAG. Multi-factorial analysis including the level of glycemic control

may be neccessary to more fully address this question. There were statistically higher levels of % binding (cross-reacting type) for patients treated with lispro in several of the clinical trials. The clinical significance of these differences remains unknown at this time.

12. Studies in special populations
12.1. Effect of obesity or subcutaneous fat thickness on the rate of absorption
No specific PK-PD studies were performed to address this issue although results from several outliers have suggested that this might be an important parameter. (Refer to 8.3.2. Variables influencing absorption-Weight and Characteristics of patients enrolled-Body Mass Index.)

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

12.3. Pregnancy
There have been no clinical trials with women who desire pregnancy or who are pregnant. This product is likely to be used women with IDDM or gestational diabetes. Altered gastric emptying is one of the variables in pregnancy and can influence the blood glucose levels as well as the timing of hypoglycemia. The different pharmacokinetics of Humalog will need to be carefully considered before dosing in the various stages of pregnancy.

The following tabulation outlines what is known about the women who became pregnant during the trial. (Refer to volume 3.2 of 4 from 7/13/95 submission.) The rates of pregnancy were similar in the controlled trials: Humulin R 7 and Lispro 5. There was a major complication in each treatment group. Although urogenital abnormalities are more common in male children and the listed concomitant medications have not been associated with such, the information is too limited to draw any definitive conclusions about this particular complicating event or the role of Lispro in pregnancy.

Table 17

Humulin R
IOAA Mother with age of 24 years-discontinued from trial
Outcome unknown
IOAC Mother with age of 20 years-discontinued from trial
Elective abortion
IOAC Mother with age of 29 years-completed trial-4 months pregnant at study end
Pregnancy complicated by toxemia-->C-section (30 weeks)
Birthweight-2 kg
Follow-up ~1 year later-normal mother and baby
Follow-up at ~2 years-child with milk allergy and otitis
IOAC Mother with age of 36 years-discontinued from trial
Baby normal at birth

IOAE Mother with age of 25 years-discontinued from trial XXX
Pregnancy and delivery unremarkable
Follow-up at ~2 years-baby healthy
IOAG Mother with age of 23 years-discontinued from trial
Baby delivered (status unknown)
IOAG Mother with age of 32 years-discontinued from trial
Elective abortion

Lispro
IOAA Mother with age of 22 years-discontinued from trial
Elective abortion
IOAA Mother with age of 27 years-discontinued from trial
Follow-up at one year-baby healthy
IOAE Mother with age of 20 years-discontinued from trial
Outcome unknown
IOAG Mother with age of 38 years-discontinued from trial
HgbA1c at time of pregnancy 7.2%
Mother also treated for longstanding hypothyroidism
Vaginal delivery induced at 38 weeks
Baby large for gestational age-4.6 kg
Follow-up at ~6 months-baby healthy
IOAN Mother with age of 32 years
Spontaneous abortion (Lispro subsequently discon' ued)
Follow-up at ~1 month-woman healthy
IOAN Mother with age of 19 years-discontinued from t
HgbA1c prior to conception 5.8-8.1%
Concomitant Rx: Femulen (with ethynodiol diacetate) and
Amoxil
On Lispro ~5 weeks
Vaginal delivery at 35 weeks
Birthweight-3.1 kg
Male baby with dysplastic kidney

12.4. Nursing mothers
No clinical trials have been performed in nursing mothers. It is known that insulin is secreted in breast milk, but it is unknown whether the levels are sufficient to induce any biological response. On a more speculative note, there is an association between ingestion of cow's milk and the risk of developing IDDM (Karjalainen J, Martin JM, Knip M, Ilonen J, Robinson BH, Savilahti E, Akerblom HK, Dosch HM; A bovine albumin as a possible trigger of IDDM N Eng J Med 1992 327(17):1252). It is known that the gut barriers to foreign proteins are incomplete. Although the authors postulated that bovine albumin was the culprit, it is also thought that oral ingestion of insulin may confer protection against IDDM (Muir A, Schatz D, Maclaren N; Antigen specific immunotherapy: oral tolerance and subsutaneous immunization in the treatment of IDDM Diabetes-Met Rev 1993; 9(4):279). Whether ingestion of a foreign insulin protein versus a human insulin protein could alter the risk for IDDM is unknown.

12.5 Children
Children can become hypoglycemic with their high level of physical activity and/or their erratic eating habits. Lispro

could potentially be given after meals. Children, however, are likely to be thinner than adults, and the onset of glucose lowering may be even more rapid. Only 118 subjects between the ages of 12 and 17 inclusive were enrolled in the controlled trials presented for the NDA. Younger children were excluded from trials. The sponsor previously submitted two protocols for evaluation of the drug in adolescents (F3Z-MC-IOBJ; submitted 10/13/94) and young children (F3Z-MC-IOCF; submitted 2/8/95). Their designs may limit the safety and efficacy conclusions that can be drawn.

12.6. Autonomic neuropathy
Abnormal gastric emptying can occur secondary to autonomic neuropathy or may be iatrogenic. Patients with delayed gstric emptying may be less tolerant of a rapid acting insulin.

In addition, abnormal vasodilitory responses after the administration of insulin are more likely to occur in patients with autonomic neuropathy. These may be intepreted as hypoglycemia. In more severe cases, probably also confounded by atherosclerosis, presumably blood flow to the brain and/or other organs is temporarily. Whether these responses would be aggravated by an insulin with a higher Cmax and a shorter tmax is unknown.

No specific PK-PD studies were performed to address this variable. Furthermore, patients with autonomic neuropathy are likely to have more problems with hypoglycemia, and although these patients were not specifically excluded from the studies and neuropathy was noted under both TESS and non-TESS listings, the exclusionary criterium for patients with problematic hypoglycemia introduced bias against their selection.

12.7. Renal disease
No adequate studies in diabetic patients with renal complications have been performed. Studies with Humalog in renal patients are limited to one, small, single-dose pharmacokinetic study in non-diabetic renal patients. Analysis was complicated and no clear conclusions could be drawn. (Refer to Biopharmaceutics Review.) Diabetic patients with elevated serum creatinine levels (>2 mmol/L or >3 mmol/L) were excluded from the clinical trials.

12.8. Cardiac disease
Refer to 11.3.1. Death

13. Discussion
The sponsor has demostrated that the modified insulin can be absorbed more quickly from subcutaneous tissue than regular huamn insulin (U100). This more rapid absorption is followed by a more rapid time to glucose nadir. This offers some convenience in administration. Insulin can be taken immediately prior to food intake. Mixing with NPH, however, can attenuate the rapid absorption by 20-30%.

In the clinical trials, the early postprandial (1 and 2 hour) glucose values tended to be approximately 10% lower with lispro than those found after the administration of human regular insulin, but these values were still markedly abnormal. Late postprandial data, which would probably favor regular human insulin was not collected in studies F3Z-MC-IOAA through IOAH. In at least one of the trials, F3Z-MC-IOBN, human regular insulin was given at a time known to be disadvantageous. The unblinded insulin adminstration and non-standardized meals confounded interpretation of postprandial data. Both the one and two hour glucose excursion and postprandial glucose remain unvalidated as outcome variables. It is unclear whether the magnitude of the differences in the postprandial glucose parameters between the two insulins will sustained over time.

The integrated glucose control, as measured by HgbA1c, and fasting glucose are not superior to that achieved with regular human insulin.

With the exception of allergic type reactions, there were no clear safety problems associated with lispro in the populations tested for the time interval used. The rates of hypoglycemia appear to be similar to those seen with human regular insulin although there may be differences in the timing. Safety assessment, however, was limited by several factors:
a) the lack of baseline assessment, e.g., retinal exams
b) the lack of follow-up for abnormal tests, e.g., abnormal spot urines
c) the absence of electrocardiographic data at times post dosing when changes might be expected to be most prominent
d) the lack discharge physical examinations
e) the duration of the studies may be too short to assess adverse events with an altered rate of progression
f) the exclusion of populations with potentially more adverse risk (including patients with autonomic neuropathy abnormal gastric emptying, more severe cardiac disease, and/or renal disease)
g) the codification of adverse events and medications into diverse sections of the database limiting integrated data retrieval and analysis.

14. Conclusions

The drug is approvable for subcutaneous use (not including pumps) with reservations and stipulations. The Sponsor has shown that Humalog does lower glucose and that HgbA1c and overall hypoglycemia rates are similar to that seen with regular human insulin. The rate of absorption may offer convenience in administration. The trials, however, were not well conducted. There are significant deficiencies in the pharmacokinetic information for the drug. Population subgroups who are major potential users of the drug were specifically excluded from the clinical trials and other, more limited, pharmacokinetic-pharmacodynamic evaluation.

The drug should be limited to prescription use only. The label should be sufficient to clearly outline how this insulin is different from other available insulins and how this will alter patient selection and patient management. The physician should have the information to decide whether any increase in convenience is balanced by the potential for antigenicity and other, less well-defined risks. The sponsor should distinguish between information (toxicologic or clinical) known to true for human insulin and that which has been specifically established for Humalog.

The patient package insert should, at a minimum, indicate that not all diabetic patients may be candidates for this drug, that the glycemic control and overall hypoglycemic rates are comparable for human insulin and Humalog, that the timing of hypoglycemia might be different, and that mixing with NPH will decrease its absorption rate and delay the onset of glucose lowering.

The Sponsor should be limited in the claims that can be made, in part, because the some of the outcome parameters have not been validated and are artifacts of study design.

15. Labeling Review
(Refer to sponsor and reviewer drafts.)
15.1 General
Physician labeling was not required for animal and human recombinant/semi-synthetic insulins because of grandfathering clause. By their design, insulin analogues have different properties than those of human insulin. To provide the physician with adequate information for proper patient selection and modifying dosing regimens, a physician insert clarifying what is known and what might be extrapolated is recommended.

This recommendation was informally conveyed to the sponosr prior to the submission of the NDA and formally conveyed to the sponsor in the 10/5/1995. Labels (physician insert, patient insert for drug in vials, and patient insert for drug in pen cartridges) were submitted by the sponsor in writing 4/1/96 (letter date) and by diskette 4/3/96 (letter date).

15.2. Comments on proposed label
15.2.1. Description
The sponsor draft indicated the structure of the molecule, the recombinant technology used to prepare the insulin analogue, and the availability. The sponsor did not indicate the analogy of the structural changes to the IGF-I molecule, the amount of phenol in the excipient, and the limitation of the cartridges to certain pens. The sponsor also indicated that hydrochloric acid and sodium hydroxide could be used to adjust the pH, but no data have been submitted clarifying for what clinical conditions this should be done.

15.2.2. Clinical Pharmacology
The sponsor included general data on the activity of insulin. The sponsor indicated that lispro analogue had equal potency with recombinant human insulin, that it had bioavailability equal to that of human insulin, that it was absorbed more quickly than human insulin in normal and diabetic volunteers, that it had a volume of distribution equal to that of human insulin, that it had a shorter elimination t1/2 than human insulin, that it had a more rapid onset of glucose lowering activity in normal and diabetic volunteers, and that it had a shorter duration of glucose lowering activity.

15.2.2.1. General
The sponsor does not clearly indicate that this insulin is intended for subcutaneous injection and that the pharmacokinetic and glucodynamic profiles were comparable when administered to normal volunteers by an IV route. (The sponsor indicates that the elimination t1/2 are identical for the analogue and regular human insulin.)

15.2.2.2. Potency
Very early PK-PD studies suggested that Lispro was slightly less potent. Subsequent studies showed equipotency. There has been no explanation for the discrepancy in the results. The sponsor has reported that equal milligrams per unit of human and analogue insulin were used in the formulations for the trials.

15.2.2.3. Absorption
The sponsor does not indicate that the control insulin was U100. (U40 preparations of insulins appear to have more rapid subcutaneous absorption than U100 preparations.)

The sponsor does not indicate that absorption studies using different injection sites were not conducted with diabetic patients, only normal volunteers.

The sponsor does not clearly state to what degree the mixing of the insulin analogue with NPH blunts the absorption rate of the insulin and it onset of glucose lowering activity, and that this does not occur with ultralente preparations. The sponsor has submitted no data to clarify the effect of time on this attenuation.

15.2.2.4. Metabolic studies
The sponsor indicates that the metabolism of Humalog is identical to that of human regular insulin. The Agency biopharmacologist has indicated that no metabolic studies were submitted for review.

15.2.2.5. Clinical trial data
The sponsor includes postprandial and glucose excursion data from the clinical trials under pharmacology. Clinical data should go into a clinical section. The sponsor should not be permitted to

present data on unvalidated paramaters (unless it is clearly indicated that there is no validation). The sponsor should comment on the tendency for higher or equivalent fasting glucose and HgbAlc levels.

The sponsor's statments regarding hypoglycemia are also misleading. The overall hypoglcemia rates (glucose </=36 mg/dl or requiring assistance) at end of study were equivalent when adjusted for HgbAlc. By post hoc analysis, using an unspecified definition of hypoglycemia, and using an unspecified interval for frequency, the sponsor is claiming reduced nocturnal hypoglycemia. The number of events during the evening hours were relatively few for both insulins. The Sponsor's analysis claims statistical significance for the hours between midnight and 6 AM, but does not present data analyzed in other blocks of time.

15.2.2.6. Special Populations
Although the sponsor states that no pharmacokinetic-pharmacokinetic data was collected on patients of different age or sex, the sponsor reports that the analysis of clinical trials did not reveal any differences. The clinical trials did not include children under 12 years of age.

A small number of non-diabetic patients with vaying degrees of renal impairment were assessed in a single dose study. The sponsor indicates that there were no PK differences for Humalog between renal patients and normal controls. Very limited data was submitted for review, the analysis very complicated, and the interpretation contradicts some of the literature. To assist physicians in dosing, the following was suggested to the sponsor: "Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. Information on the effect of renal impairment on the pharmacokinetics of Humalog is limited. Caution should be used when administering any insulin product to patients with any significant renal dysfunction."

The effect of smoking on pharmacokinetics was not assessed. Information in the literature suggests that this is a relevant variable. Vasoconstriction may impact on the rate of absorption.

Studies evaluating the effect of obesity on pharmacokinetics were not performed. Because obesity is a significant risk factor for NIDDM, a large number of diabetics will be overweight. An obese, non-diabetic, male volunteer demonstrated outlier pharmacokinetics for insulin Lispro. (Obesity was an exclusion criterium for basic PK studies so other subjects were not obese.) Whether total weight, subcutaneous fat thickness at the site of injection, or some other factor is explanatory is unknown.

Information on the effect of the various stages of pregnancy on the pharmacokinetic-pharmacokinetic properties of Humalog

is not available. Insulin usage by pregnant patients is routine. Gastric emptying, trimester-dependent insulin resistance, and other factors contribute to differences in the management of pregnant versus non-pregnant patients.

15.2.2.7. Drug Interactions
The sponsor should clearly state that no drug interaction studies have been performed using Humalog with the exception of other insulin preparations. It is appropriate to list drugs that are known to increase or decrease insulin requirements as well as drugs that may mask hypoglycemia.

15.2.3. Indications and Usage
The sponsor should clearly indicate that Humalog is to be used subcutaneously in conjunction with a longer-acting insulin in the regimen. No trials were conducted using intravenous administration. No trials were conducted without a basal or longer-acting insulin although a few subjects did not use/require an overnight insulin. The coverage for glucose control provided by Humalog is dissipated by four hours and may be followed by hyperglycemia. Because of this short activity, fasting glucose values may be higher and compensatory adjustments in the basal/longer-acting insulin coverage may be necessary.

15.2.4. Contraindications
The sponsor indicates that hypoglycemia, hypersensitivity to Humalog, and hypersensitivity to excipients in the formulation are contraindications to use. There is some data to suggest that cresol can result in localized reactions and systemic myalgias. Specific information on the reactions seen with excipients is not included in the label submitted by the sponsor. Humalog use should also be relatively contra-indicated in patients who are unable to tolerate rapid changes in serum glucose or potassium.

15.2.5. Warnings
The sponsor indicates that Humalog differs from human regular insulin by its rapidity of onset and shorter duration of activity. For this reason, it should be given in conjunction with food. Changes to a new insulin may necessitate changes in short-term dose, long-term dose, and dosing times. Hypo-glycemia is the most common side-effect. The sponsor does not include the major dose interaction with NPH which occurs with mixing.

15.2.6. Precautions
15.2.6.1. General
The sponsor should clearly indicate that rebound or late hypeglycemia may occur and that the timing of hypoglycemia may be different.

15.2.7. Laboratory tests
The sponsor recommends blood glucose and glycosylated

hemoglobin tests to assess the therapeutic response to the insulin analogue. Improvement in the latter has been validated as a parameter which corresponds to the reduction of diabetic complications in the DCCT.

15.2.8. Drug interactions
Drug interactions were addressed under Clinical Pharmacology. The sponsor should clearly state that no drug interaction studies have been performed using Humalog with the exception of other insulin preparations. It is appropriate to list drugs that are known to increase or decrease insulin requirements as well as drugs that may mask hypoglycemia.

15.2.9. Toxicology
15.2.9.1. Carcinogenesis, mutagenesis, impairment of fertility
The sponsor states that chronic one-year toxicology studies were performed in dogs and rats and showed no evidence of toxic effects, proliferative changes or tumors. The sponsor did not conduct studies in an Agency approved format for the evaluation of the carcinogenic potential of Humalog so the prior statement is misleading (per discussion with the Supervisory Division Pharmacologist). (The sponsor indicated in volume 30, page 5, that carcinogenicity studies were not applicable.)

The Agency agrees that Humalog was not mutagenic in a battery of in vivo and in vitro genetic toxicity assays (per discussion with the Supervisory Division Pharmacologist).

Available data support the statement "There is no evidence from animal studies to date of Humalog-induced impairment of fertility.

15.2.9.2. Pregnancy/labor and delivery
The sponsor states that reproduction studies in pregnant rats at parenteral doses up to 20 unit/kg/day of Humalog (40 times the average human dose) and pregnant rabbits at parenteral doses up to 0.75 units/kg/day (1.5 times the average human dose) have revealed no evidence of harm to the fetus. Data suggest that mg/meter squared dosing may provide for better comparison of animal-animal and animal-human dosing data than the mg/kg expression. The Agency has adopted this practice. In addition, it was unclear what dose the Sponsor was using as the average human dose. To facilitate clinician interpretation of these animal data, the following restatement of the animal data is recommended: Reproduction studies have been performed in rats and rabbits using single parenteral doses up to 4 and 0.3 times respectively, the normal human dose (40 Units/70 kg person/day) based on body surface area.

Because no controlled clinical trials have been conducted with Humalog in pregnant patients, dosing regimens require

change during the various stages of pregnancy, and the timing of hypglycemia may be different with Humalog, this drug cannot be recommended. Nonetheless, the following guidance could assist the clinician: Although there have been no clinical studies Humalog and pregnant women to date, published studies with human insulins suggest that optimizing overall glycemic control prior to conception and during pregnancy improves fetal outcome. Although fetal complications of maternal hyperglycemia have been well documented, fetotoxicity has also been reported with maternal hypoglycemia. Insulin requirements usually fall during the first trimester and increase during the second and third timesters. careful monitoring is required throughout the pregnancy process. The timing of hypoglycemia may vary with the type of insulin used. Careful monitoring of the baby during the peri-delivery period is warranted.

15.2.9.3. Nursing mothers
The sponsor clearly states that there have been no clinical studies with Humalog in mothers and that caution should be exercised. Because it is known that human insulin is excreted in the milk, there is a high likelihood that Humalog will also be excreted. The sponsor should state that the effects of oral ingestion of human insulin versus Humalog during infancy are unknown.

15.2.9.4. Pediatric use
The sponsor states that safety and efficacy of Humalog has not been established in diabetic children under the age of twelve.

15.2.10. Adverse Reactions
The sponsor lists hypoglycemia, injection site reaction, lipodystrophy, allergic reaction, pruritus, and rash under "adverse reactions" and describes these reactions under "precautions". The sponsor does not supply specific data regarding the incidence and/or prevalence of allergic-like reactions associated with Humalog.

In controlled trials of Humalog versus Humulin R with over 2500 patients, there were 14 more cases (0.56%) of unexplained pruritis lasting one week or longer in patients on Humalog than in patients on Humulin R. In a total of over 3000 patients who have received Humalog, there are nine reports (0.3%) in whom Humalog was discontinued because of episodes described as "allergic reaction", "anaphylactoid reaction", or "uticaria". These figures problably underestimate the number of reactions because abnormal or allergic reactions to insulin were exclusionary criteria in the clinical trials.

15.2.11. Drug Abuse and Dependence
The sponsor does not specifically address the issue of drug abuse. The potential for abuse is low. Indeed, the literature suggests that diabetics with eating disorders may reduce their compliance to facilitate glycosuria and weight loss.

15.2.12. Overdosage
The sponsor includes a section on hypoglycemia and its management.

15.2.13. Dosage and Administration
The sponsor does not give clear guidelines as to how this insulin is different from other preparations and how this might impact on patient selection. The sponsor draft does not clearly indicate that this preparation is for subcutaneous injection from cartridges or vials and not for pump use or intravenous administration. The implications of mixing with NPH and the probable need for a longer acting insulin (particularly overnight) are not spelled out. The probability that a different hypoglycemic profile can be expected based on the kinetics is not made clear. The sponsor also attempts to extrapolate to use in non-tested populations and does not explicitly indicate what data is from human insulin and not lispro.

15.2.14. How supplied
The sponsor clearly indicates that the formulation is U100 and that both 10 ml vials and packages of 5 1.5 ml cartridges are available. The sponsor indicates that only specific cartridge pens should be used.

15.2.15. Patient inserts (vials and cartridges)
The sponsor goes into great detail about how insulin should be given, but does not indicate to the patient the general reasons why all diabetics may not be candidates for this insulin product. The inserts do not indicate the problems with mixing and the probable need for a basal insulin. The patient is not informed that there may be a different temporal profile of hypoglycemia. (Refer to sponsor and reviewer drafts.)

Elizabeth Koller, M.D.
Medical Officer
Division of Endocrine and Drug Products

JAN - 5 1996

Medical Officer's Review

Insulin Lispro, NDA 20-563

submission of December 18, 1995

Study F3Z-MC-IOBN - A Double Blind Controlled Comparison of Glycemic Control Using Insulin Lispro and Human Soluble Insulin in Type 1 Diabetics who take Multiple Injections

Summary:

This is a double- blind cross- over study of insulin Lispro versus Humulin R in type 1 diabetics who had been taking multiple insulin injections. Each of 93 patients received three months of Humulin R and three months of insulin Lispro in randomized order. Insulin Lispro was better than Humulin R with respect to control of postprandial glucose; however Humulin was better than Insulin Lispro in controlling fasting glucose. Overall glycemic control, as measured by hemoglobin A1c and seven point average glucose concentration, was the same with both groups. There was also no difference in reporting of hypoglycemic reactions. The dose of Insulin Lispro at the end of treatment was approximately 5 % higher than the dose of Humulin R. Reporting of " flu-like" symptoms was greater with Lispro. Otherwise, there was no significant difference in adverse events.

Study Design:

This double- blind cross-over study was done at ten centers in Britain. The study groups consisted of 114 patients who had had type 1 diabetes for one year or greater and who normally injected insulin four times per day. Obese patients (body mass > 35 kg/m2), patients with progressive diabetic complications and those in poor glycemic control (hemoglobin A1C greater than 1.5 the upper limit of normal) were excluded. Patients were randomly assigned to receive insulin lispro or Humulin R before each meal for three months, before crossing over to the other therapy for an additional three months. NPH insulin (Humulin N) was given as a single dose at bedtime. A second dose of NPH could be given at the discretion of the investigator if preprandial blood glucose remained over 7.8 mM(140 mg/dl). Patients were instructed to give the dose of test insulin ten minutes before meals and to adjust the dose in order to achieve a 2 hour postprandial glucose less than 10 mM(180 mg/dl). Primary efficacy measures were hemoglobin A1c in addition to seven glucose measurements done at various times throughout the day.

Patient characteristics:.

Of the 114 patients who enrolled, 93 were randomized. Of the 21 patients who were not randomized, 20 did not meet the entrance criteria and one elected not to participate. 41 patients received three months of lispro followed by three months of Humulin R. 52 patients received Humulin R first followed by Lispro. Six patients discontinued before the completion of the study (see below). All patients were Caucasian with a predominance of men(59%) to women(41%).

Their average age was 35 years (18-63) and average duration of diabetes was 13 years(1-51).

Efficacy:

Results of the seven point blood glucoses are shown in table 6.17 and figure 6.15. Significantly lower fasting and evening preprandial glucoses were observed with Humulin R than with Lispro. However significantly lower 2 hour postprandial glucoses were observed with Lispro. Bedtime glucose was lower with Humulin but the difference was of borderline significance (p=0.079). The differences between Humulin R and Lispro with respect to time of glucose peak tended to cancel each other out. The mean of the seven point glucose determinations were 156 mg/dl with Lispro and 155mg/dl with Humulin R. There was also no significant difference with respect to hemoglobin A1c which was 7.4 % with Lispro and 7.5 % with Humulin R. The incidence of hypoglycemic reactions (defined as blood glucose less than 2.5 mM) was also the same in the two groups and was approximately three per month. However a small difference (p=0.065) existed between the two groups in the amount of test insulin used which was 0.43 U/kg with Humulin R and 0.45 U/kg with Lispro.

Safety and Tolerability:

Two patients dropped out of the study because of adverse events. One discontinued due to " hypoglycemic coma" while on Humulin R. A second discontinued because of " emotional lability" while on Humulin R although it may be worth noting that this patients(802-8048) had complained of pruritus on Lispro. There was an unexplained increase in reporting of " flu syndrome" with Lispro. This occurred with 29.3 % of lispro patients and 7.7% with Humulin R , p=0.006.

Reviewer's Comment

Although this study is small, it is probably the most important in the NDA because it is free from the methodological flaws that limited interpretation of many of the other studies. As a double-blind cross-over study, problems relating to lack of baseline data, patient and investigator bias, and non-standardization of test meals are minimized. However, the result of this study are largely the same and therefore validate the larger studies previously submitted. Since it involved patients who had previously been on an intensive regimen of four insulin injects per day, it the best test yet for the hypothesis that multiple injections of a rapidly acting insulin will result in better glycemic control. The results show that Lispro does indeed result in less postprandial hyperglycemia but this is achieved at the expense of fasting hyperglycemia which is better controlled with Humulin R. Overall glycemic exposure as measured by hemoglobin A1c and seven point average glucose level was the same in both groups as was the incidence of hypoglycemia. As has been observed in previous studies the dose of Lispro required to achieve equilivalent results is about 5% higher with Lispro than with Humulin R.

Robert I Misbin MD
Medical Officer
January 3, 1996

1/5/96

HFD 510, NDA-20-563
HFD Dr Fleming/Dr Koller

Sponsor: [redacted]
Lilly [redacted] Research Center
Indianapolis, Indiana 46285

12.F.

Drug: Ly275585 (Lys B28, Pro B29) human insulin

AFR

Amendment

Protocol #: F3Z-MC-10AH(1)

Protocol Title: A Comparison of the Glycemic Response to Exercise in Persons with Type II Diabetes treated with a Rapid Acting Analog [Lys(B28), Pro (B-29)] or Humulin Regular Insulin.

Objective: To determine if there is less hypoglycemia associated with exercise in individuals treated with comparable amounts of rapid acting insulin analog [Lys(B28), Pro(B29)] and human regular insulin.

Procedure: The addendum proposes to study the glycemic response to exercise which takes place 2 hours after a standard breakfast meal in individuals given insulin analog [LYS(B28), Pro(B29)] compared to human regular insulin. The supposition being there will be less hypoglycemia following the analog since there should be lower insulin levels present 2 hours after injection.

The study will involve 15 Type II diabetic patients who will be asked to exercise immediately after the conclusion of the 2 hour post prandial glucose scheduled at visit 7 or 8, and again at visit 13 or 14.

If the 2 hour post prandial value is less than 70 mg/dl one CHO exchange will be given. Determinations will be made prior to inclusions in the amendment to exclude subjects with known contraindications to exercise on a sedentary bicycle.

Under the supervision of a qualified health professional with exercise tending experience, each subject will ride a stationary bicycle at a level of 60% of predicted maximum heartrate for 20 minutes. Additional capillary glucose testing will be obtained at specified time points.

The exercise sessions will occur once during each treatment phase of the standard protocol. Each patient will serve as his/her own control. Exercise will take place at 12 weeks of therapy. If a patients has attained excellent overall glucose control (HbAlc within 1% of the upper limits of normal) by 8 weeks, exercise will be done at that time.

Recommended Regulatory Action:

The study may proceed.

Eileen S. Parish, M.D.

Eileen Parish, M.D.
Medical Officer

cc: IND Arch
HFD-510
HFD-510/Parish/rd/dj/10.14.93/ft/dj/11.12.93/).MOR

11/11/93

STATISTICAL REVIEW AND EVALUATION

NDA #: 20-563/ Drug Class 1S

APPLICANT: Eli Lilly and Company

MAR 14 1996

NAME OF DRUG: Humalog™ (insulin lispro)

INDICATION: Hypoglycemic Agent

DOCUMENTS REVIEWED: Volumes 1.133 thru 1.190 & 1.203 thru 1.388

MEDICAL REVIEWERS: Elizabeth Koller, MD (HFD-510)
Robert Misbin, MD (HFD-510).

This review is arranged in five sections. Section I gives a brief introduction of the studies under this submission. Sponsor's efficacy results, efficacy discussions and conclusions are described in Section II. This reviewer's evaluation of these studies is contained in Section III. Section IV gives the results of the three analyses performed by the sponsor that were requested by the FDA. Section V contains reviewer's conclusions that may be conveyed to the sponsor.

I. INTRODUCTION

The sponsor submitted eight multicenter, multinational clinical studies comparing Humalog™ (insulin lispro) with Humulin® R in patients with diabetes (see a brief description on the next page). These eight studies involved patients with either Type I or Type II diabetes using multiple dose therapy consisting of either Humulin® U or Humulin® N as a basal insulin, and lispro or Humulin® R as the pre-meal insulin. These studies included patients who had been previously treated with insulin as well as patients initiating insulin treatment.

Efficacy was measured by glucose control as determined by hemoglobin A_1c (HbA_1c), fasting blood glucose (FBG), 1- and 2-hour postprandial blood glucose values, and 1- and 2-hour glucose excursions following a test meal. In addition, hypoglycemia rate per 30 days, total daily insulin dose, body weight and plasma lipids were also obtained.

Key Words: Multicenter Studies, Multinational Studies, Cross-over Studies, Parallel Studies, Insulin.

TABLE: BRIEF SUMMARY OF EIGHT STUDIES

Study No. & Type of Diabetes	Number of Centers	Total Sample Size	Type of Control	Design	Duration of Treatment
IOAA Type I	14	Enr. 171 Ran. 167	Active: Humulin R	Randomized Parallel Open-label	12 months
IOAB Type II	13	Enr. 157 Ran. 145	Active: Humulin R	Randomized Parallel Open-label	12 months
IOAC Type I	17	Enr. 174 Ran. 169	Active: Humulin R	Randomized Parallel Open-label	12 months
IOAD Type II	13	Enr. 160 Ran. 150	Active: Humulin R	Randomized Parallel Open-label	12 months
IOAE Type I	22	Enr. 98 Ran. 98	Active: Humulin R	Randomized Parallel Open-label	12 months
IOAF Type II	48	Enr. 377 Ran. 375	Active: Humulin R	Randomized Parallel Open-label	12 months
IOAG Type I	101	Enr. 1037 Ran. 1008	Active: Humulin R	Randomized Two-Period Cross-Over Open-label	6 months
IOAH Type II	78	Enr. 777 Ran. 722	Active: Humulin R	Randomized Two-Period Cross-Over Open-label	6 months

II. SPONSOR'S EFFICACY RESULTS

This section reviews the sponsor's results and conclusions of the primary and secondary efficacy variables (defined by the sponsor) from the eight multicenter, multinational studies comparing the rapid-acting insulins, lispro and Humulin® R.

Studies IOAA(n=167), IOAB(n=145), IOAC(n=169) and IOAD(n=150) were 12-month, randomized, parallel studies in patients with diabetes having used insulin for at least 2 months prior to enrolling in the study. Each of these studies required patients to use a

similar insulin regimen (either Humulin® U or Humulin® N, given one or two times per day) and a rapid-acting insulin (either lispro or Humulin® R) before each meal. The recommended therapeutic goals, dosing guidelines and endpoints were identical for each of these studies. These four studies differed only in the type of diabetes (IOAA, IOAC: Type I; IOAB, IOAD: Type II) and the type of basal insulin (IOAA, IOAB: Humulin U; IOAC, IOAD: Humulin N) used. The sponsor analyzed these studies separately as well as combined.

Studies IOAE(n=98) and IOAF(n=375) were also 12-month, randomized, parallel studies. These two studies were identical with the exception that IOAE enrolled patients recently diagnosed with Type I diabetes and IOAF enrolled patients with Type II diabetes who had recently began therapy with human insulin. These two studies were analyzed separately rather than combined due to the disparity of the patient populations.

Studies IOAG(n=1008) and IOAH(n=722) were 6-month, randomized, two-period cross-over studies involving patients with Type I (IOAG) or Type II (IOAH) diabetes who used human insulin for at least 2 months prior to the start of the study. These two studies were analyzed separately as well as combined.

1. 2-Hour Postprandial Blood Glucose Excursion

The following table gives the summary and analysis of 2-hour blood glucose excursion at endpoint for each of the eight studies as well as combined studies: IOAA through IOAD, and IOAG through IOAH.

TABLE: 2-Hour Blood Glucose Excursion (mmol/L) at Endpoint by Study

Protocol	LISPRO			Humulin R			Treatment Comparison
	n	Mean	SD	n	Mean	SD	
IOAA	81	0.07	4.87	85	2.92	4.28	p=.001
IOAB	72	1.04	3.66	72	2.49	3.94	p=.016
IOAC	80	1.99	5.08	88	2.75	4.64	p=.458
IOAD	71	1.74	3.76	77	2.84	3.25	p=.025
A-D Combined	304	1.19	4.47	322	2.76	4.07	p<.001
IOAE	50	1.31	4.29	45	2.78	4.37	p=.206
IOAF	175	2.38	3.64	179	2.83	2.94	p=.296
IOAG	979	-0.51	4.88	987	1.52	5.05	p<.001
IOAH	709	1.40	3.67	703	2.97	3.73	p<.001
G-H Combined	1688	0.29	4.51	1690	2.12	4.60	p<.001

The 2-hour postprandial glucose excursion was consistently lower during therapy with lispro in each of the eight clinical studies and achieved statistical significance ($p<0.05$) in five of these studies.

2. *Hypoglycemic Rate per 30 Days*

The following table gives the summary and analysis of hypoglycemic rate per 30 days at endpoint for each of the eight studies as well as combined studies.

TABLE: Hypoglycemia Rate per 30 Days at Endpoint by Study

Protocol	LISPRO			Humulin R			Treatment Comparison
	n	Mean	SD	n	Mean	SD	
IOAA	81	5.41	6.74	86	5.40	6.36	p=.413
IOAB	72	2.12	3.21	72	2.52	4.58	p=.511
IOAC	81	3.44	4.79	88	3.59	4.15	p=.799
IOAD	73	0.82	2.33	77	0.78	2.14	p=.647
A-D Combined	307	3.03	4.95	323	3.16	4.89	p=.740
IOAE	50	3.38	4.18	47	3.42	5.01	p=.677
IOAF	182	0.85	2.13	183	0.75	1.91	p=.386
IOAG	986	6.44	7.63	994	7.19	8.08	p<.001
IOAH	713	2.67	4.59	709	2.79	4.64	p=.310
G-H Combined	1699	4.85	6.79	1703	5.36	7.19	p<.001

A statistically significant decrease in the mean hypoglycemia rate during therapy with lispro when compared to therapy with Humulin R was observed in study IOAG. In the studies involving patients with type II diabetes, the rate of hypoglycemia was consistently less than in the studies of patients with type I diabetes.

3. *Hemoglobin A_1c (%)*

The following table gives the summary and analysis of hemoglobin A_1c (%) at endpoint for each of the eight studies as well as combined studies.

TABLE: Hemoglobin A_1c (%) at Endpoint by Study

Protocol	LISPRO			Humulin R			Treatment Comparison
	n	Mean	SD	n	Mean	SD	
IOAA	81	8.14	1.30	84	8.38	1.37	p=.031
IOAB	72	8.00	1.21	72	8.20	1.64	p=.690
IOAC	80	8.08	1.43	88	8.22	1.44	p=.251
IOAD	71	8.38	1.52	77	8.50	1.73	p=.525
A-D Combined	304	8.15	1.37	321	8.32	1.54	p=.134
IOAE	50	7.77	2.24	46	7.84	2.35	p=.958
IOAF	179	8.32	1.57	182	8.08	1.54	p=.063
IOAG	984	8.24	1.49	991	8.17	1.46	p=.089
IOAH	710	8.18	1.30	705	8.18	1.38	p=.924
G-H Combined	1694	8.22	1.42	1696	8.18	1.43	p=.149

There is a tendency for the hemoglobin A_1c to be lower in the lispro group than in the Humulin R group in the one-year studies of patients previously treated with insulin. This contrasts to studies IOAG and IOAH where the therapy period was only 3 months which may be insufficient to see changes in hemoglobin A_1c, or in the new patient studies (IOAE and IOAF) in which the disease state was changing during the time of the study.

4. Total Daily Insulin Dose (Rapid-Acting and Basal)

The following tables give the summary and analysis at endpoint for total daily rapid-acting insulin dose and basal insulin dose at endpoint for each of the eight studies as well as combined studies: IOAA through IOAD, and IOAG through IOAH.

TABLE: Total Daily Rapid-Acting Insulin Dose (Units/Kg) at Endpoint

Protocol	LISPRO			Humulin R			Treatment Comparison
	n	Mean	SD	n	Mean	SD	
IOAA	81	0.29	0.14	86	0.32	0.13	p=.304
IOAB	72	0.36	0.27	72	0.40	0.21	p=.188
IOAC	80	0.29	0.12	88	0.30	0.12	p=.323
IOAD	73	0.34	0.24	77	0.34	0.25	p=.654
A-D Combined	306	0.32	0.20	323	0.34	0.19	p=.211
IOAE	50	0.19	0.15	46	0.20	0.17	p=.480
IOAF	175	0.25	0.18	179	0.25	0.13	p=.997
IOAG	985	0.36	0.18	993	0.36	0.17	p=.907
IOAH	713	0.34	0.22	709	0.34	0.21	p=.784
G-H Combined	1698	0.35	0.19	1702	0.35	0.19	p=.713

TABLE: Total Daily Basal Insulin Dose (Units/Kg) at Endpoint

Protocol	LISPRO			Humulin R			Treatment Comparison
	n	Mean	SD	n	Mean	SD	
IOAA	81	0.44	0.16	86	0.39	0.18	p=.065
IOAB	72	0.34	0.21	72	0.33	0.17	p=.839
IOAC	80	0.37	0.15	88	0.38	0.20	p=.940
IOAD	73	0.36	0.19	77	0.39	0.23	p=.397
A-D Combined	306	0.38	0.18	323	0.37	0.20	p=.677
IOAE	50	0.31	0.23	46	0.34	0.25	p=.400
IOAF	175	0.31	0.20	180	0.29	0.18	p=.606
IOAG	985	0.35	0.18	993	0.33	0.18	p<.001
IOAH	713	0.36	0.23	708	0.36	0.23	p=.002
G-H Combined	1698	0.36	0.20	1701	0.34	0.20	p<.001

The sponsor stated that in most of the multicenter, multinational clinical studies, the total daily rapid-acting insulin dose and the total daily basal insulin dose were similar during therapy with both lispro and Humulin R; however, a statistically significant, although not clinically meaningful, difference in the total daily basal insulin dose was observed for studies IOAG and IOAH, $p \leq .002$.

Sponsor's Conclusions

The sponsor stated that in patients previously receiving insulin therapy, therapy with lispro significantly reduced postprandial glucose excursion, and overall glycemic control was improved compared to regular insulin. The sponsor further stated that in patients new to insulin therapy, postprandial glucose excursion with lispro was less than with regular insulin therapy. However, this improvement was not statistically significant. While improvements in hemoglobin A_1c were seen in some studies, consistent differences in hemoglobin A_1c with patients receiving lispro versus regular insulin were not observed.

In summary, the sponsor concluded that, the time activity profile of lispro more closely approximated the physiologic release of insulin in response to a meal; as a result, lispro produced better postprandial and better or equivalent overall glucose control with equivalent dosages to regular insulin, with no increased (or less) risk of hypoglycemia.

III. STATISTICAL REVIEWER'S EVALUATION

This reviewer's evaluation of the eight studies is contained in this section. Patient disposition for efficacy evaluation is in the following tables. The first table gives the number of patients at each visit for the studies: IOAA, IOAB, IOAC, IOAD, IOAE and IOAF. The second table gives the number of patients at each visit for the crossover studies: IOAG and IOAH.

TABLE : Number of Patients at Each Visit for Studies IOAA, IOAB, IOAC, IOAD, IOAE and IOAF.

Protocol	Treatment	VISIT								
		V1	V2	V3	V4	V5	V6	V7	V8	V9
IOAA	*Lispro*	81	81	81	81	80	80	79	78	75
	Humulin-R	86	86	86	86	84	83	82	81	80
IOAB	*Lispro*	72	72	72	72	71	71	71	71	71
	Humulin-R	73	73	72	72	72	72	72	72	71
IOAC	*Lispro*	81	81	81	80	80	79	79	77	76
	Humulin-R	88	88	88	88	88	88	86	85	84
IOAD	*Lispro*	73	73	73	72	72	72	71	70	69
	Humulin-R	77	77	77	77	77	76	75	73	72
IOAE	*Lispro*	50	50	50	50	49	48	46	46	45
	Humulin-R	48	47	45	45	45	45	45	44	43
IOAF	*Lispro*	186	182	174	172	171	171	167	163	157
	Humulin-R	189	183	179	176	176	175	175	170	164

TABLE : Number of Patients at Each Visit for Studies IOAG and IOAH.

Protocol	Sequence	Baseline		Period 1						Period 2					
		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
IOAG	*Hum-R/Lispro*	500	500	499	499	497	496	492	485	482	482	481	481	477	474
	Lispro/Hum-R	508	508	504	502	501	501	498	496	495	495	494	492	490	487
IOAH	*Hum-R/Lispro*	368	368	368	367	365	365	365	363	360	360	359	359	357	355
	Lispro/Hum-R	354	354	353	352	350	350	347	346	341	341	341	341	340	339

Clearly, the percentage of dropouts for both the drugs is under 8% for IOAA, under 3% for IOAB, under 7% for IOAC, under 7% for IOAD, under 11% for IOAE, and under 16% for IOAF. For crossover studies, it is under 6% for IOAG and under 5% for IOAH for both the sequences.

We present the efficacy results in the same sequential order as that of the sponsor, i.e., we follow the same order for the efficacy variables as that of the sponsor. We have

also included the results for fasting blood glucose and 2-hour postprandial glucose. The 95% confidence intervals for the difference of the means for the actual measurements as well as for the change from baseline for several efficacy variables are included in appendices. There may be a small disparity between the p-values and the corresponding confidence intervals because the p-values were based on an analysis with treatment, investigator and the interaction in the model whereas the confidence intervals are based on the unadjusted actual treatment means. The CIs are presented to guide the clinicians regarding the clinical significance of any results favoring the control.

1. 2-Hour Postprandial Blood Glucose Excursion

The following table gives the summary statistics and 95% confidence intervals for the difference of means of 2-hour blood glucose excursion at endpoint for each of the eight studies as well as combined studies: IOAA through IOAD, and IOAG through IOAH.

TABLE: 2-Hour Blood Glucose Excursion (mmol/L) at Endpoint by Study

	LISPRO			Humulin R			95% CI for the
Protocol	n	Mean	SD	n	Mean	SD	Difference* in Means
IOAA	81	0.07	4.87	85	2.92	4.28	(1.50, 4.20)
IOAB	72	1.04	3.66	72	2.49	3.94	(0.24, 2.66)
IOAC	80	1.99	5.08	88	2.75	4.64	(-0.68, 2.20)
IOAD	71	1.74	3.76	77	2.84	3.25	(0.04, 2.16)
A-D Combined	304	1.19	4.47	322	2.76	4.07	(0.90, 2.24)
IOAE	50	1.31	4.29	45	2.78	4.37	(-0.18, 3.12)
IOAF	175	2.38	3.64	179	2.83	2.94	(-0.21, 1.11)
IOAG	979	-0.51	4.88	987	1.52	5.05	(1.69, 2.37)
IOAH	709	1.40	3.67	703	2.97	3.73	(1.28, 1.86)
G-H Combined	1688	0.29	4.51	1690	2.12	4.60	(1.59, 2.07)

*Difference in Means=Humulin R Mean - Lispro Mean.

The 2-hour postprandial glucose excursion mean was consistently lower during therapy with lispro than Humulin R in each of the eight clinical studies. In five of these studies (namely, IOAA, IOAB, IOAD, IOAG and IOAH), lispro appears to be statistically superior to Humulin R whereas in the remaining studies, lispro appears to be statistically similar to Humulin R. The plots for 95% confidence intervals are included in Appendix I for studies IOAA, IOAB, IOAC, IOAD, IOAA thru IOAD combined, IOAE, IOAF, IOAG, IOAH and IOAG thru IOAH combined.

2. Hypoglycemic Rate per 30 Days

The following table gives the summary and analysis of hypoglycemic rate per 30 days at endpoint for each of the eight studies as well as combined studies: IOAA through IOAD, and IOAG through IOAH.

TABLE: Hypoglycemia Rate per 30 Days at Endpoint by Study

Protocol	LISPRO			Humulin R			95% CI for the Difference* in Means
	n	Mean	SD	n	Mean	SD	
IOAA	81	5.41	6.74	86	5.40	6.36	(-1.67, 1.65)
IOAB	72	2.12	3.21	72	2.52	4.58	(-0.75, 1.55)
IOAC	81	3.44	4.79	88	3.59	4.15	(-0.95, 1.25)
IOAD	73	0.82	2.33	77	0.78	2.14	(-0.74, 0.66)
A-D Combined	307	3.03	4.95	323	3.16	4.89	(-0.60, 0.86)
IOAE	50	3.38	4.18	47	3.42	5.01	(-1.67, 1.75)
IOAF	182	0.85	2.13	183	0.75	1.91	(-0.47, 0.27)
IOAG	986	6.44	7.63	994	7.19	8.08	(0.39, 1.11)
IOAH	713	2.67	4.59	709	2.79	4.64	(-0.14, 0.38)
G-H Combined	1699	4.85	6.79	1703	5.36	7.19	(0.27, 0.75)

*Difference in Means=Humulin R Mean - Lispro Mean.

In the studies enrolling patients with Type II diabetes (IOAB, IOAD, IOAF, and IOAH), the hypoglycemia rate was less than the studies enrolling patients with Type I diabetes (IOAA, IOAC, IOAE, and IOAG). In only one study (namely, IOAG), lispro is statistically superior to Humulin R whereas in the remaining seven studies, lispro appears to be statistically similar to Humulin R.

3. Hemoglobin A_1c (%)

The following table gives the summary and analysis of hemoglobin A_1c (%) at endpoint for each of the eight studies as well as combined studies.

TABLE: Hemoglobin A_1c (%) at Endpoint by Study

Protocol	LISPRO			Humulin R			95% CI for the Difference* in Means
	n	Mean	SD	n	Mean	SD	
IOAA	81	8.14	1.30	84	8.38	1.37	(-0.12, 0.60)
IOAB	72	8.00	1.21	72	8.20	1.64	(-0.24, 0.64)
IOAC	80	8.08	1.43	88	8.22	1.44	(-0.28, 0.56)
IOAD	71	8.38	1.52	77	8.50	1.73	(-0.40, 0.64)
A-D Combined	304	8.15	1.37	321	8.32	1.54	(-0.06, 0.40)
IOAE	50	7.77	2.24	46	7.84	2.35	(-0.83, 0.97)
IOAF	179	8.32	1.57	182	8.08	1.54	(-0.55, 0.07)
IOAG	984	8.24	1.49	991	8.17	1.46	(-0.13, -0.01)
IOAH	710	8.18	1.30	705	8.18	1.38	(-0.06, 0.06)
G-H Combined	1694	8.22	1.42	1696	8.18	1.43	(-0.08, 0.00)

*Difference in Means=Humulin R Mean - Lispro Mean.

In one study (namely, IOAG), lispro appears to be statistically inferior to Humulin R whereas in the remaining seven studies, lispro appears to be statistically similar to Humulin R. The plots for 95% confidence intervals are included in Appendix II for

studies IOAA, IOAB, IOAC, IOAD, IOAA thru IOAD combined, IOAE, IOAF, IOAG, IOAH and IOAG thru IOAH combined. Note that, there is a disparity between the p-value and the confidence interval for the study IOAA because the p-value was based on the analysis with treatment, investigator and the interaction in the model whereas the confidence interval is based on the unadjusted actual treatment means. The p-value should be used to judge statistical significance while the CIs are presented to assist in a determination of clinical significance.

4. Total Daily Insulin Dose (Rapid-Acting and Basal)

The following tables give the summary for total daily rapid-acting insulin dose and basal insulin dose at endpoint for eight studies as well as combined studies.

TABLE: Total Daily Rapid-Acting Insulin Dose (Units/Kg) at Endpoint

	LISPRO			Humulin R			95% CI for the
Protocol	n	Mean	SD	n	Mean	SD	Difference* in Means
IOAA	81	0.293	0.14	86	0.321	0.13	(-0.009, 0.065)
IOAB	72	0.355	0.27	72	0.400	0.21	(-0.034, 0.124)
IOAC	80	0.287	0.12	88	0.295	0.12	(-0.026, 0.042)
IOAD	73	0.345	0.24	77	0.341	0.25	(-0.069, 0.061)
A-D Combined	306	0.318	0.20	323	0.336	0.19	(-0.012, 0.048)
IOAE	50	0.194	0.15	46	0.200	0.17	(-0.063, 0.075)
IOAF	175	0.254	0.18	179	0.251	0.13	(-0.034, 0.028)
IOAG	985	0.363	0.18	993	0.361	0.17	(-0.008, 0.004)
IOAH	713	0.338	0.22	709	0.337	0.21	(-0.007, 0.005)
G-H Combined	1698	0.353	0.19	1702	0.351	0.19	(-0.006, 0.002)

*Difference in Means=Humulin R Mean - Lispro Mean.

TABLE: Total Daily Basal Insulin Dose (Units/Kg) at Endpoint

	LISPRO			Humulin R			95% CI for the
Protocol	n	Mean	SD	n	Mean	SD	Difference* in Means
IOAA	81	0.438	0.16	86	0.392	0.18	(-0.092, 0.000)
IOAB	72	0.342	0.21	72	0.328	0.17	(-0.077, 0.049)
IOAC	80	0.367	0.15	88	0.376	0.20	(-0.040, 0.058)
IOAD	73	0.364	0.19	77	0.391	0.23	(-0.034, 0.088)
A-D Combined	306	0.379	0.18	323	0.373	0.20	(-0.036, 0.024)
IOAE	50	0.313	0.23	46	0.345	0.25	(-0.049, 0.113)
IOAF	175	0.310	0.20	180	0.292	0.18	(-0.054, 0.018)
IOAG	985	0.351	0.18	993	0.331	0.18	(-0.024, -0.016)
IOAH	713	0.365	0.23	708	0.358	0.23	(-0.011, -0.003)
G-H Combined	1698	0.360	0.20	1701	0.342	0.20	(-0.021, -0.015)

*Difference in Means=Humulin R Mean - Lispro Mean.

In six studies (namely, IOAA, IOAB, IOAC, IOAD, IOAE and IOAF), the total daily rapid-acting insulin dose and the total daily basal insulin dose were statistically similar during therapy with both lispro and Humulin R. However, a statistical dissimilarity was observed for studies IOAG and IOAH as 95% confidence intervals for the difference of means for total daily basal insulin dose contained all negative values.

5. Fasting Blood Glucose (mmol/L)

The following table gives the summary and analysis of fasting blood glucose (mmol/L) at endpoint for each of the eight studies as well as combined studies.

TABLE: Fasting Blood Glucose (mmol/L) at Endpoint

Protocol	LISPRO			Humulin R			Treatment Comparison
	n	Mean	SD	n	Mean	SD	
IOAA	81	11.17	4.91	86	10.73	5.08	p=.497
IOAB	72	10.37	4.16	72	10.11	3.66	p=.531
IOAC	80	11.06	4.99	88	9.90	4.32	p=.198
IOAD	73	10.55	3.79	77	10.29	3.71	p=.544
A-D Combined	306	10.81	4.51	323	10.26	4.26	p=.128
IOAE	50	9.99	4.39	46	9.51	4.32	p=.481
IOAF	175	10.00	3.44	180	10.00	3.13	p=.878
IOAG	985	11.64	5.09	993	11.34	4.96	p=.274
IOAH	713	10.67	3.77	708	10.17	3.67	p=.002
G-H Combined	1698	11.23	4.61	1701	10.85	4.50	p=.002

The fasting blood glucose was consistently higher during therapy with lispro than Humulin R in each of the eight clinical studies. In one study (namely, IOAH), lispro is statistically significantly inferior to Humulin R. The plots for 95% confidence intervals are included in Appendix III for studies IOAA, IOAB, IOAC, IOAD, IOAA thru IOAD combined, IOAE, IOAF, IOAG, IOAH and IOAG thru IOAH combined.

6. 2-Hour Postprandial Glucose (mmol/L)

The following table gives the summary and analysis of 2-hour postprandial glucose (mmol/L) at endpoint for each of the eight studies as well as combined studies.

The 2-hour postprandial glucose was consistently lower during therapy with lispro than Humulin R in seven of the eight clinical studies, whereas statistical significance was achieved in only four studies. Study IOAB achieved marginal significance. The plots for 95% confidence intervals are included in Appendix IV for studies IOAA, IOAB, IOAC, IOAD, IOAA thru IOAD combined, IOAE, IOAF, IOAG, IOAH and IOAG thru IOAH combined.

TABLE: 2-Hour Postprandial Glucose (mmol/L) at Endpoint

Protocol	LISPRO			Humulin R			Treatment Comparison
	n	Mean	SD	n	Mean	SD	
IOAA	81	11.32	5.20	86	13.29	5.20	p=.048
IOAB	72	11.41	4.38	72	12.69	4.82	p=.096
IOAC	80	13.06	5.83	88	12.76	5.03	p=.740
IOAD	73	12.32	4.30	77	13.19	4.24	p=.290
A-D Combined	306	12.03	5.03	323	12.99	4.84	p=.016
IOAE	50	11.44	6.07	46	12.39	6.43	p=.679
IOAF	175	12.31	4.60	180	12.95	4.22	p=.300
IOAG	985	11.16	5.30	993	12.87	5.77	p<.001
IOAH	713	12.08	4.62	708	13.14	4.48	p<.001
G-H Combined	1698	11.55	5.05	1701	12.98	5.27	p<.001

IV. SPONSOR'S RESPONSE TO FDA REQUESTED ANALYSES

On January 31, 1996, medical officer (Robert Misbin, MD) and statisticians (Dan Marticello and Baldeo Taneja, Ph.D.) at FDA requested the sponsor to provide the following three analyses for the study IOAG:

1. Analysis of the hypoglycemia rate per 30 days as presented in Table 6.4 on page 97 (of a draft briefing document for the advisory committee, dated January 26, 1996) using only hypoglycemic episodes with a blood glucose value of ≤ 2 mmol/L or if the patient reported that they were not able to self treat this hypoglycemic episode.

2. Give the statistical details on the statement of an inverse relationship mentioned in the last paragraph on page 98 and redo this analysis using the new definition of hypoglycemia.

3. Compare hypoglycemia rate (new definition) to HbA_1c using a scatter plot without the grouping or quartiles and to fit regression lines for each treatment and compare the regression lines between the treatments.

Sponsor's Response

1. The following table presents a summary of results of the analysis for hypoglycemic rate per 30 days using the new definition of hypoglycemia.

TABLE: Rate of Hypoglycemia per 30 Days Using the New Definition of Hypoglycemia at Endpoint

Protocol	LISPRO			Humulin R			Treatment
	n	Mean	SD	n	Mean	SD	Comparison
IOAG (Original)	986	6.44	7.63	994	7.19	8.08	p<.001
IOAG (New)	985	0.37	1.12	994	0.42	1.26	p=.368

When using a nonparametric analysis, the treatment comparison p-value is 0.096. The nonparametric analyses may be preferred over the parametric analyses due to the large number of hypoglycemia rate with zero values due to the new definition.

When we compare the results for hypoglycemia rates per 30 days for the original and the new definitions of hypoglycemia, we find that the decrease in the mean hypoglycemia rate during therapy with lispro is not statistically significant any more with the new definition.

2. The following table presents a summary of results of the analysis for hypoglycemia versus metabolic control using the new definition of hypoglycemia.

TABLE: Percent of Patients at Endpoint with a Hypoglycemia Rate per 30 Days > 2 by Level of Hemoglobin A_1c for Study IOAG

Study/Hypo Definition	HbA1c Quartiles	Lispro (%)	Humulin R (%)	Treatment Comparison
IOAG Original Definition	Q1 (≤ 7.2)	69.9	75.6	p=0.878
	Q2 (7.2 thru 8.3)	72.9	67.5	
	Q3 (8.3 thru 9.5)	61.5	67.8	
	Q4 (> 9.5)	46.8	49.7	
	Linear Trend p-value	p<0.001	p<0.001	
IOAG New Definition	Q1 (≤ 7.2)	12.5	14.1	p=0.846
	Q2 (7.2 thru 8.3)	5.3	5.9	
	Q3 (8.3 thru 9.5)	4.6	4.9	
	Q4 (> 9.5)	2.5	3.4	
	Linear Trend p-value	p=0.002	p=0.001	

The frequency and percent of patients with hypoglycemic rate per 30 days > 2 for each of the quartiles of HbA_1c was greatly reduced with the new definition of hypoglycemia but the relationship was similar to that observed in the analysis using the original definition of hypoglycemia.

3. Figures 1, 2 and 3 present the scatter plots of hypoglycemia rate per 30 days using the new definition versus hemoglobin A_1c for each period and for both periods

combined. Even though the slopes within each treatment group are small, as well as very small R^2, the slopes were statistically significantly different from zero in all cases ($p<0.05$). A (marginally) statistically significant difference between the treatments for these slopes was observed during period 1 ($p=0.088$) and a statistically significant difference between the treatments for these slopes was observed during period 2 ($p=0.045$). However, no difference between the treatments was observed for the composite analysis combining both periods ($p=0.959$). Patients receiving Humulin R first and Lispro second had a larger negative slope than did patients that received Lispro first and Humulin R second.

V. STATISTICAL REVIEWER'S CONCLUSION THAT MAY BE CONVEYED TO THE SPONSOR

If one uses HbA_1c as the primary efficacy variable, then lispro appears to be statistically **inferior** to Humulin R in one study (namely, IOAG), whereas in the remaining seven studies, lispro appears to be statistically similar to Humulin R. Thus, on the basis of hemoglobin A_1c, lispro appears to be **inferior or similar** to Humulin R. But, if one uses the 2-hour postprandial glucose excursion as the primary efficacy variable, it was consistently lower during therapy with lispro in each of the eight clinical studies and it achieved statistical significance ($p<0.05$) in five of these studies. Thus, on the basis of 2-hour postprandial glucose excursion, lispro appears to be **superior or similar** to Humulin R. Clinical input is needed to judge the relative importance of these two endpoints.

In the studies enrolling patients with Type II diabetes (IOAB, IOAD, IOAF, and IOAH), the hypoglycemia rate (original definition) was less than the studies enrolling patients with Type I diabetes (IOAA, IOAC, IOAE, and IOAG). With the original definition of hypoglycemia, in only one study (namely, IOAG), lispro appeared to be statistically superior to Humulin R whereas in the remaining seven studies, lispro appeared to be statistically similar to Humulin R. For the study IOAG, when we compare the results for hypoglycemia rates per 30 days for the original and the new definitions of hypoglycemia, we find that the decrease in the mean hypoglycemia rate during therapy with lispro is not statistically significantly different than that with Humulin R with the new definition.

For study IOAG, the frequency and percent of patients with hypoglycemic rate per 30 days > 2 for each of the quartiles of HbA_1c was greatly reduced with the new definition of hypoglycemia but the relationship was similar to that observed in the analysis using the original definition of hypoglycemia.

BK Taneja

Baldeo K. Taneja, Ph.D.
Mathematical Statistician (Biomed)

Concur: Mr. Marticello

Dr. Nevius 3-12-96

cc:
Archival NDA 20-563
HFD-510
HFD-510/Mr. Short
HFD-510/Dr. Sobel/Dr. Fleming/Dr. Koller/Dr. Misbin
HFD-715/Division File/Dr. Nevius/Mr. Marticello/Dr. Taneja
[redacted]
HFD-344/Dr. Lisook

This review contains 15 pages of text, 40 pages of Appendices and 3 figures.

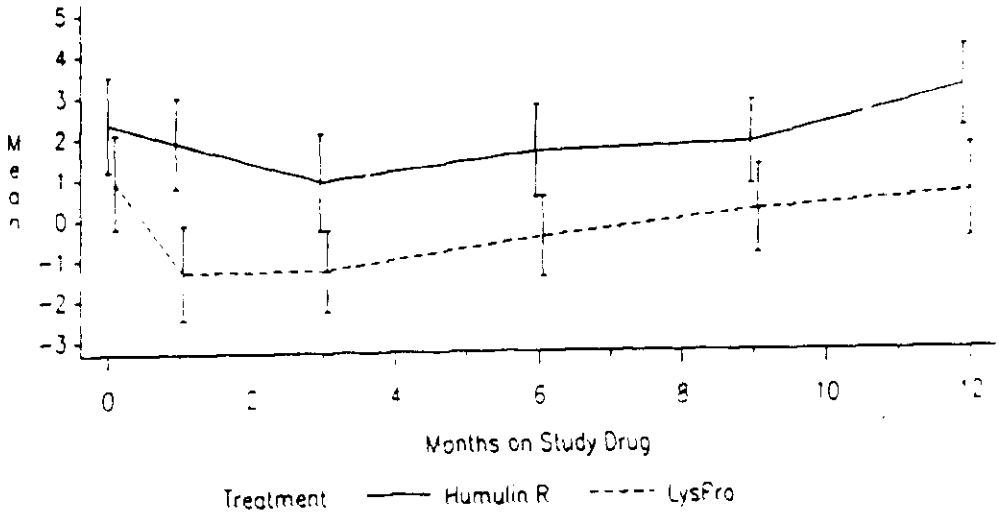
BKT/02-14-96/03-11-96/Humalog Review

APPENDIX I

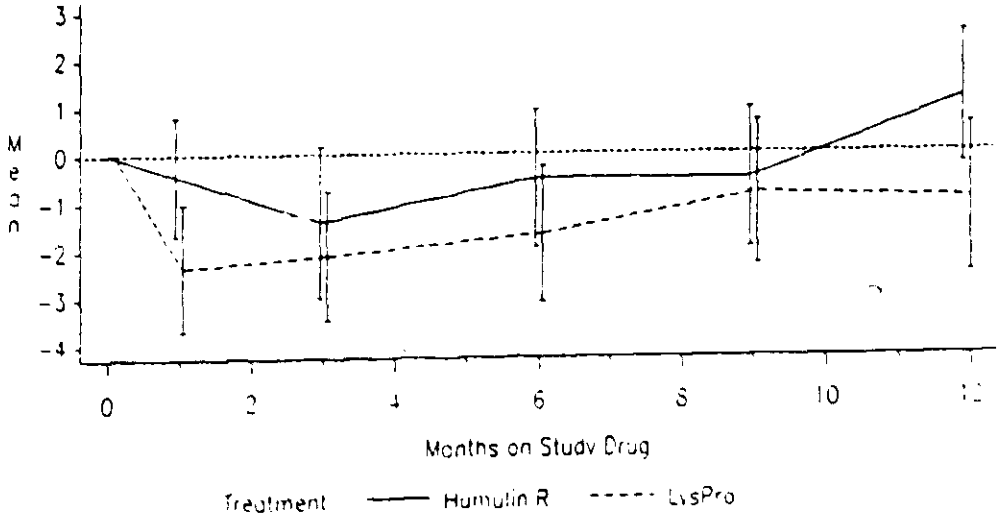
Study IOAA
2-Hour Glucose Excursion

Means of Efficacy Measurements by Visit
All Randomized Patients
Premeal Therapy in Type I Diabetes also using Humulin U

2 hr Glucose Excursion (mmol/L)
Actual Measurements (Mean and 95% Confidence Interval)



2 hr Glucose Excursion (mmol/L)
Change from Baseline (Mean and 95% Confidence Interval)

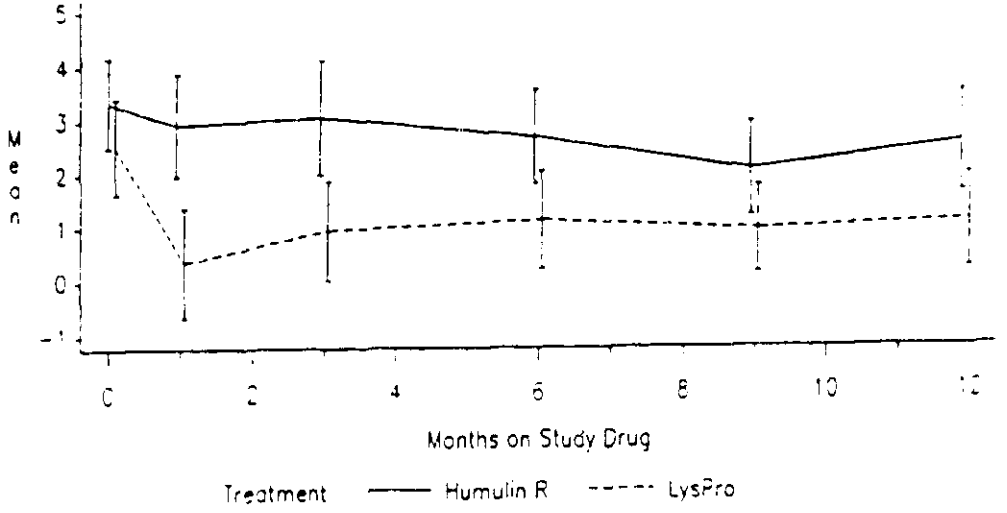


APPENDIX I (Continued)

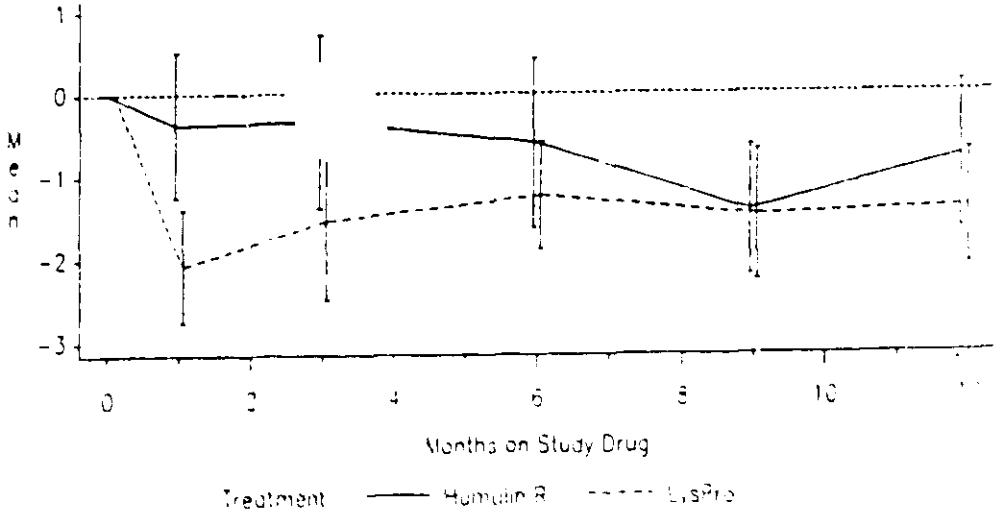
Study IOAB
2-Hour Glucose Excursion

Means of Efficacy Measurements by Visit
All Randomized Patients
Premeal Therapy in Type II Diabetes also using Humulin U

2 hr Glucose Excursion (mmol/L)
Actual Measurements (Mean and 95% Confidence Interval)



2 hr Glucose Excursion (mmol/L)
Change from Baseline (Mean and 95% Confidence Interval)

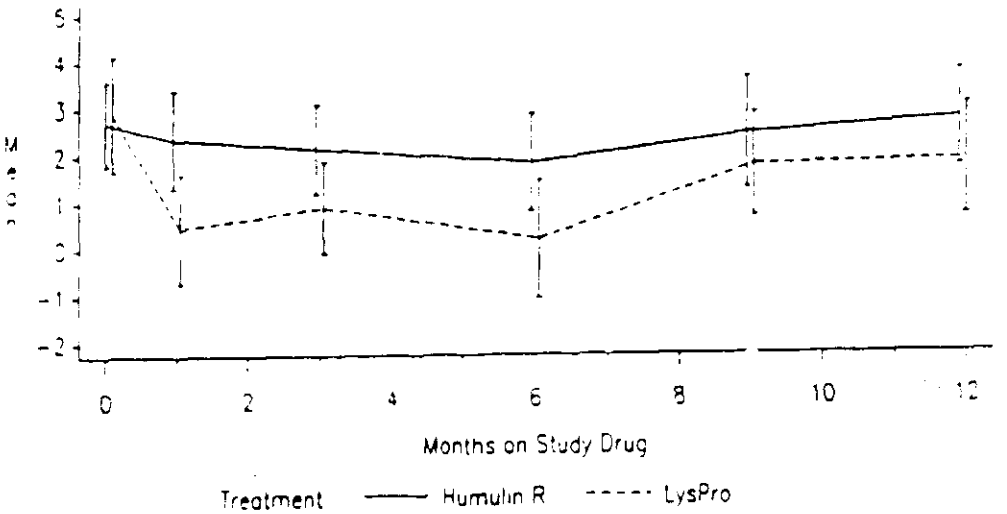


APPENDIX I (Continued)

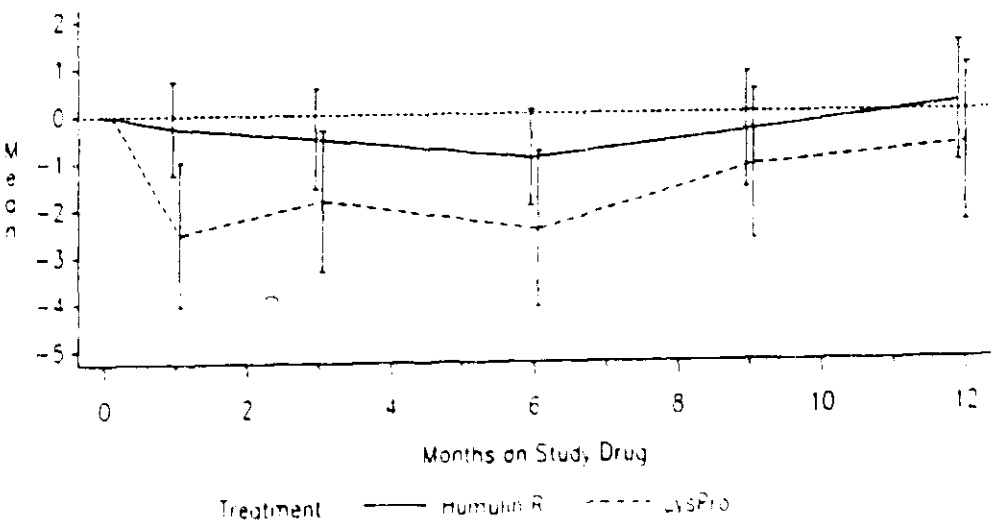
Study IOAC
2-Hour Glucose Excursion

Means of Efficacy Measurements by Visit
All Randomized Patients
Premeal Therapy in Type I Diabetes also using Humulin N

2 hr Glucose Excursion (mmol/L)
Actual Measurements (Mean and 95% Confidence Interval)



2 hr Glucose Excursion (mmol/L)
Change from Baseline (Mean and 95% Confidence Interval)

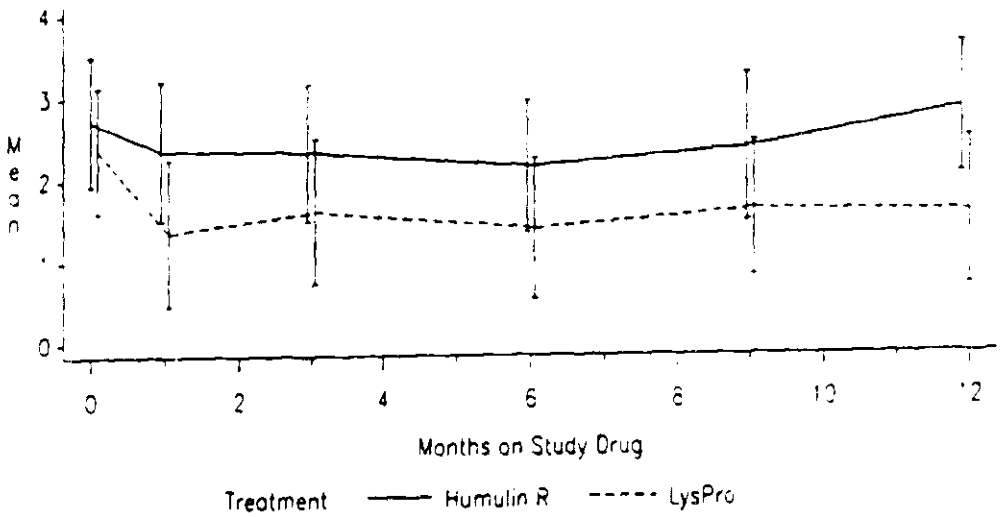


APPENDIX I (Continued)

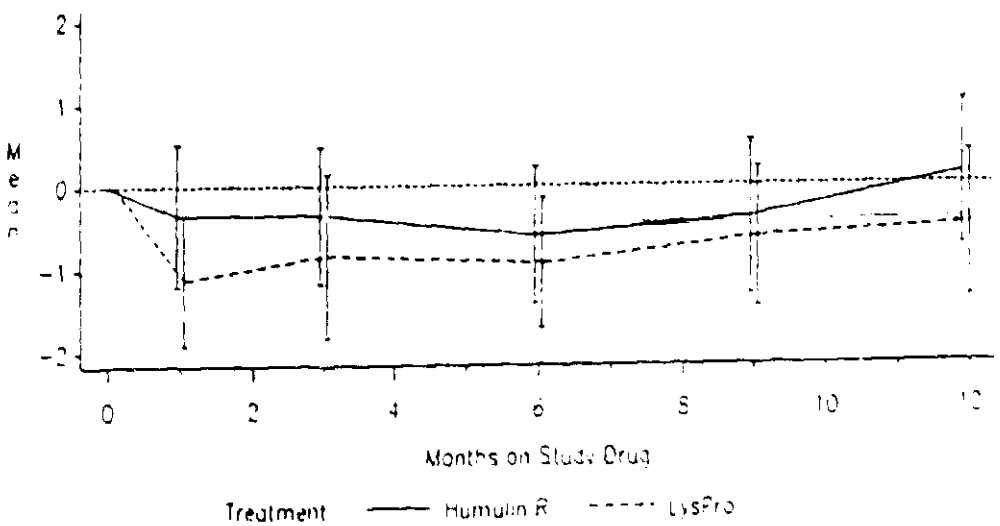
Study IOAD
2-Hour Glucose Excursion

Means of Efficacy Measurements by Visit
All Randomized Patients
Premeal Therapy in Type II Diabetes also using Humulin N

2 hr Glucose Excursion (mmol/L)
Actual Measurements (Mean and 95% Confidence Interval)



2 hr Glucose Excursion (mmol/L)
Change from Baseline (Mean and 95% Confidence Interval)

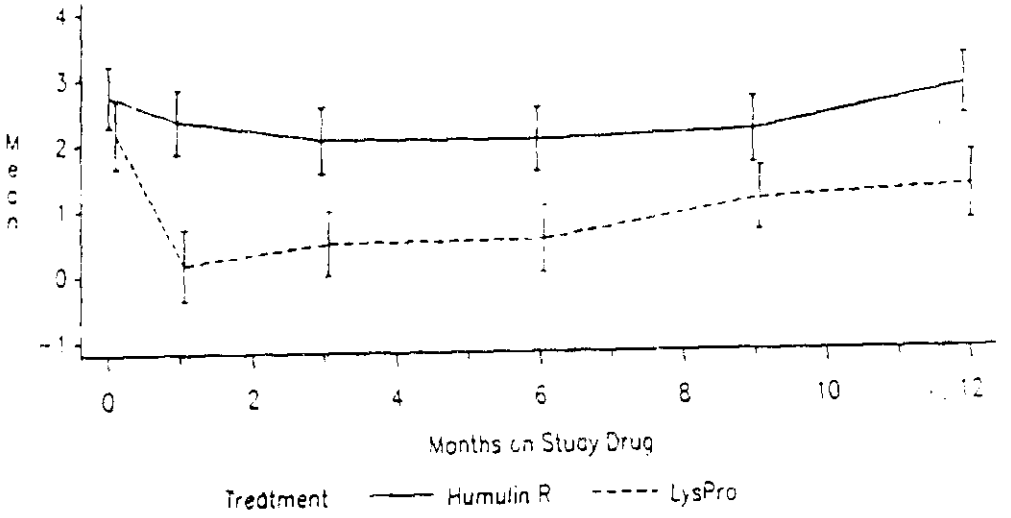


APPENDIX I (Continued)

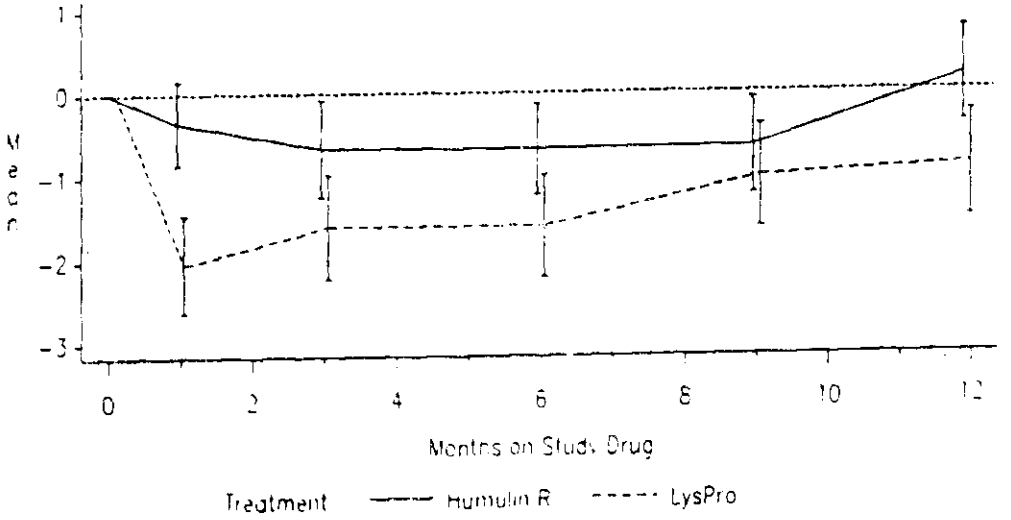
Studies IOAA thru IOAD Combined
2-Hour Glucose Excursion

Means of Efficacy Measurements by Visit
Randomized Patients
Premeal Therapy in Type I/II Diabetes also using Humulin U/N

2 hr Glucose Excursion (mmol/L)
Actual Measurements (Mean and 95% Confidence Interval)



2 hr Glucose Excursion (mmol/L)
Change from Baseline (Mean and 95% Confidence Interval)

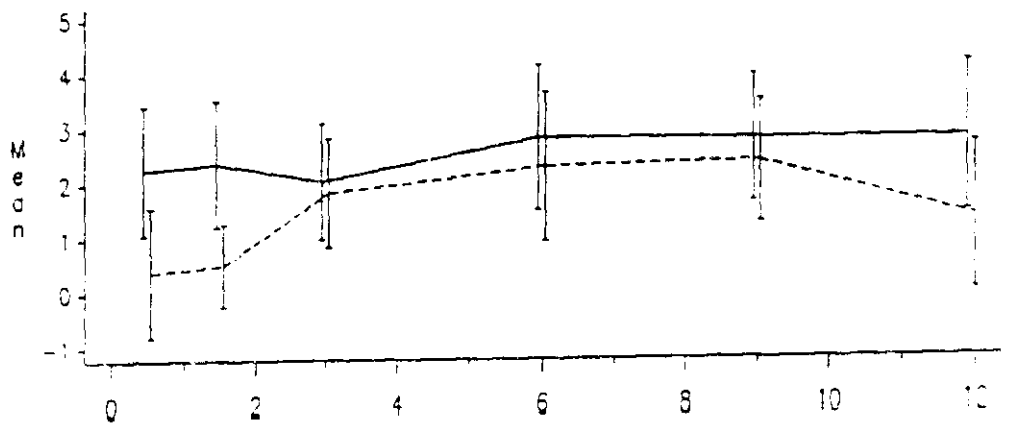


APPENDIX 1 (Continued)

Study IOAE
2-Hour Glucose Excursion

Means of Efficacy Measurements by Visit
All Randomized Patients
Premeal Therapy New Patients with Type I Diabetes

2 hr Glucose Excursion (mmol/L)
Actual Measurements (Mean and 95% Confidence Interval)



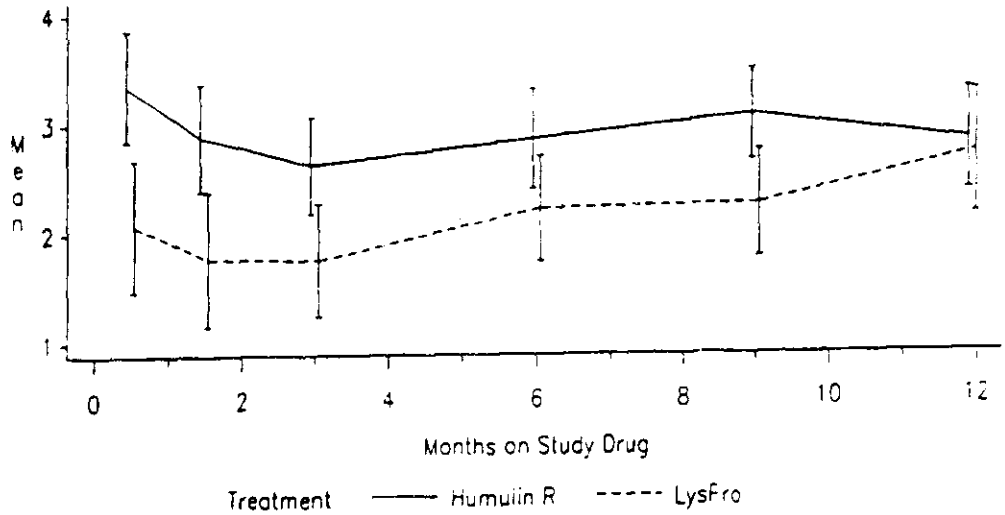
Treatment —— Humulin R ----- LysPro

APPENDIX I (Continued)

Study IOAF
2-Hour Glucose Excursion

Means of Efficacy Measurements by Visit
All Randomized Patients
Premeal Therapy New Patients with Type II Diabetes

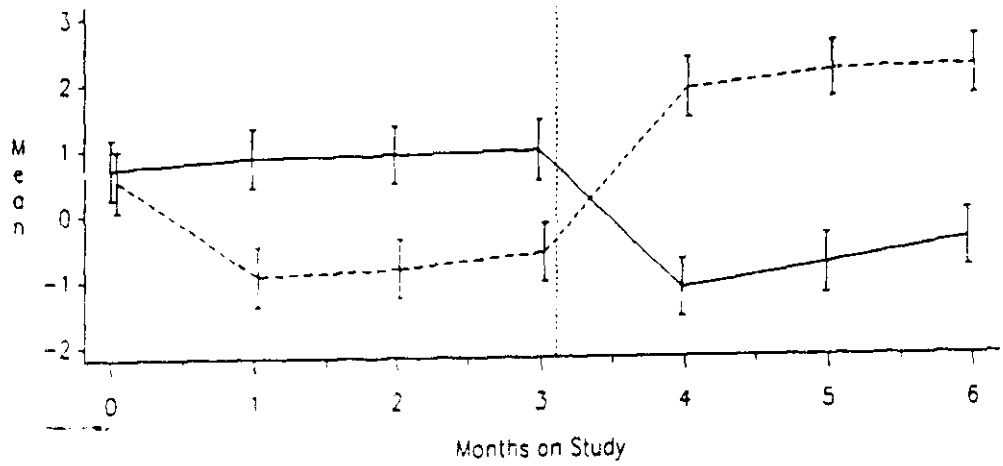
2 hr Glucose Excursion (mmol/L)
Actual Measurements (Mean and 95% Confidence Interval)



APPENDIX I (Continued)

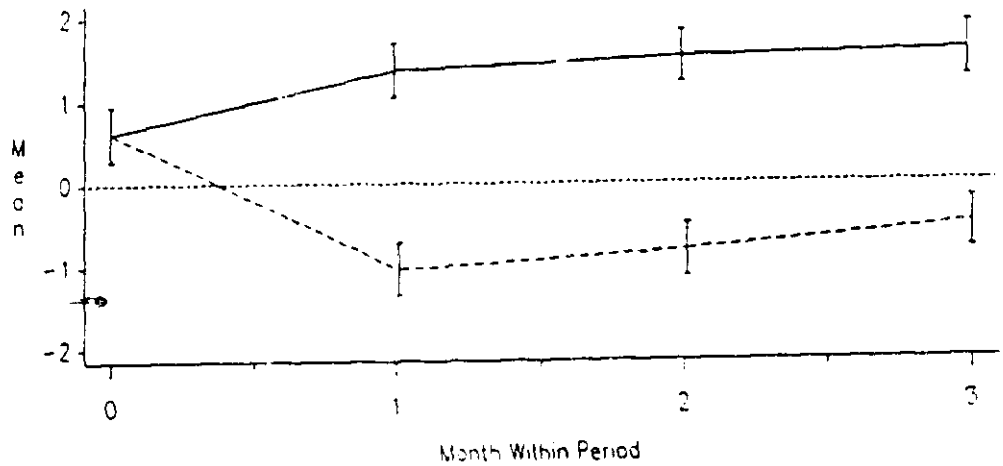
Study IOAG
2-Hour Glucose Excursion
Means of Efficacy Measurements by Visit
All Randomized Patients
Crossover Study of Premeal Therapy in Type I Diabetes

Glucose Excursion at 2 hr (mmol/L)
Sequence Groups (Mean and 95% Confidence Intervals)



Sequence Group —— Humulin R / LysP ----- LysPro / Humulin

Glucose Excursion at 2 hr (mmol/L)
Treatment (Mean and 95% Confidence Intervals)



Treatment —— Humulin R ----- LysPro

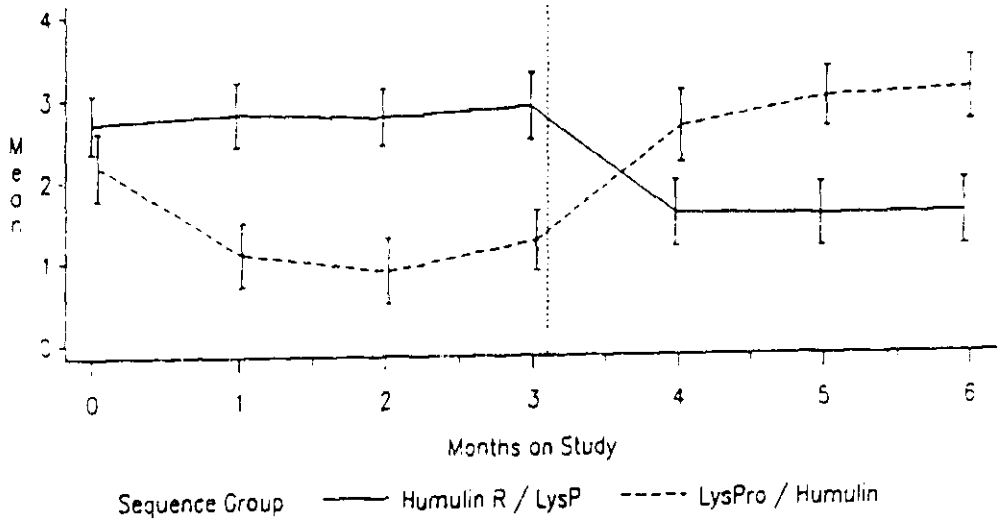
21 18 26 290C195 24128 - RMP F3ZSIOAG SASPGM(EFFPLOTG)

APPENDIX I (Continued)

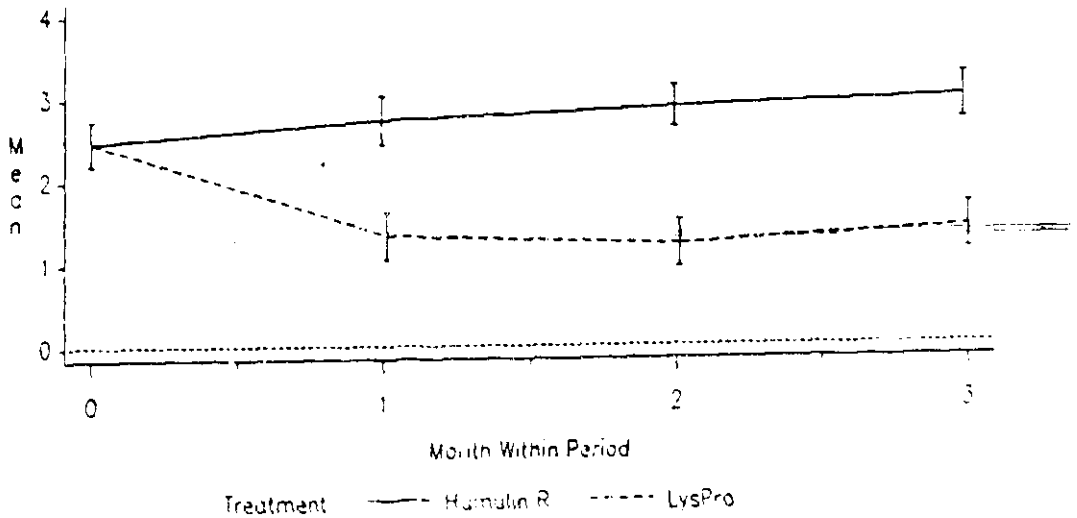
Study IOAH
2-Hour Glucose Excursion

Means of Efficacy Measurements by Visit
All Randomized Patients
Crossover Study of Premeal Therapy in Type II Diabetes

Glucose Excursion at 2 hr (mmol/L)
Sequence Groups (Mean and 95% Confidence Intervals)



Glucose Excursion at 2 hr (mmol/L)
Treatment (Mean and 95% Confidence Intervals)



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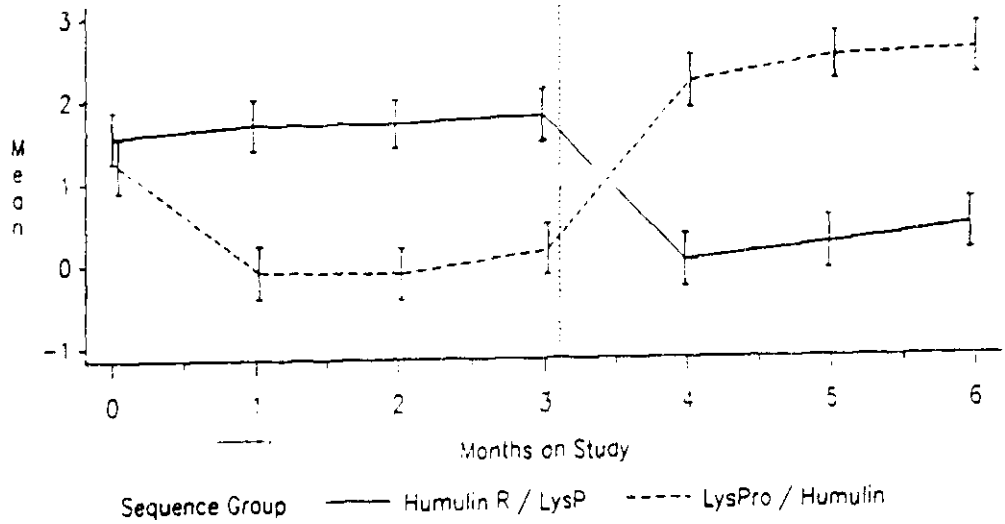
APPENDIX I (Continued)

Studies IOAG and IOAH Combined
2-Hour Glucose Excursion

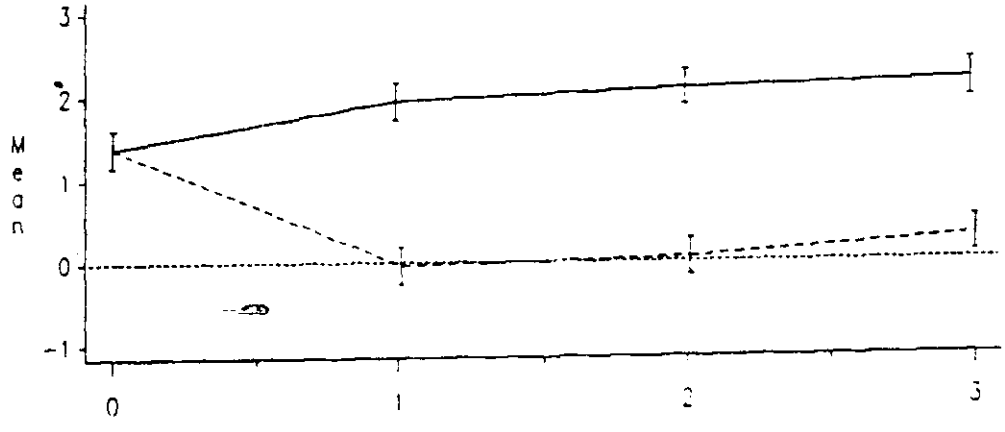
Means of Efficacy Measurements by Visit
All Randomized Patients
Crossover Study of Premeal Therapy in Type I/II Diabetes

Glucose Excursion at 2 hr (mmol/L)
Sequence Groups (Mean and 95% Confidence Intervals)



Sequence Group —— Humulin R / LysP ----- LysPro / Humulin

Glucose Excursion at 2 hr (mmol/L)
Treatment (Mean and 95% Confidence Intervals)



Treatment —— Humulin R ----- LysPro

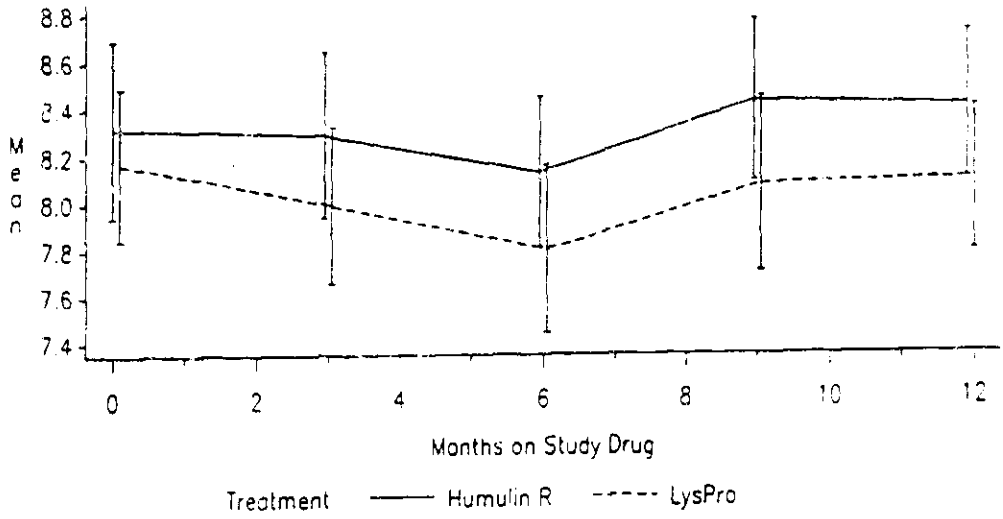
19 15 09 31OCT95 24128 - RMP F3ZSIOAC SASPGM EFFFLTGH

APPENDIX II

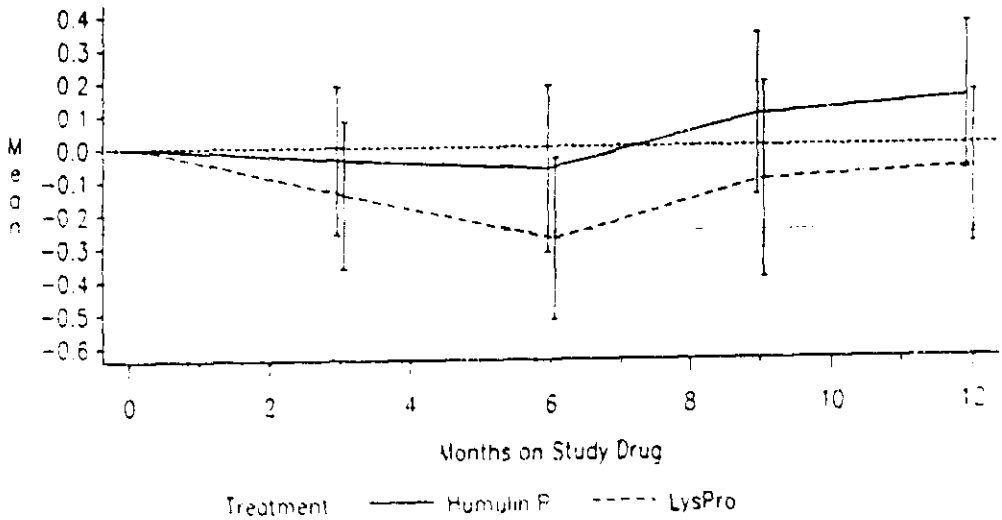
Study IOAA
Hemoglobin A_1c

Means of Efficacy Measurements by Visit
All Randomized Patients
Premeal Therapy in Type I Diabetes also using Humulin U

HbA1c (%)
Actual Measurements (Mean and 95% Confidence Interval)



HbA1c (%)
Change from Baseline (Mean and 95% Confidence Interval)



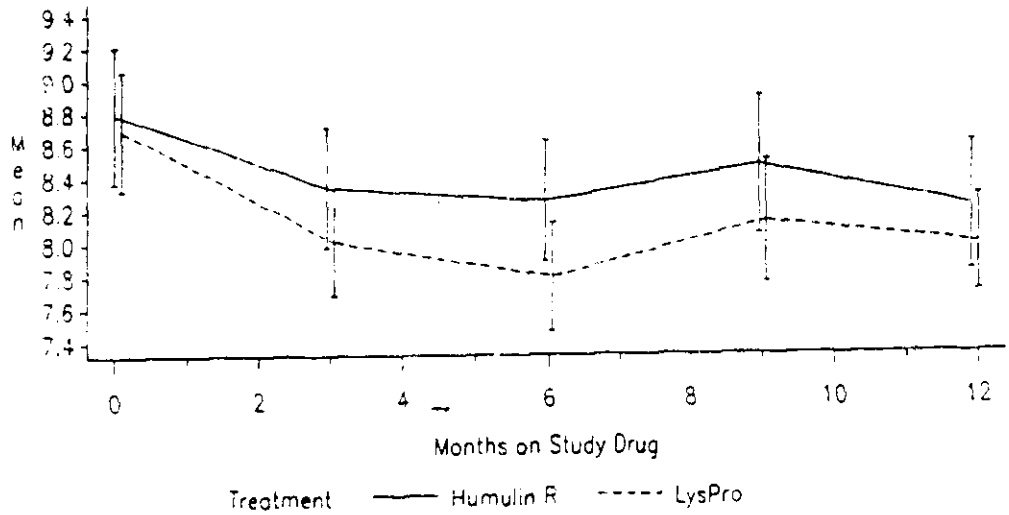
APPENDIX II (Continued)

Study 10AB

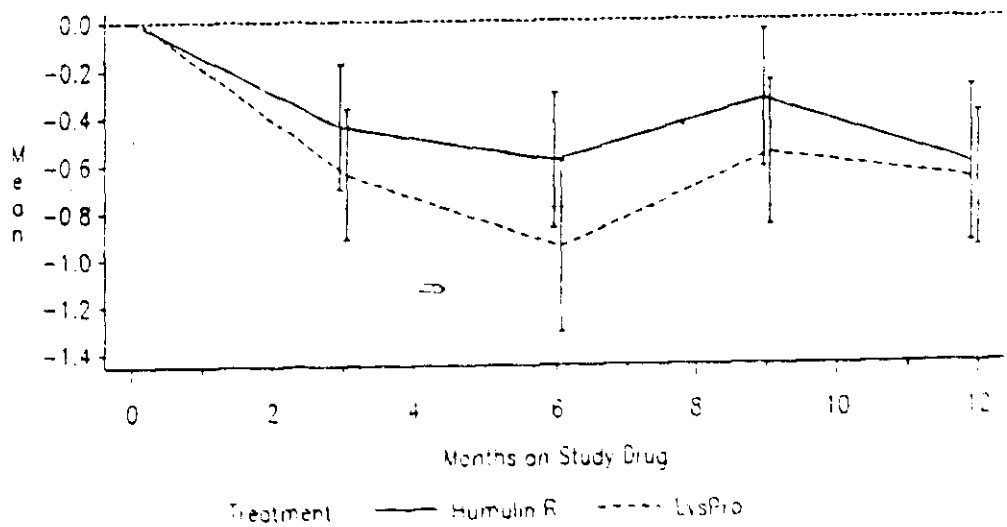
Hemoglobin A_{1c}

Means of Efficacy Measurements by Visit
All Randomized Patients
Premeal Therapy in Type II Diabetes also using Humulin U

HbA1c (%)
Actual Measurements (Mean and 95% Confidence Interval)



HbA1c (%)
Change from Baseline (Mean and 95% Confidence Interval)

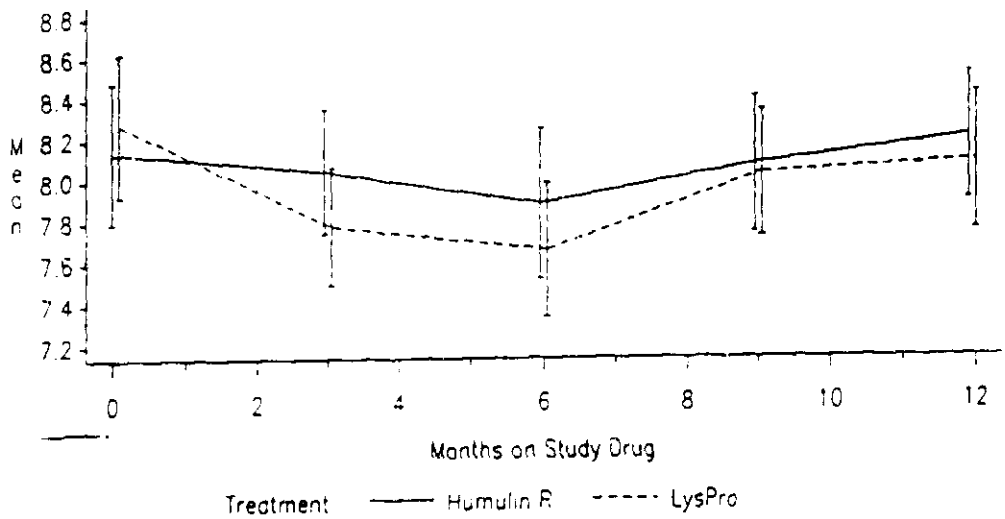


APPENDIX II (Continued)

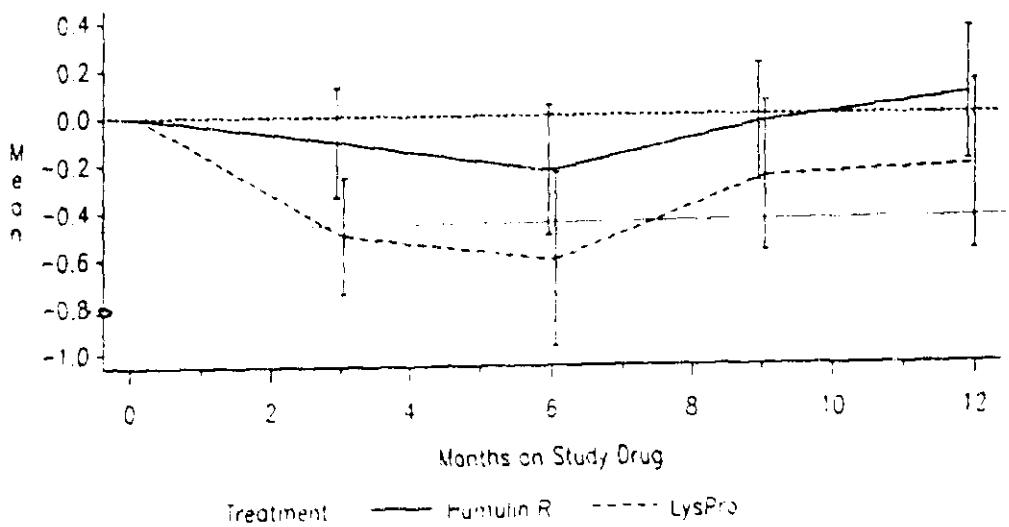
Study IOAC
Hemoglobin A_1c

Means of Efficacy Measurements by Visit
All Randomized Patients
Premeal Therapy in Type I Diabetes also using Humulin N

HbA1c (%)
Actual Measurements (Mean and 95% Confidence Interval)



HbA1c (%)
Change from Baseline (Mean and 95% Confidence Interval)

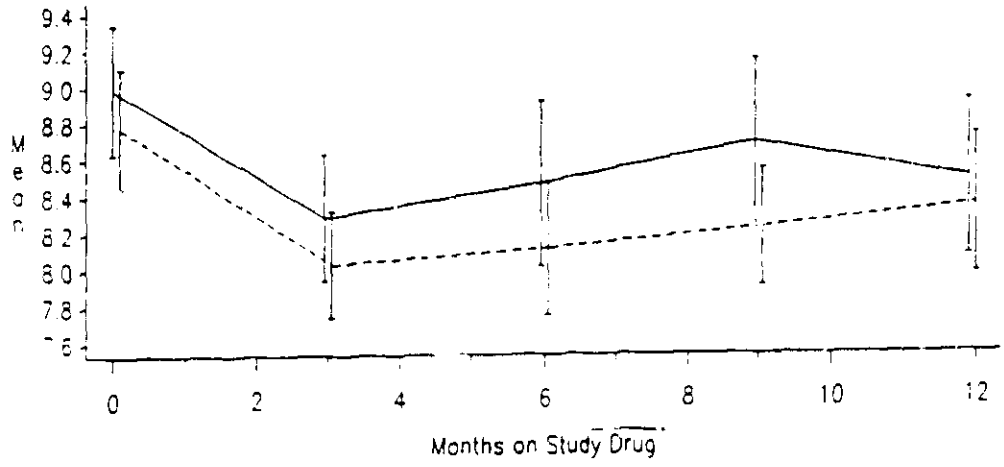


APPENDIX II (Continued)

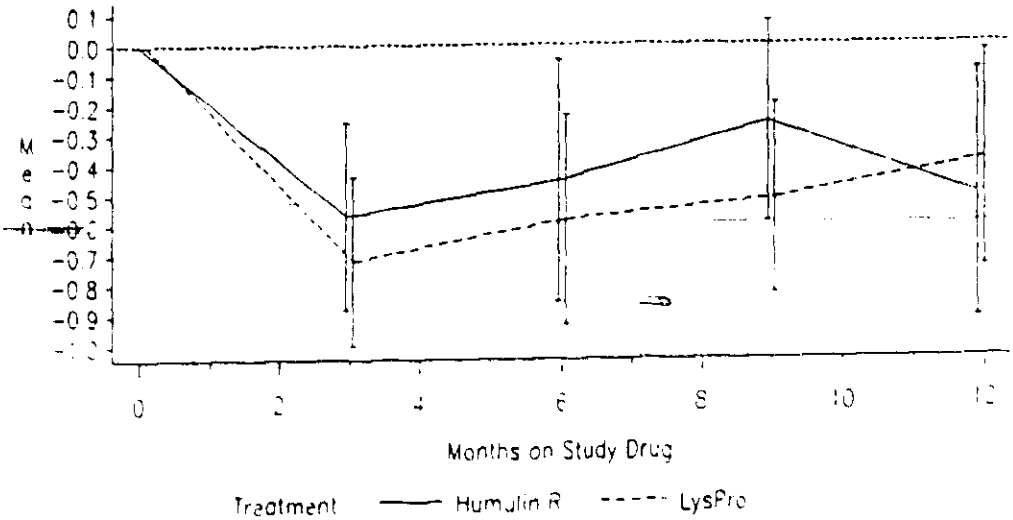
Study IOAD
Hemoglobin A_1c

Means of Efficacy Measurements by Visit
All Randomized Patients
Premeal Therapy in Type II Diabetes also using Humulin N

HbA1c (%)
Actual Measurements (Mean and 95% Confidence Interval)



HbA1c (%)
Change from Baseline (Mean and 95% Confidence Interval)

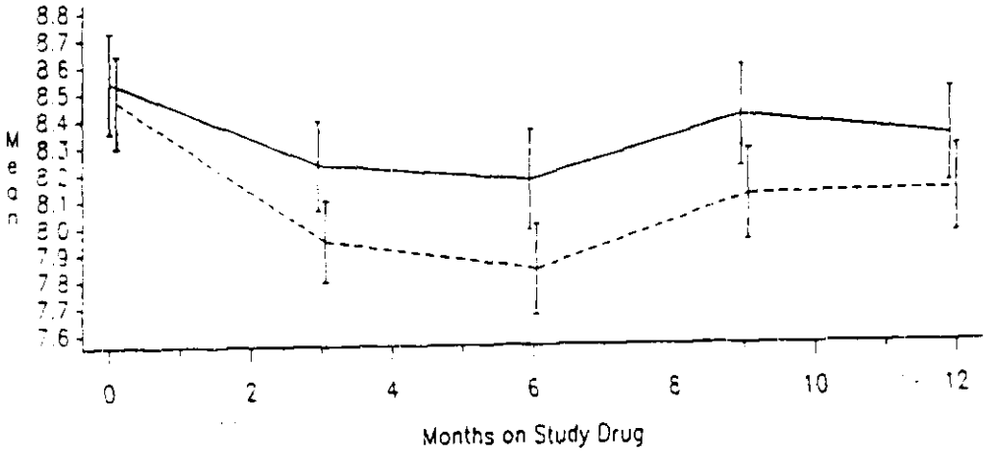


APPENDIX II (Continued)

Studies IOAA thru IOAD Combined
Hemoglobin A_1c

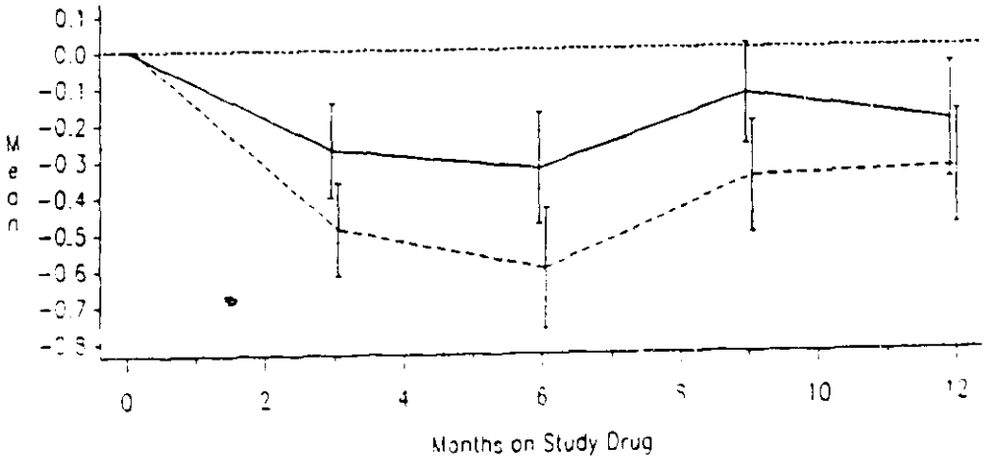
Means of Efficacy Measurements by Visit
All Randomized Patients
Premeal Therapy in Type I/II Diabetes also using Humulin U/N

HbA1c (%)
Actual Measurements (Mean and 95% Confidence Interval)



Treatment —— Humulin R ----- LysPro

HbA1c (%)
Change from Baseline (Mean and 95% Confidence Interval)



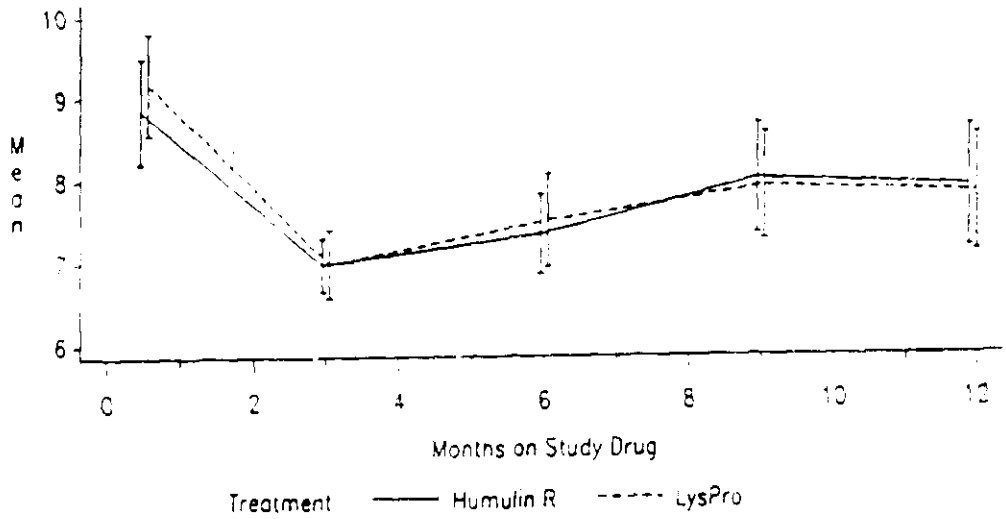
Treatment —— Humulin R ----- LysPro

APPENDIX II (Continued)

Study 10AE
Hemoglobin A_{1c}

Means of Efficacy Measurements by Visit
All Randomized Patients
Premeal Therapy New Patients with Type I Diabetes

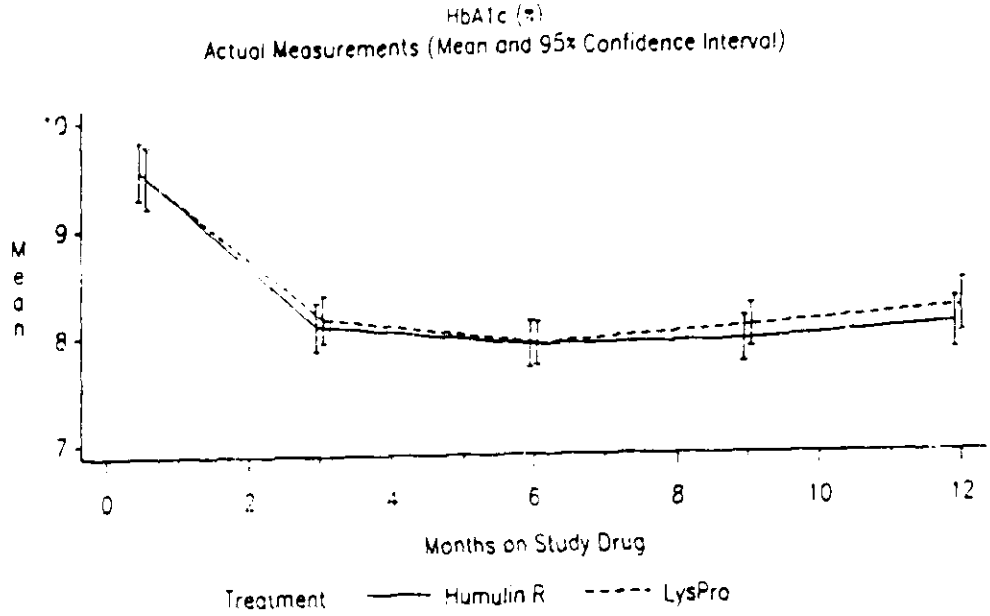
HbA1c (%)
Actual Measurements (Mean and 95% Confidence Interval)



APPENDIX II (Continued)

Study IOAF
Hemoglobin A_1c

Means of Efficacy Measurements by Visit
All Randomized Patients
Premeal Therapy New Patients with Type II Diabetes

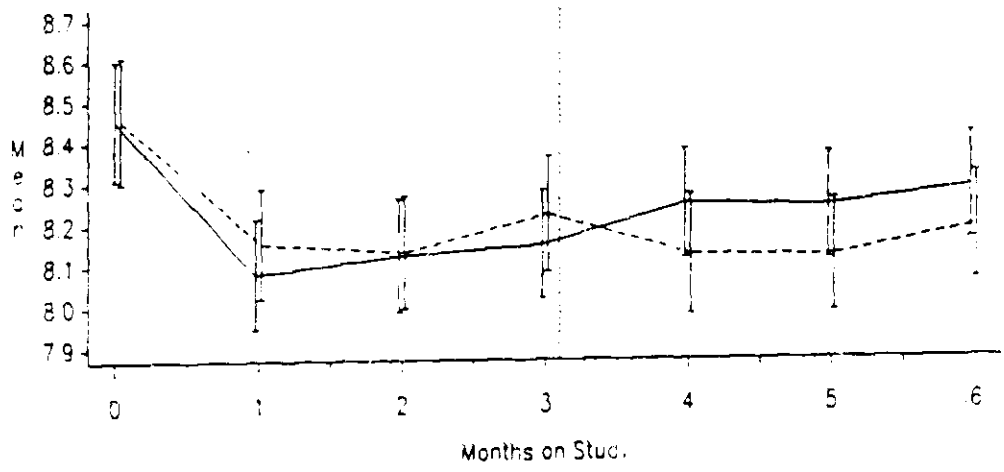


APPENDIX II (Continued)

Study IOAG
Hemoglobin A_1c

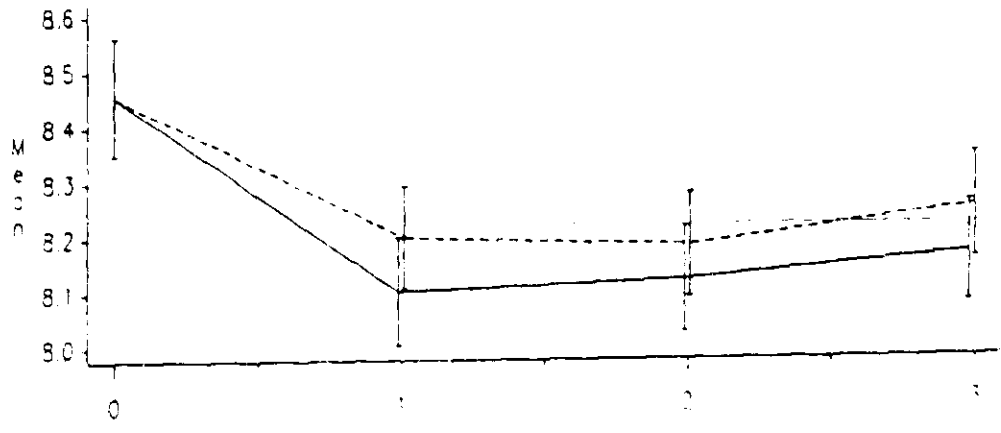
Means of Efficacy Measurements by Visit
All Randomized Patients
Crossover Study of Premeal Therapy in Type I Diabetes

HbA1c (%)
Sequence Groups (Mean and 95% Confidence Intervals)



Sequence Group —— Humulin R / LysP ----- LysPro / Humulin

HbA1c (%)
Treatment (Mean and 95% Confidence Intervals)



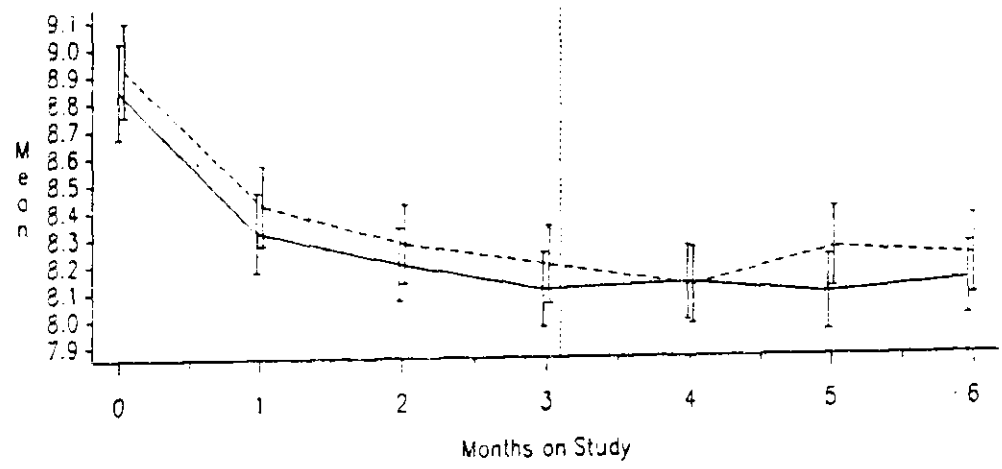
Treatment —— Humulin R ----- LysPro

APPENDIX II (Continued)

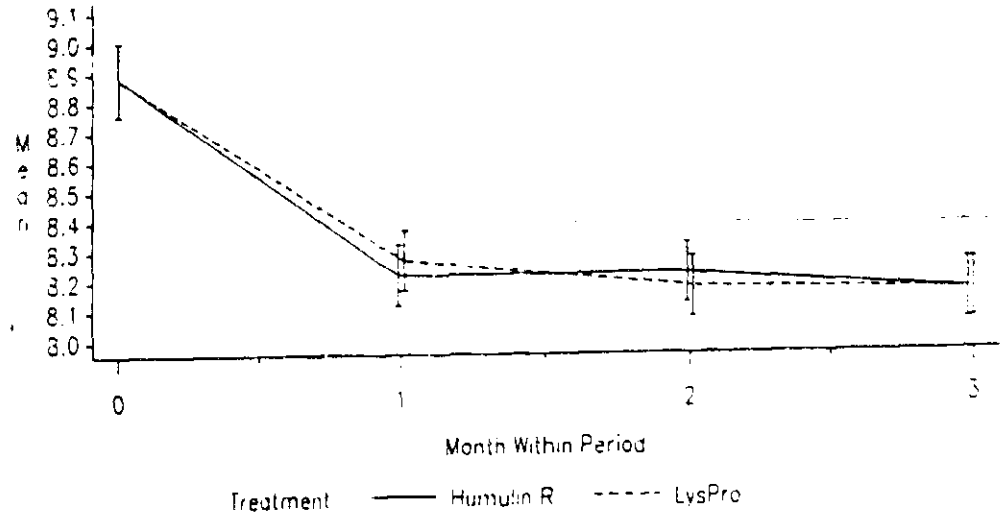
Study I0AH
Hemoglobin A_{1c}

Means of Efficacy Measurements by Visit
All Randomized Patients
Crossover Study of Premeal Therapy in Type II Diabetes

HbA1c (%)
Sequence Groups (Mean and 95% Confidence Intervals)



HbA1c (%)
Treatment (Mean and 95% Confidence Intervals)



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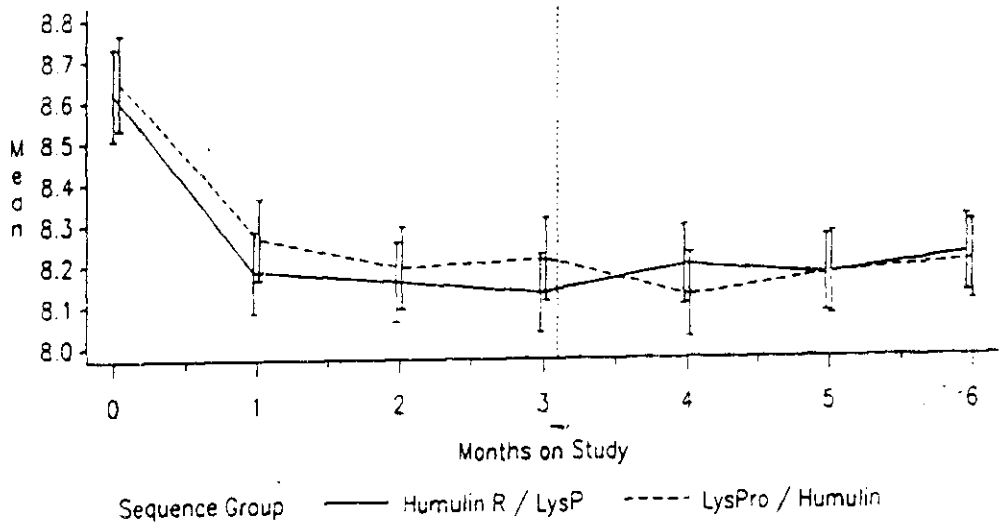
APPENDIX II (Continued)

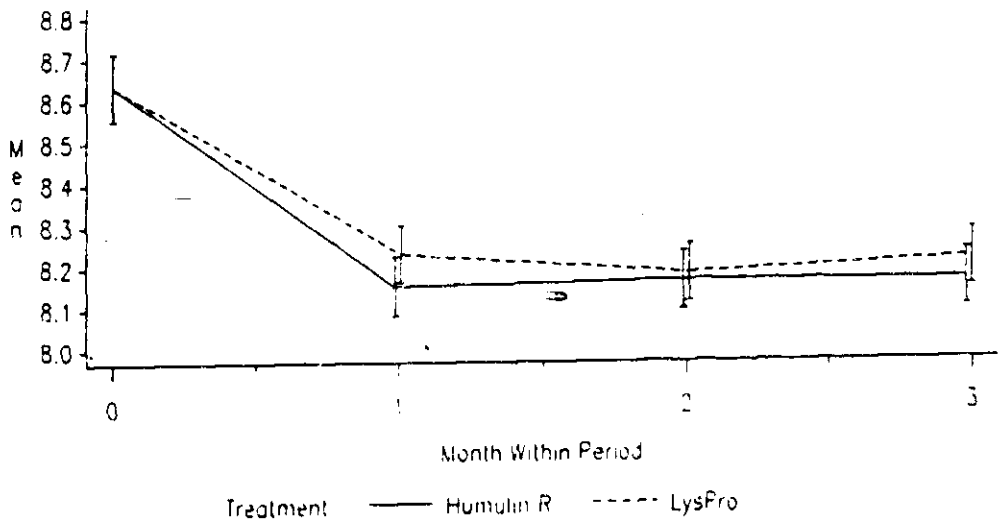
Studies IOAG and IOAH Combined
Hemoglobin A_1c

Means of Efficacy Measurements by Visit
All Randomized Patients
Crossover Study of Premeal Therapy in Type I/II Diabetes

HbA1c (%)
Sequence Groups (Mean and 95% Confidence Intervals)



HbA1c (%)
Treatment (Mean and 95% Confidence Intervals)



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APPENDIX III

Study IOAA
Fasting Blood Glucose (mmol/L)

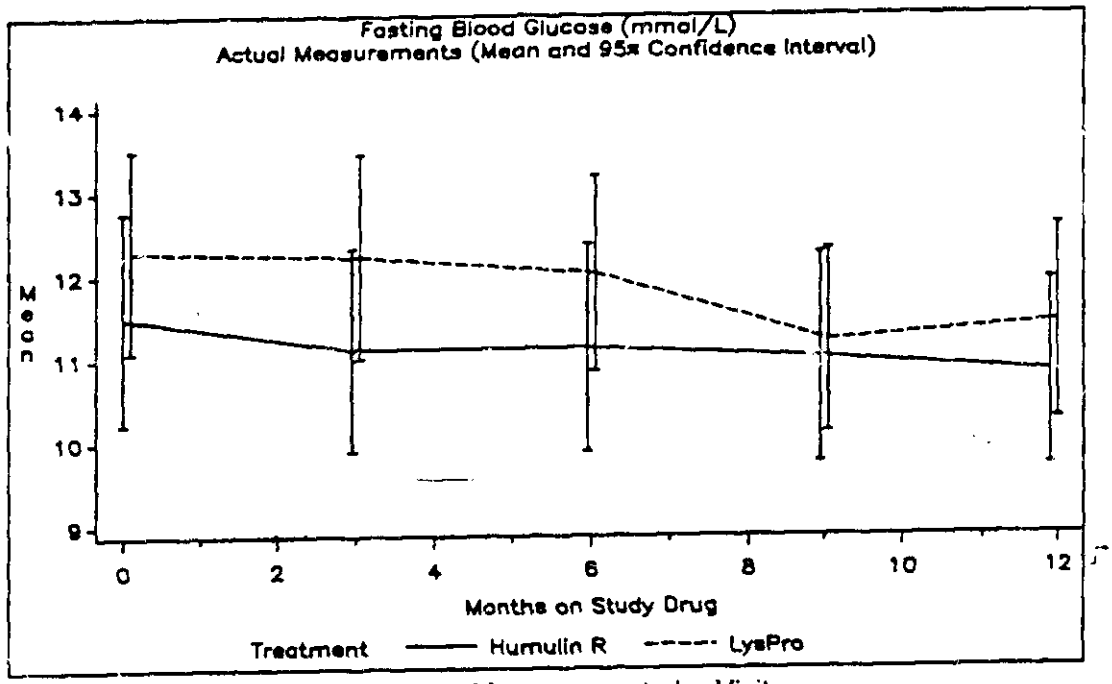

Figure IOAA.6.2. Means of Efficacy Measurements by Visit
Fasting Blood Glucose
All Randomized Patients

APPENDIX III (Continued)

Study IOAB
Fasting Blood Glucose (mmol/L)

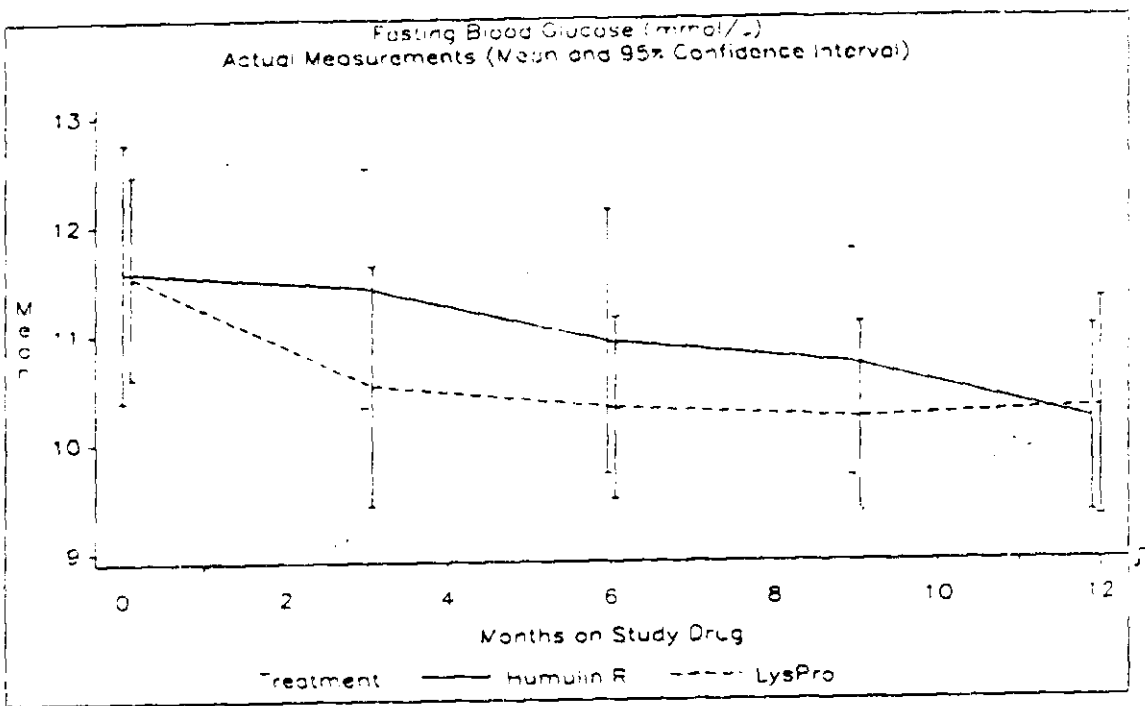

Figure IOAB.6.2. Measurements by Visit – Fasting Blood Glucose – All Randomized Patients

APPENDIX III (Continued)

Study IOAC
Fasting Blood Glucose (mmol/L)

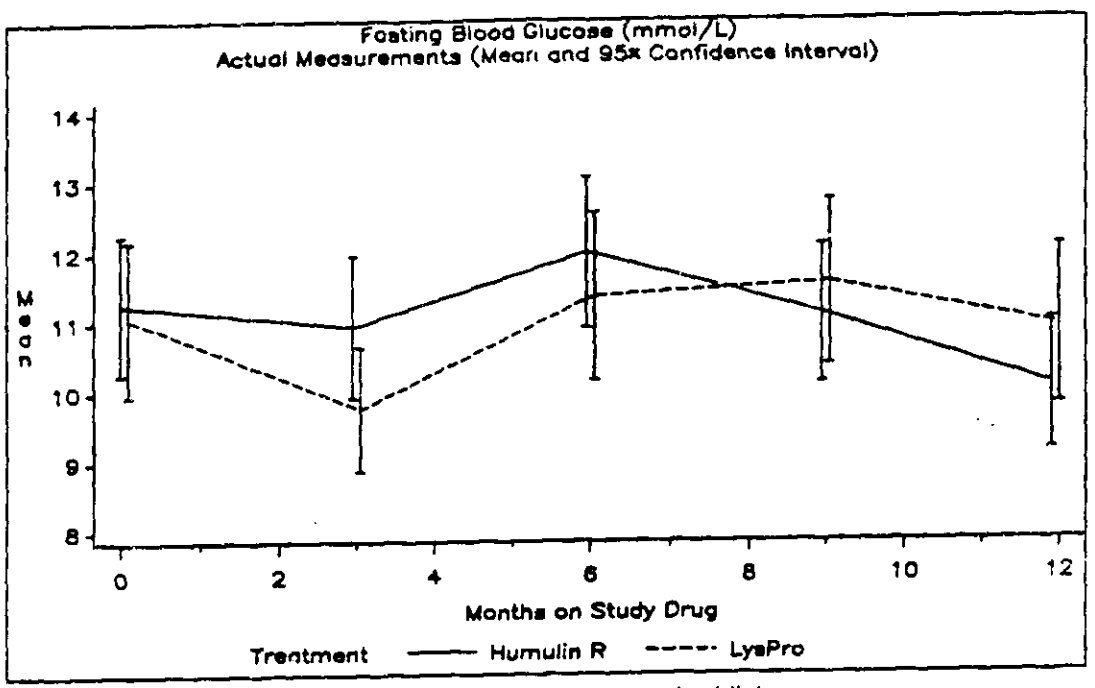

Figure IOAC.6.2. Means of Efficacy Measurements by Visit
Fasting Blood Glucose
All Randomized Patients

APPENDIX III (Continued)

Study IOAD
Fasting Blood Glucose (mmol/L)

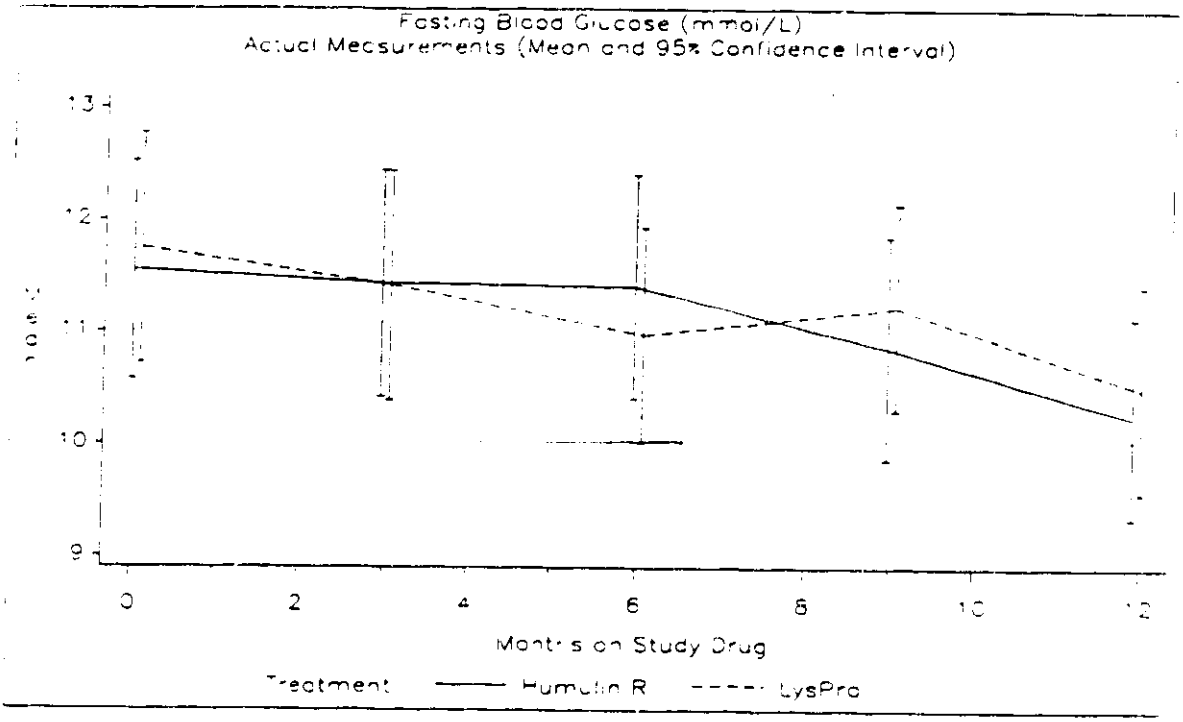

Figure IOAD.6.2. Means of Efficacy Measurements by Visit – Fasting Blood Glucose All Randomized Patients

APPENDIX III (Continued)

Studies IOAA thru IOAD Combined
Fasting Blood Glucose (mmol/L)

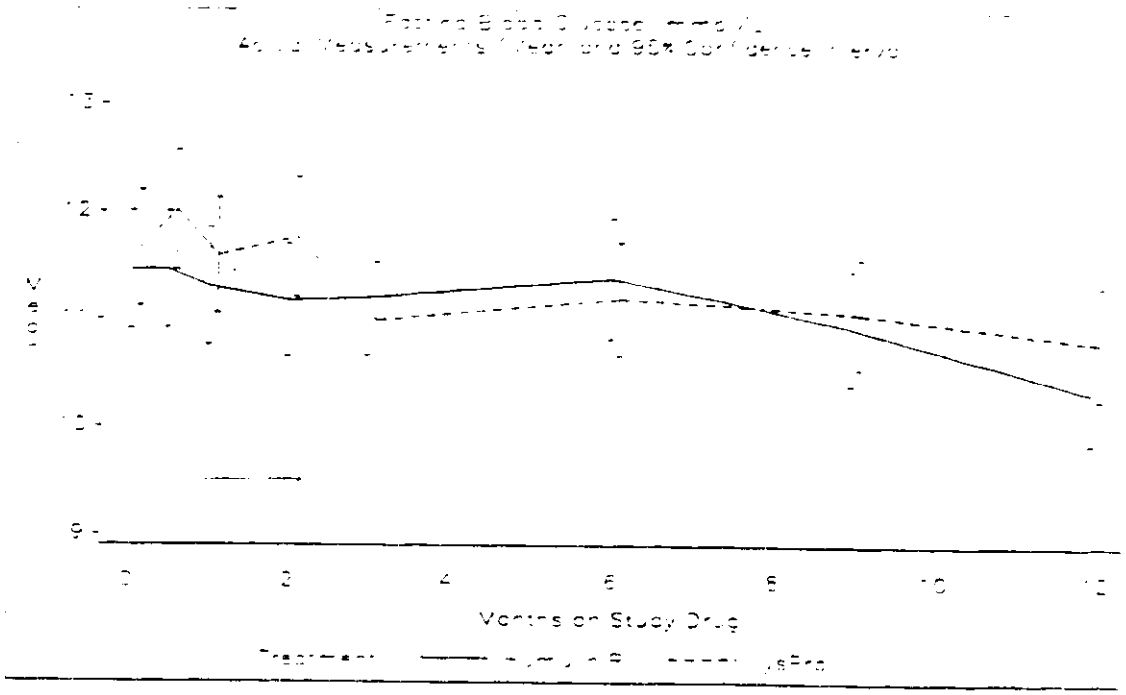

Figure IOAAD.6.2. Means of Efficacy Measurements by Visit – Fasting Blood Glucose – All Randomized Patients

APPENDIX III (Continued)

Study IOAE
Fasting Blood Glucose (mmol/L)

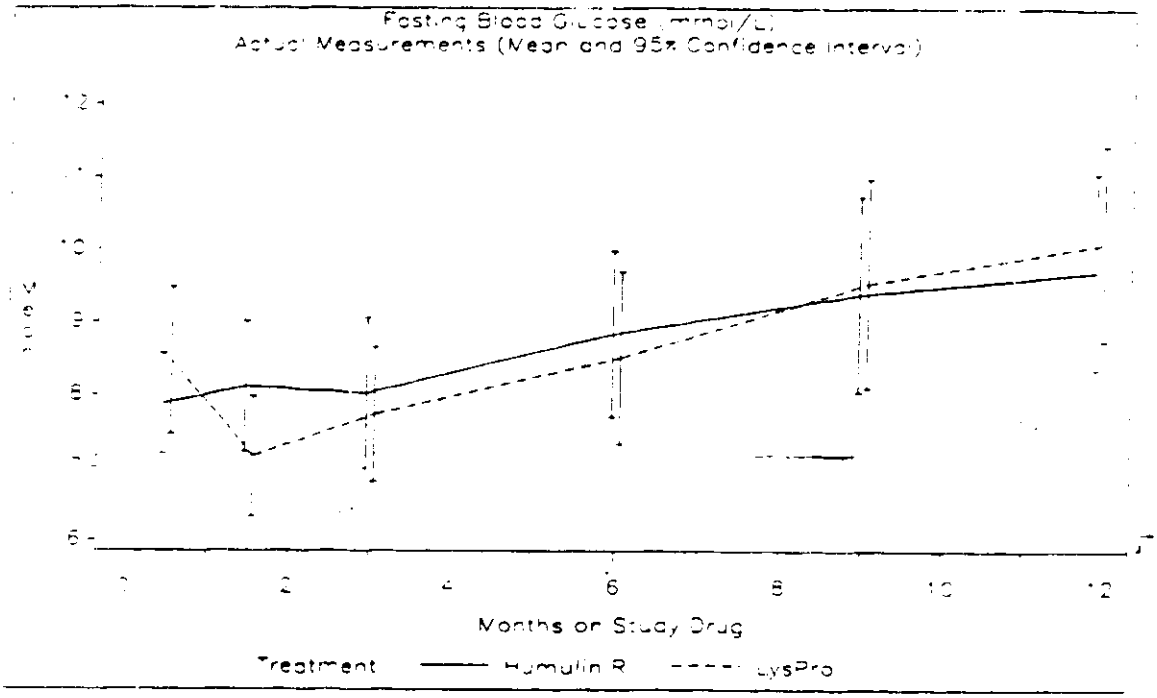

Figure IOAE.6.2. Means of Efficacy Measurements by Visit – Fasting Blood Glucose – All Randomized Patients

APPENDIX III (Continued)

Study IOAF
Fasting Blood Glucose (mmol/L)

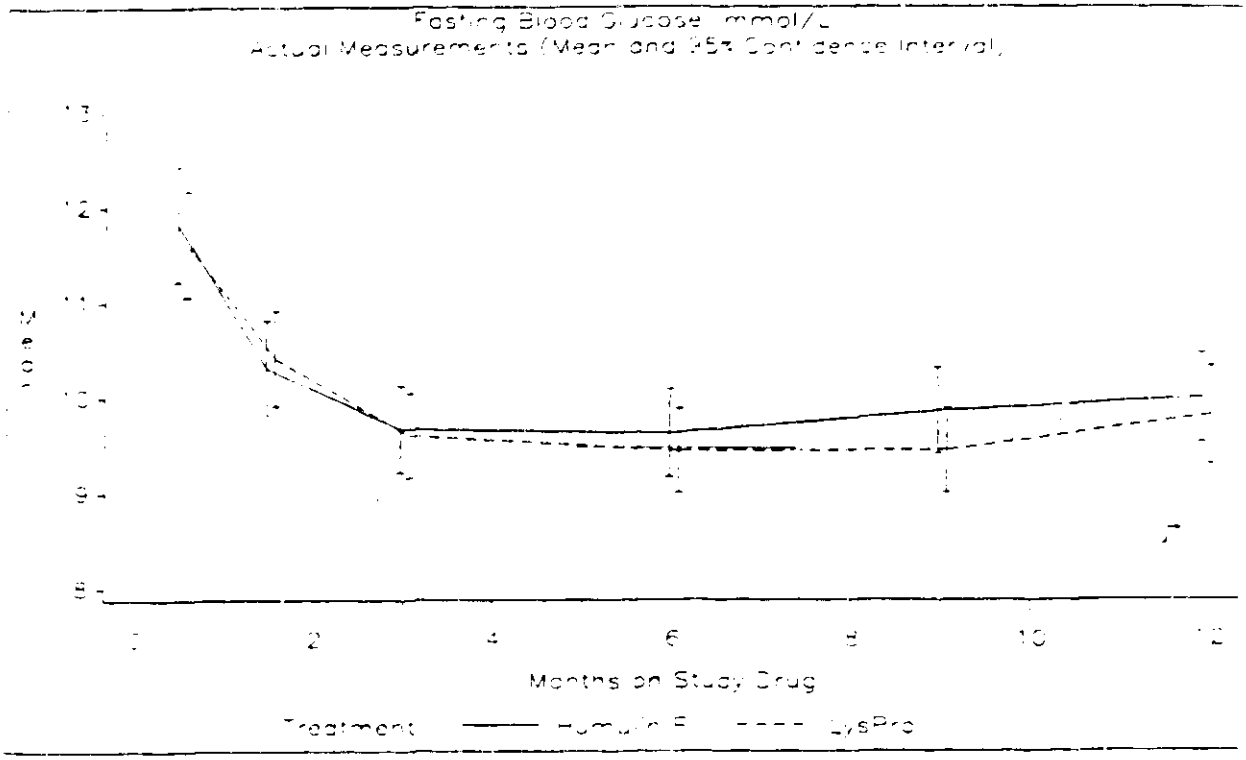

Figure IOAF.6.2. Means of Efficacy Measurements by Visit – Fasting Blood Glucose – All Randomized Patients

APPENDIX III (Continued)

Study IOAG
Fasting Blood Glucose (mmol/L)

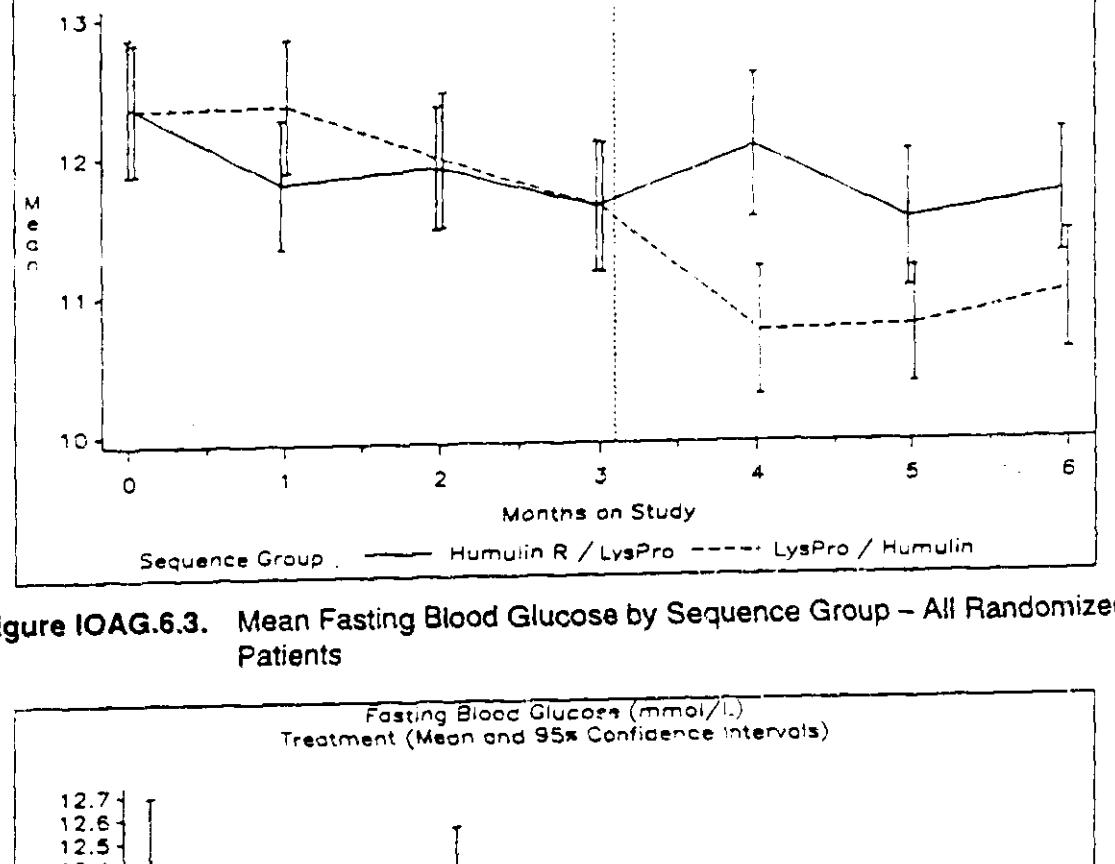

Figure IOAG.6.3. Mean Fasting Blood Glucose by Sequence Group – All Randomized Patients

Figure IOAG.6.4. Mean Fasting Blood Glucose for Combined Treatment Groups – All Randomized Patients

APPENDIX III (Continued)

Study IOAH
Fasting Blood Glucose (mmol/L)

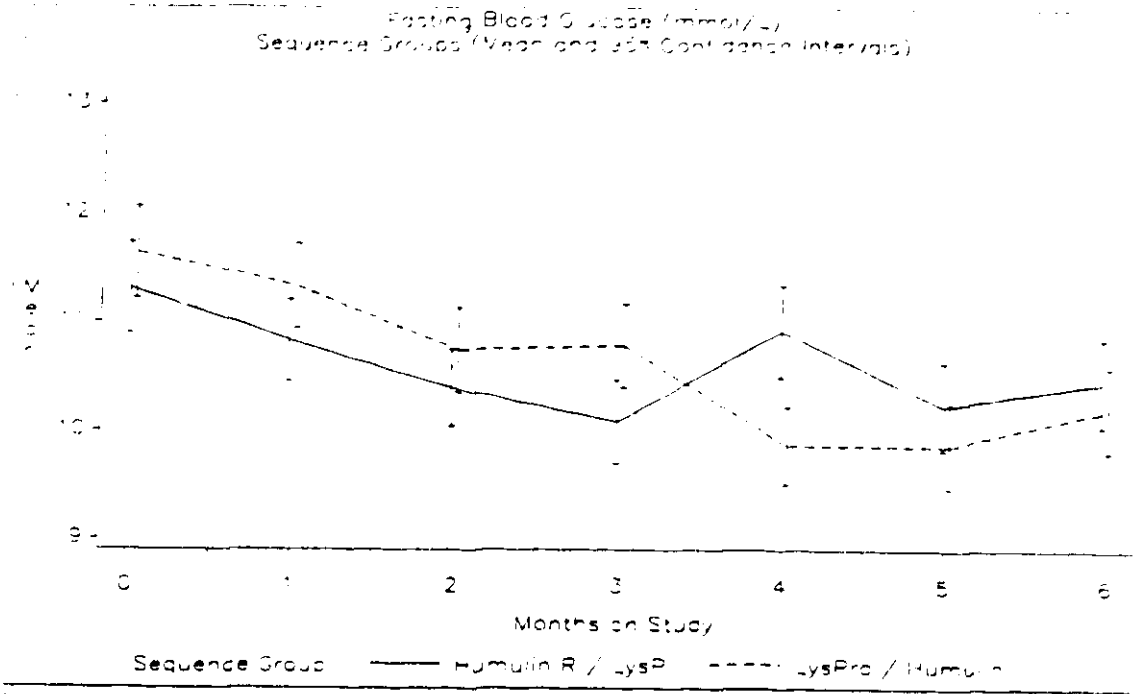

Figure IOAH.6.3. Mean Fasting Blood Glucose by Sequence Group – All Randomized Patients

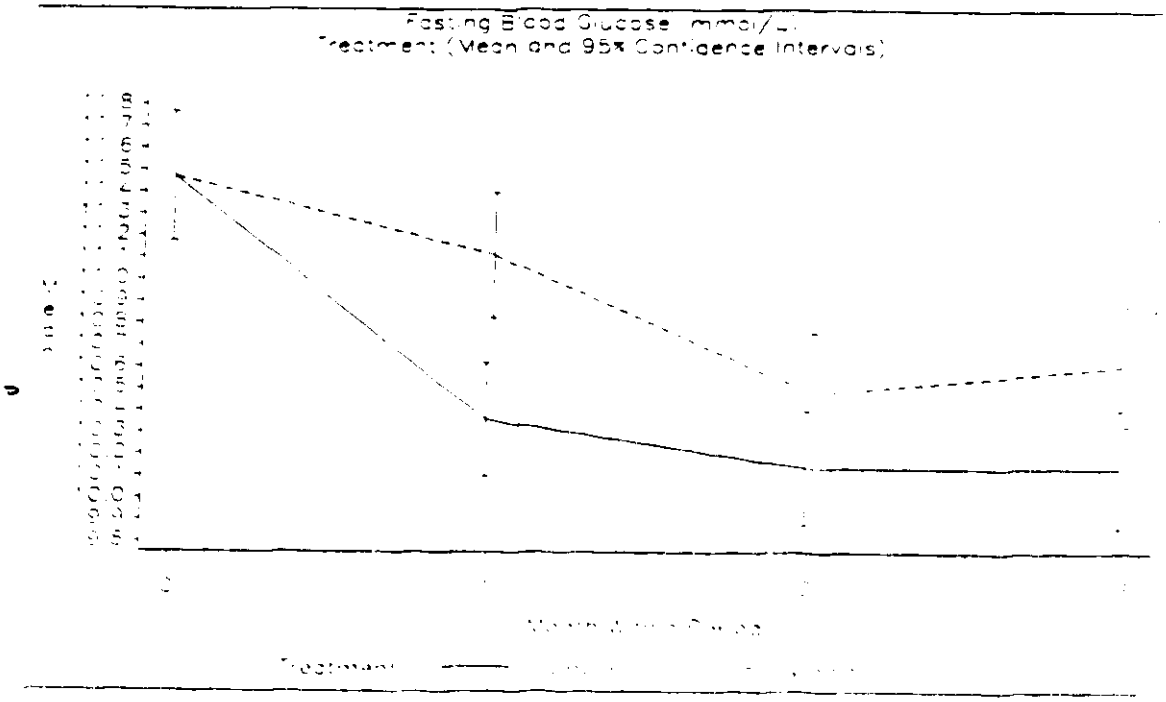

Figure IOAH.6.4. Mean Fasting Blood Glucose for Combined Treatment Groups – All Randomized Patients

APPENDIX III (Continued)

Studies IOAG and IOAH Combined
Fasting Blood Glucose (mmol/L)

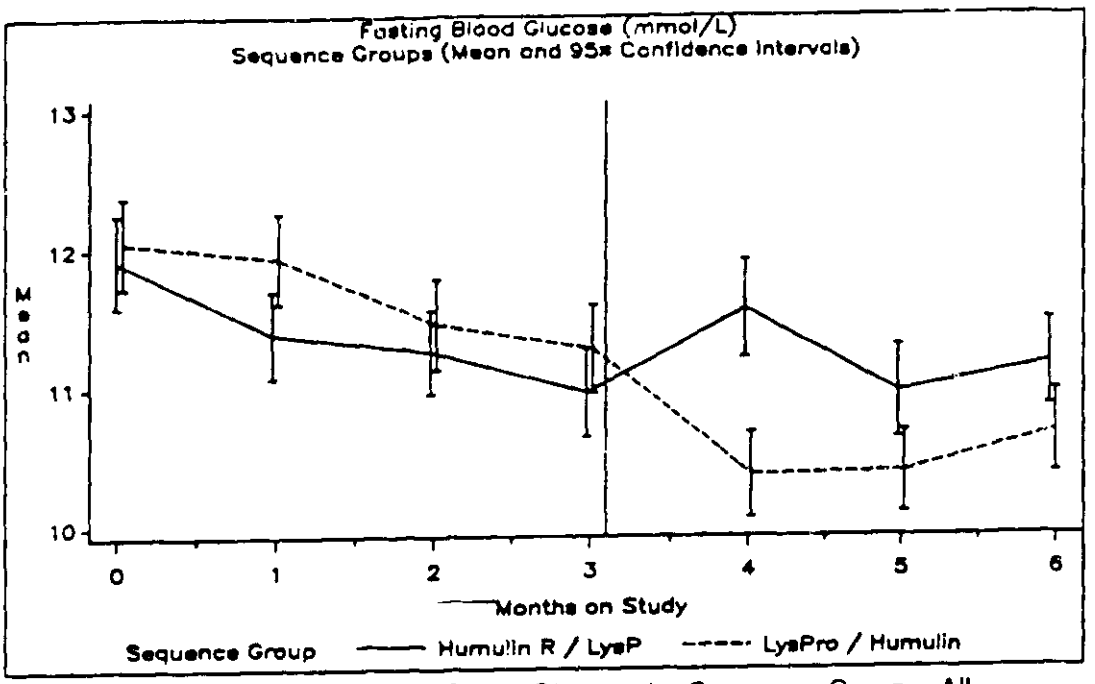

Figure IOAGH.6.3. Mean Fasting Blood Glucose by Sequence Group – All Randomized Patients

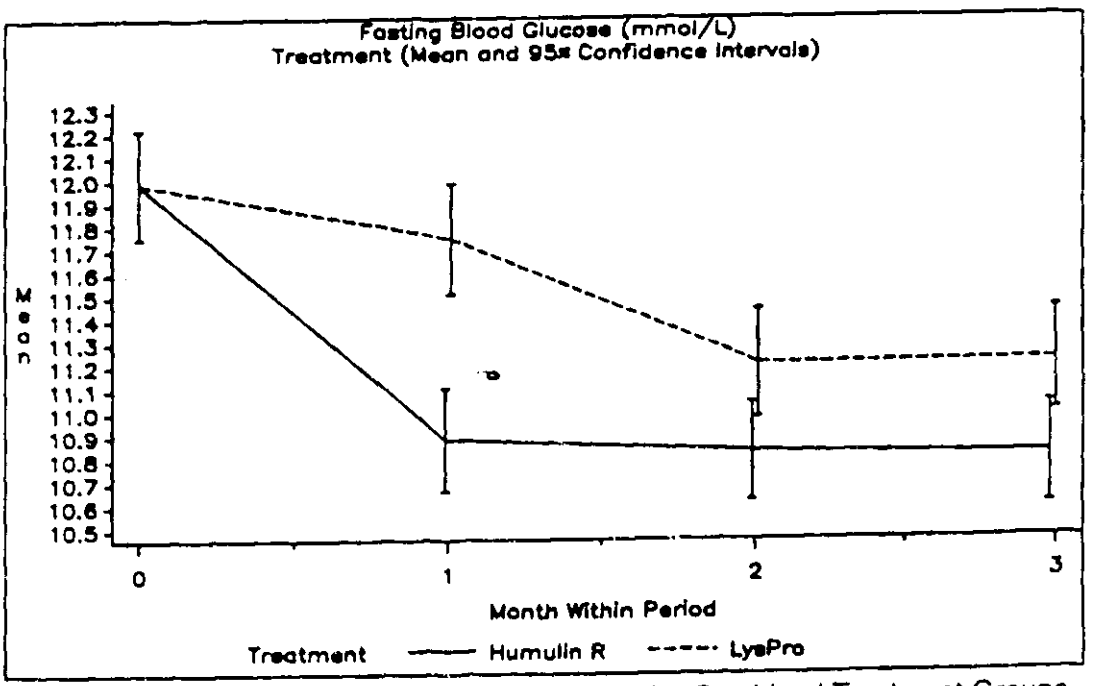

Figure IOAGH.6.4. Mean Fasting Blood Glucose for Combined Treatment Groups – All Randomized Patients

APPENDIX IV

Study IOAA
2-Hour Postprandial Glucose (mmol/L)

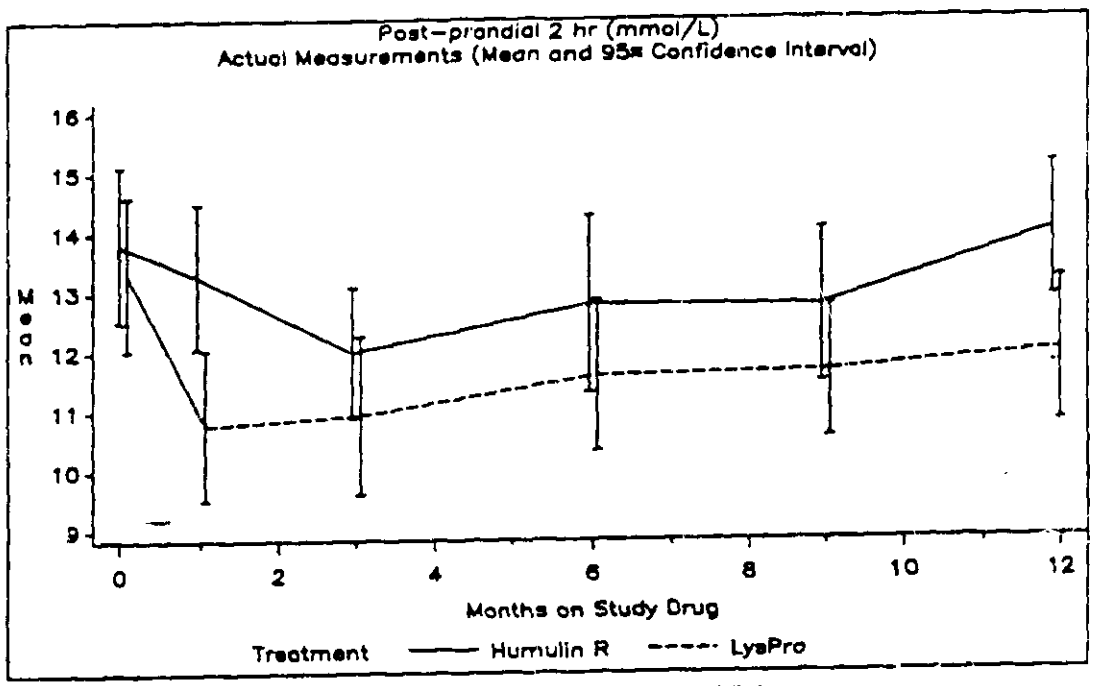

Figure IOAA.6.4. Means of Efficacy Measurements by Visit
2-Hour Postprandial Blood Glucose
All Randomized Patients

APPENDIX IV (Continued)

Study IOAB
2-Hour Postprandial Glucose (mmol/L)

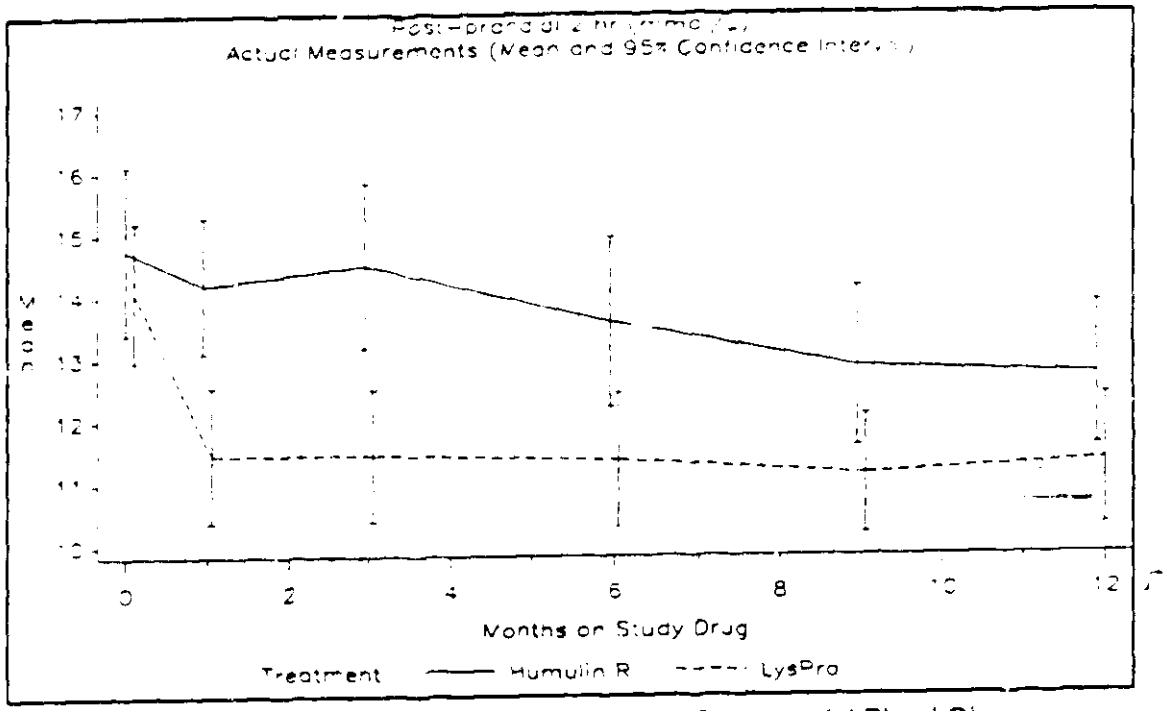

Figure IOAB.6.4. Measurements by Visit – 2–Hour Postprandial Blood Glucose
All Randomized Patients

APPENDIX IV (Continued)

Study IOAC
2-Hour Postprandial Glucose (mmol/L)

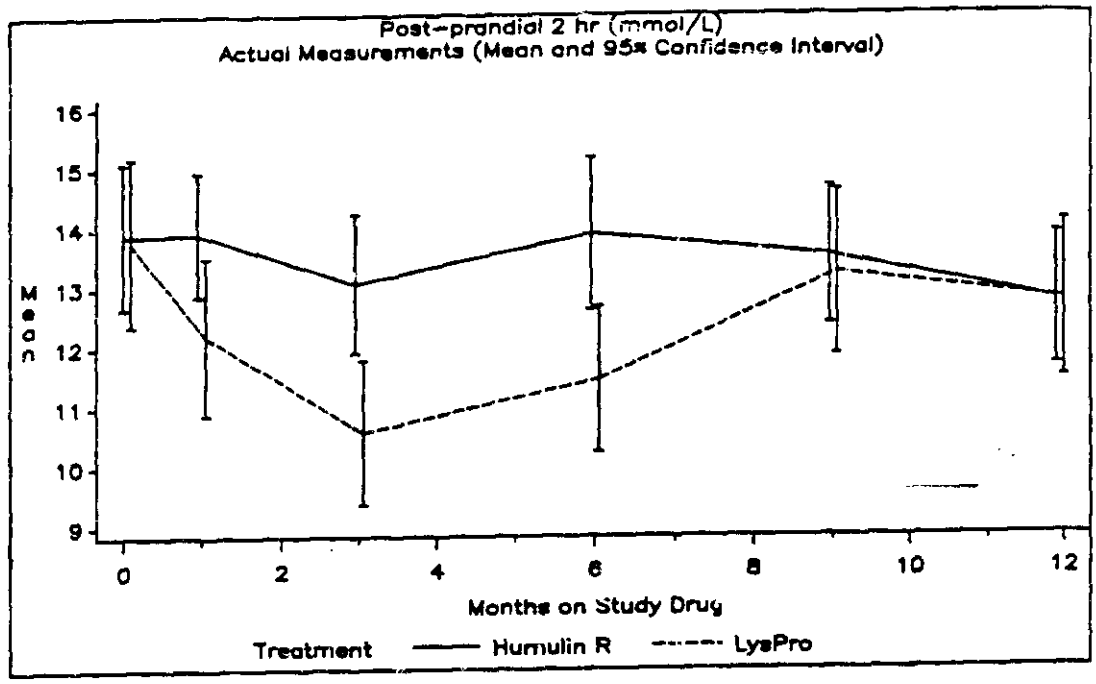

Figure IOAC.6.4. Means of Efficacy Measurements by Visit
2-Hour Postprandial Blood Glucose
All Randomized Patients

APPENDIX IV (Continued)

Study IOAD
2-Hour Postprandial Glucose (mmol/L)

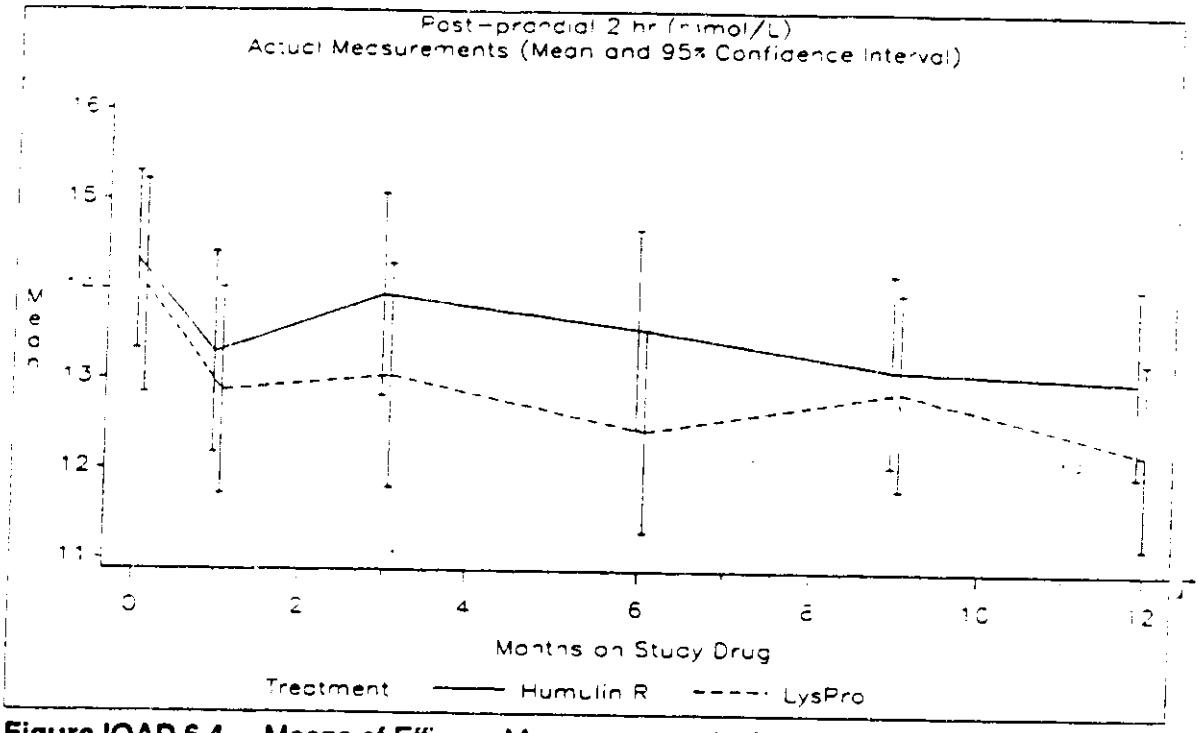

Figure IOAD.6.4. Means of Efficacy Measurements by Visit – 2-Hour Postprandial Blood Glucose
All Randomized Patients

APPENDIX IV (Continued)

Studies IOAA thru IOAD Combined
2-Hour Postprandial Glucose (mmol/L)

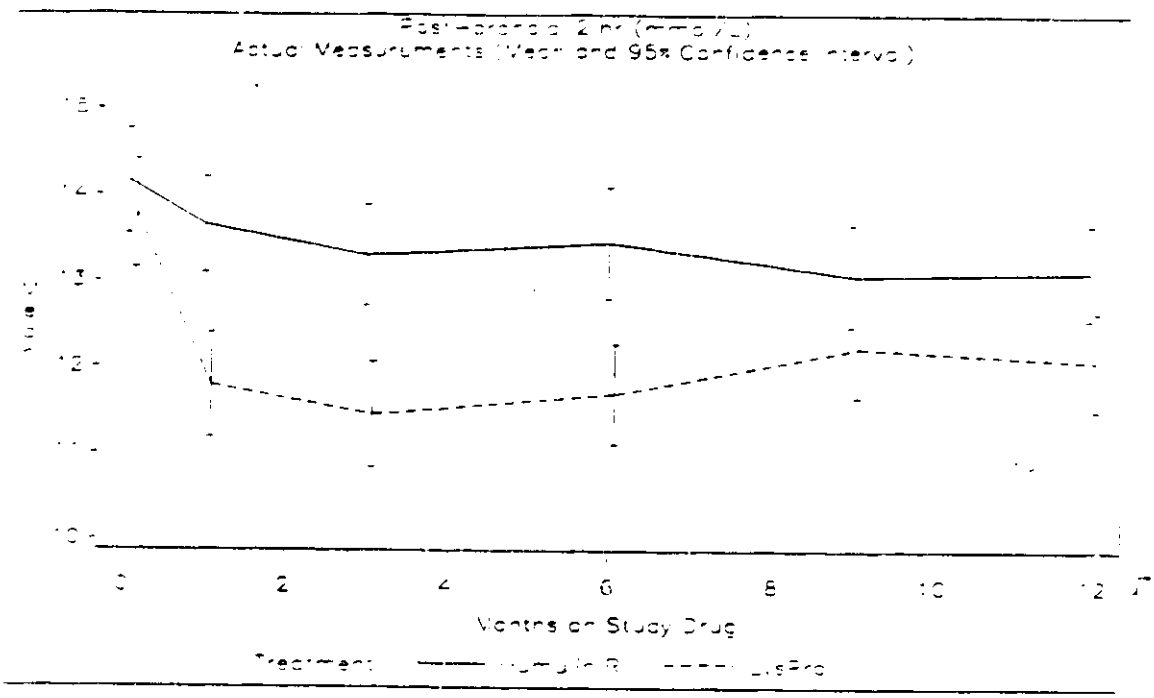

Figure IOAAD.6.4. Means of Efficacy Measurements by Visit – 2–Hour Postprandial Blood Glucose – All Randomized Patients

APPENDIX IV (Continued)

Study IOAE
2-Hour Postprandial Glucose (mmol/L)

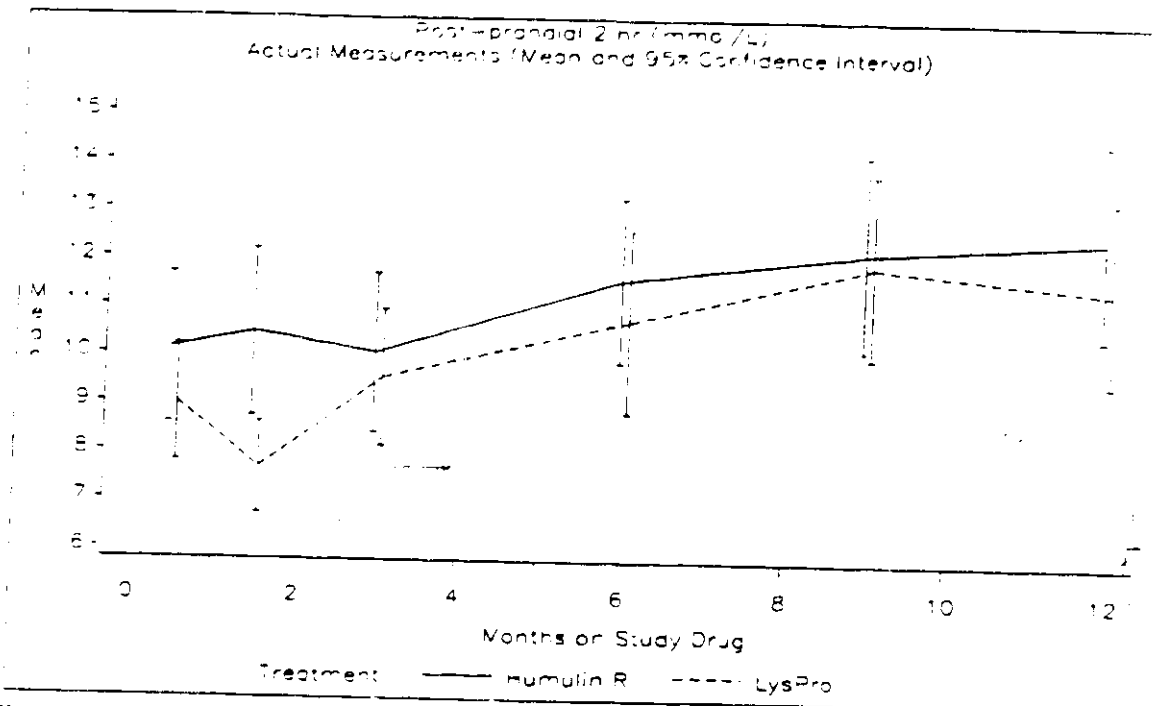

Figure IOAE.6.4. Means of Efficacy Measurements by Visit – 2–Hour Postprandial Blood Glucose – All Randomized Patients

APPENDIX IV (Continued)

Study IOAF
2-Hour Postprandial Glucose (mmol/L)

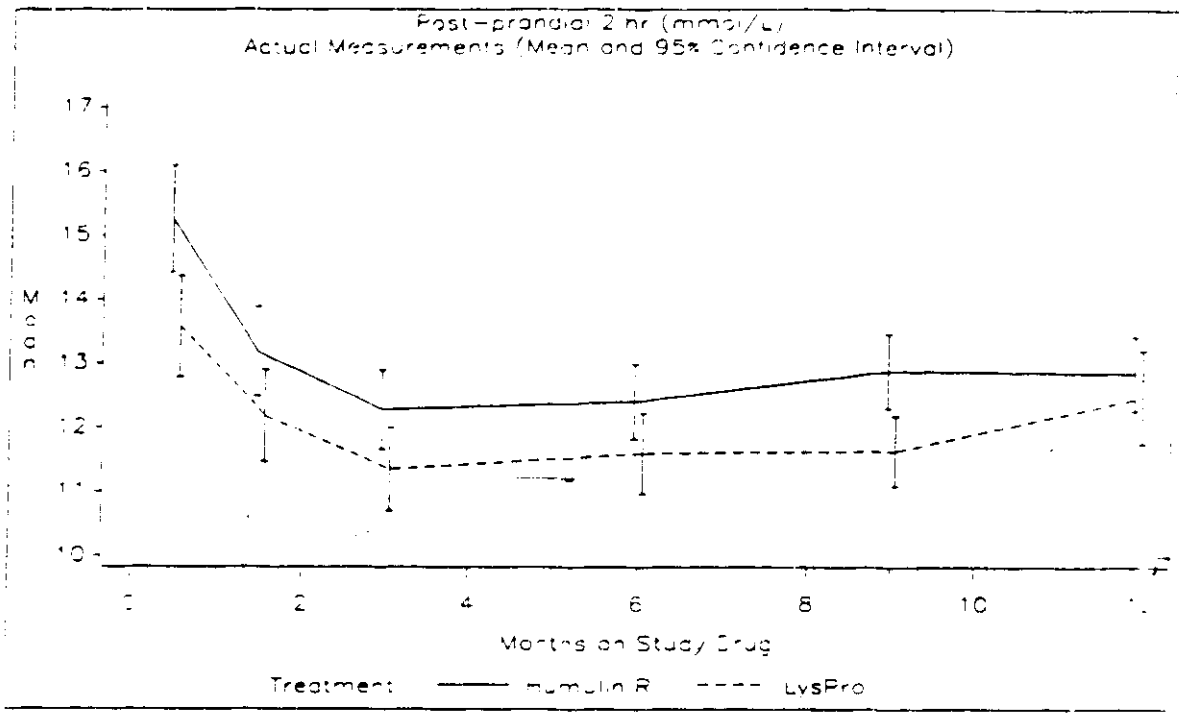

Figure IOAF.6.4. Means of Efficacy Measurements by Visit – 2–Hour Postprandial Blood Glucose – All Randomized Patients

Study IOAG
2-Hour Postprandial Glucose (mmol/L)

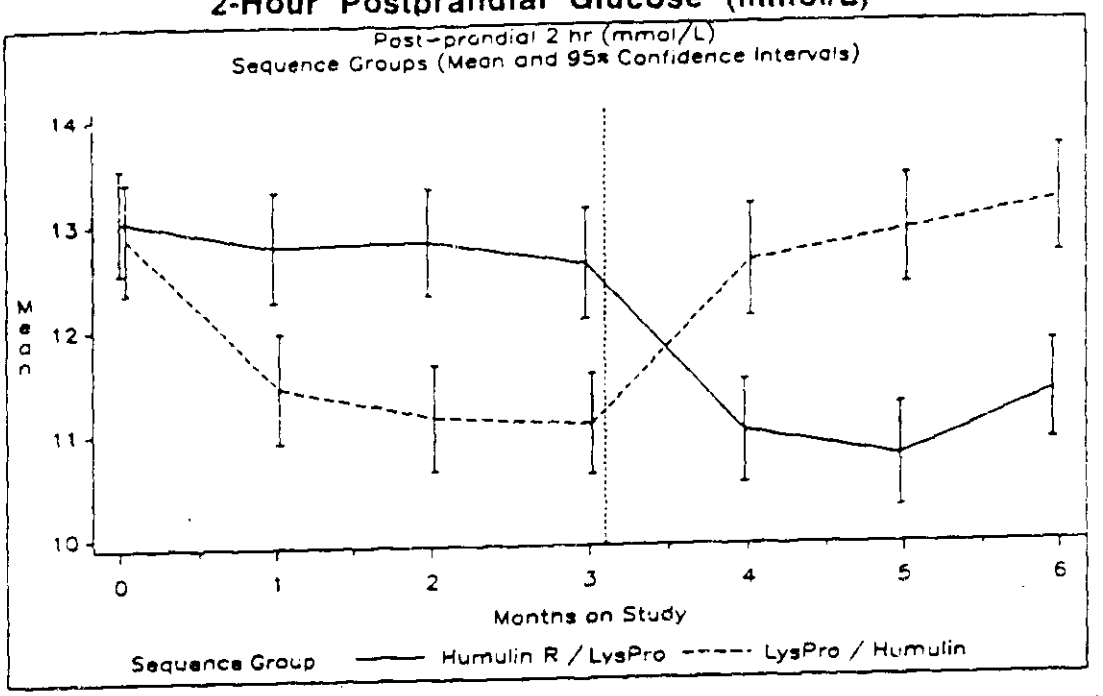

Figure IOAG.6.7. Mean 2-Hour Postprandial Blood Glucose by Sequence Group – All Randomized Patients

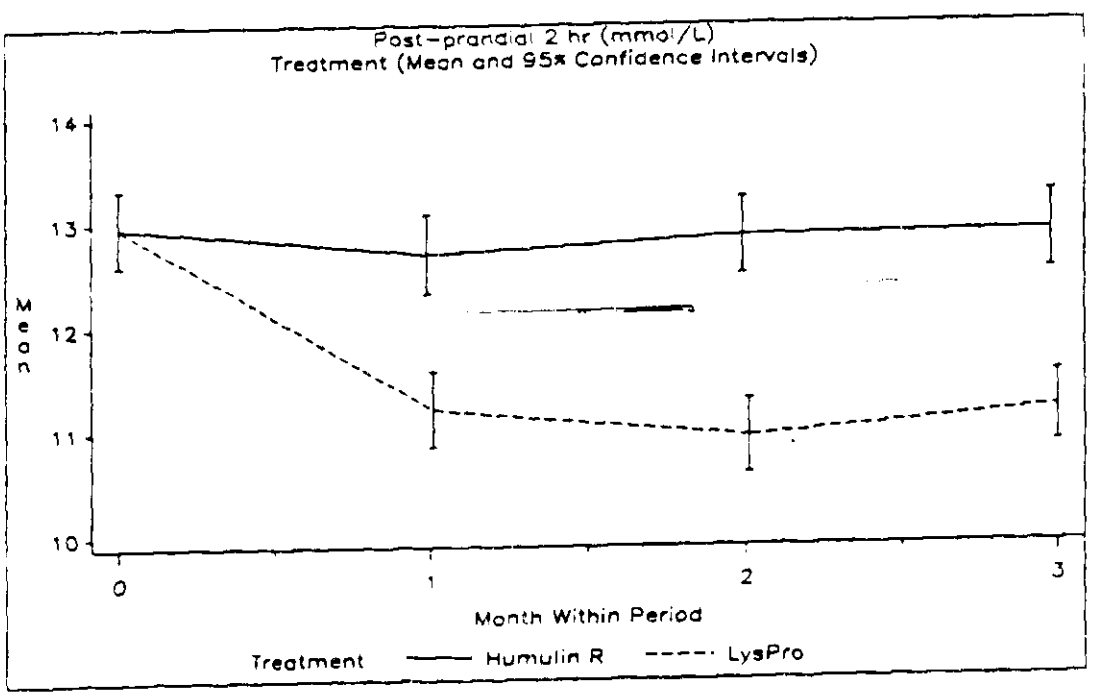

Figure IOAG.6.8. Mean 2-Hour Postprandial Blood Glucose for Combined Treatment Groups – All Randomized Patients

APPENDIX IV (Continued)

Study IOAH
2-Hour Postprandial Glucose (mmol/L)

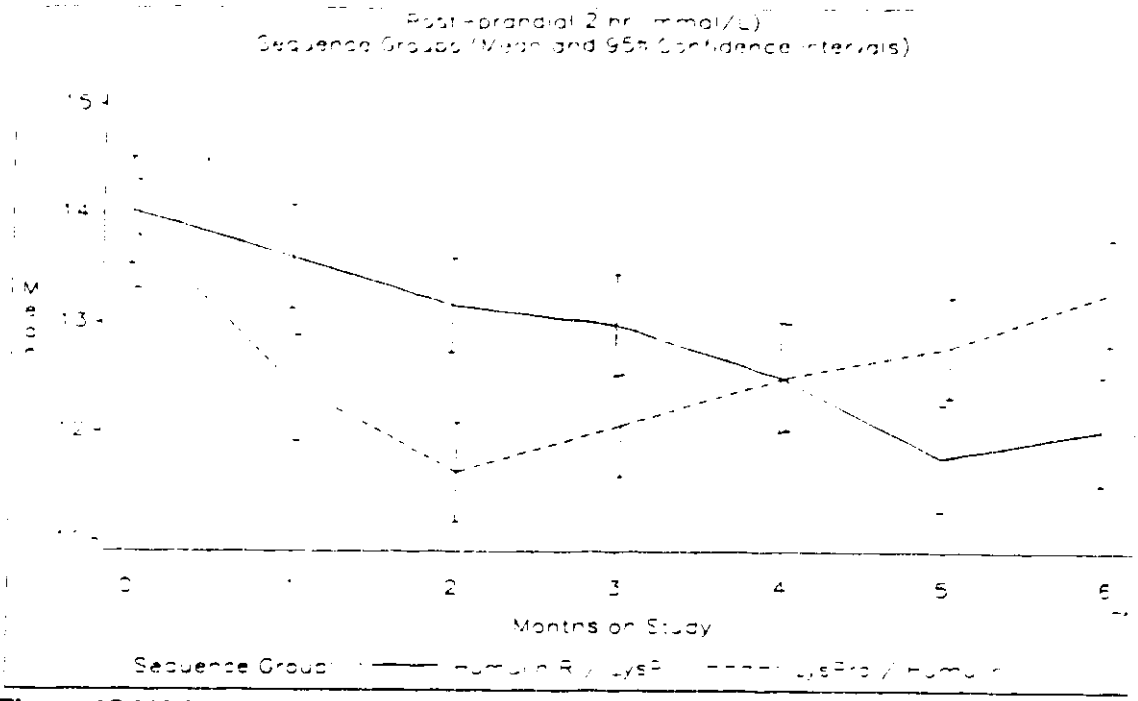

Figure IOAH.6.7. Mean 2–Hour Postprandial Blood Glucose by Sequence Group – All Randomized Patients

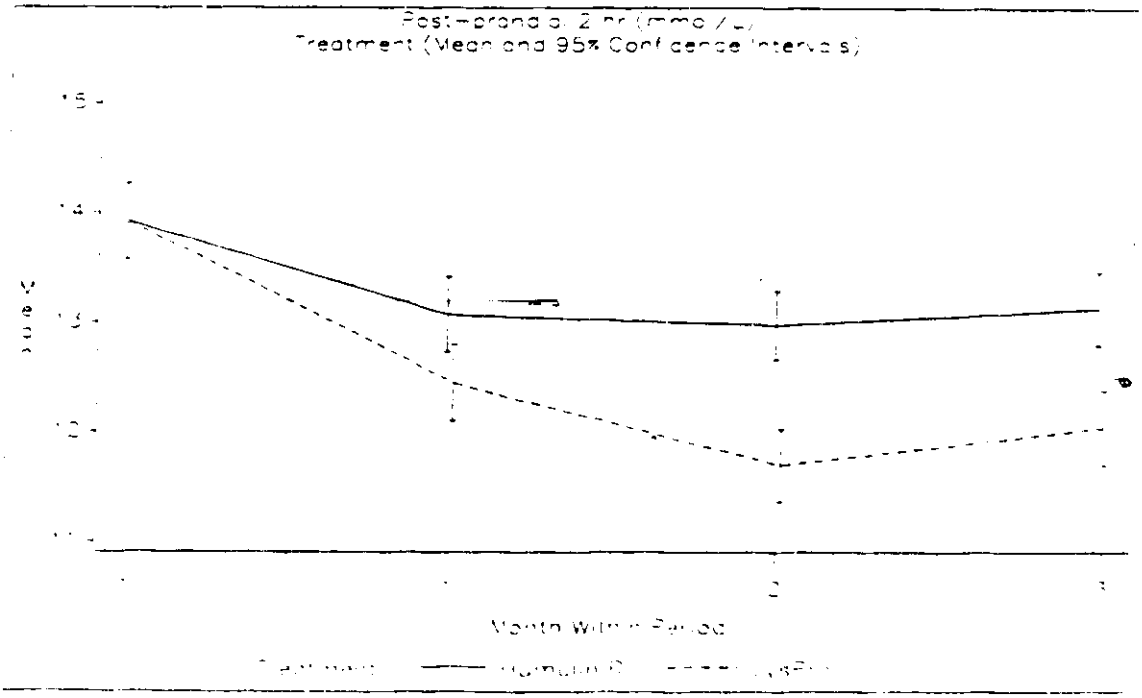

Figure IOAH.6.8. Mean 2–Hour Postprandial Blood Glucose for Combined Treatment Groups – All Randomized Patients

Studies IOAG and IOAH Combined
2-Hour Postprandial Glucose (mmol/L)

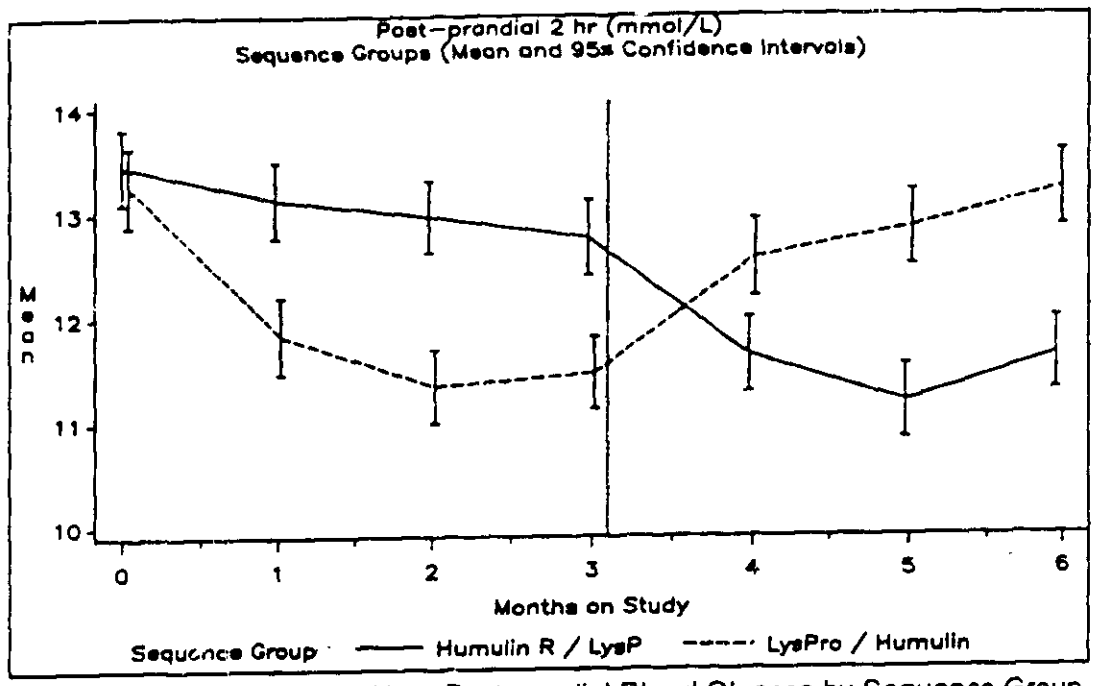

Figure IOAGH.6.7. Mean 2-Hour Postprandial Blood Glucose by Sequence Group – All Randomized Patients

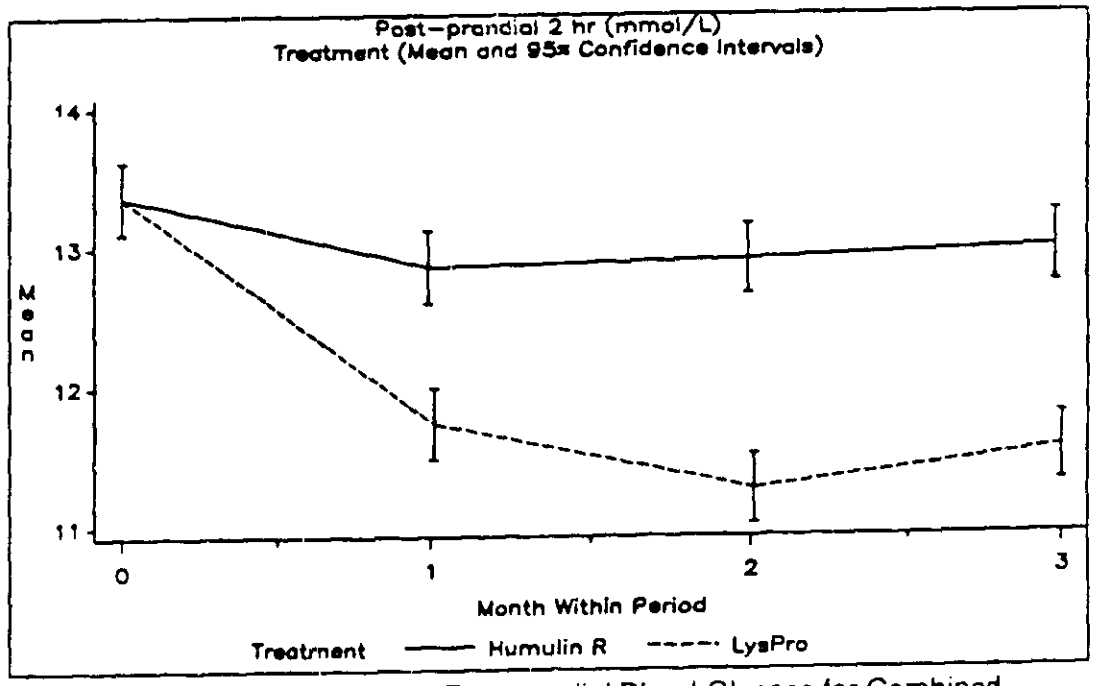

Figure IOAGH.6.8. Mean 2-Hour Postprandial Blood Glucose for Combined Treatment Groups – All Randomized Patients

Figure 1: Hypoglycemia Rate New Definition vs. HbA1c
Period 1

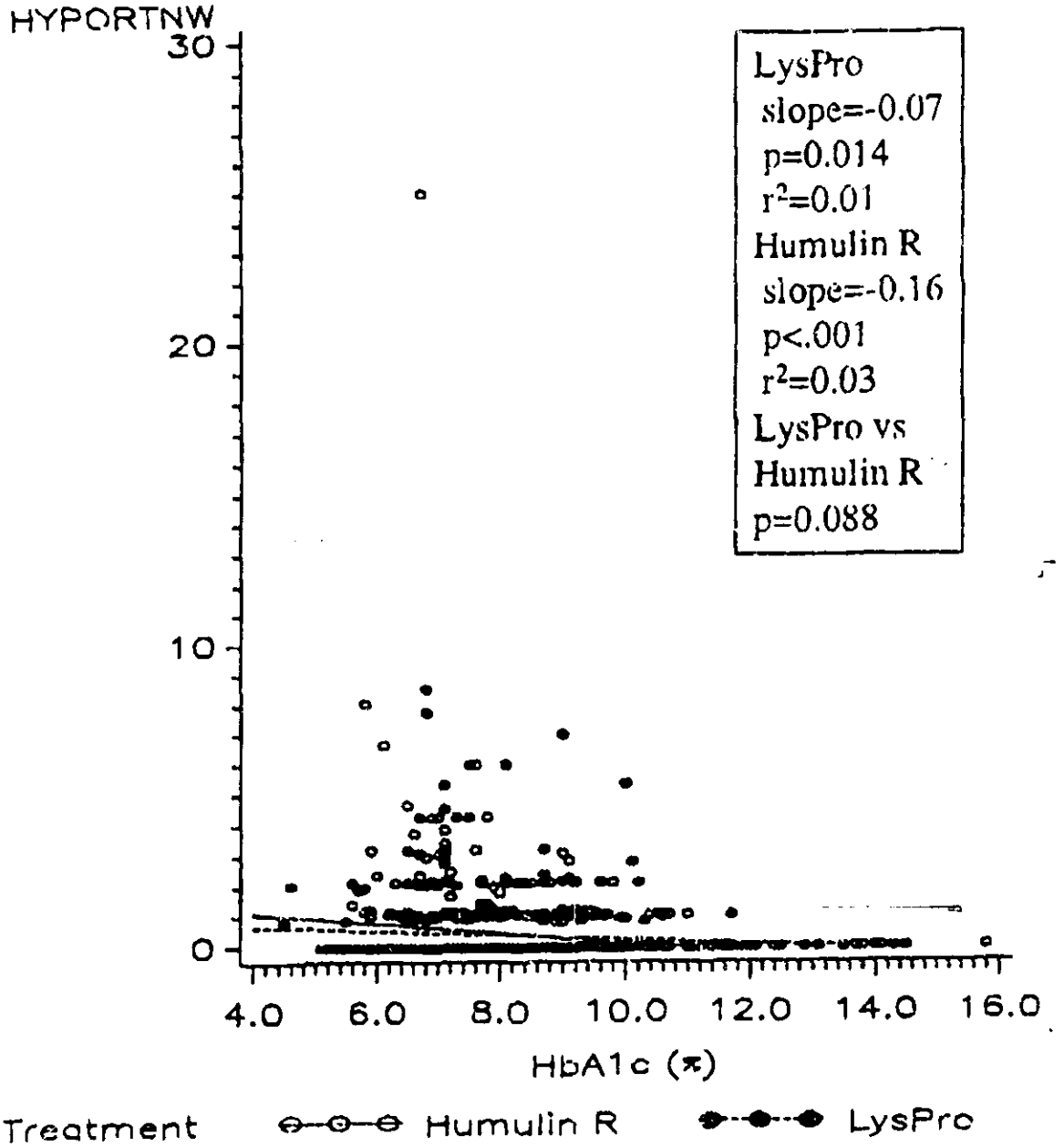

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Figure 2: Hypoglycemia Rate New Definition vs. HbA1c
Period 2

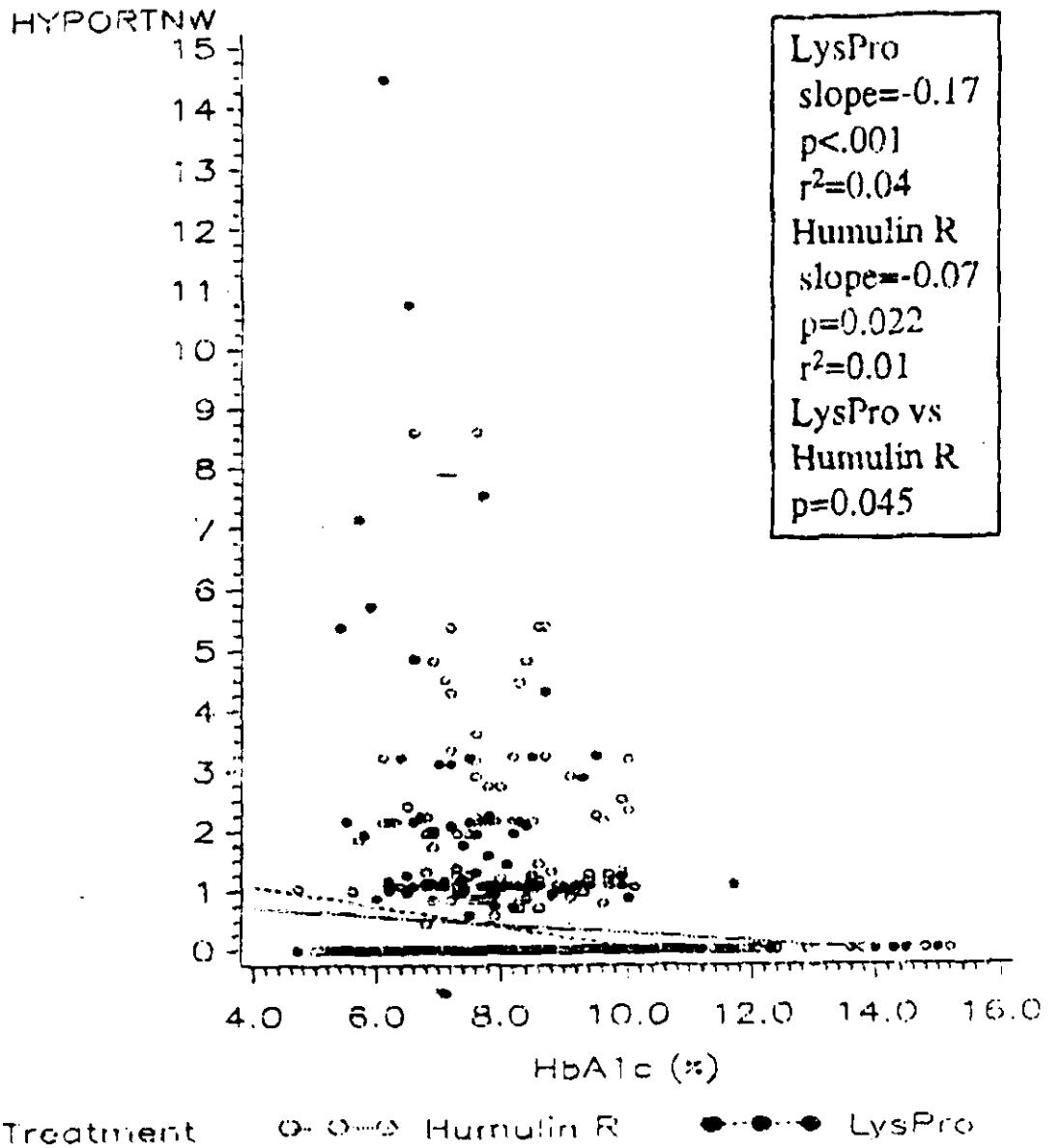

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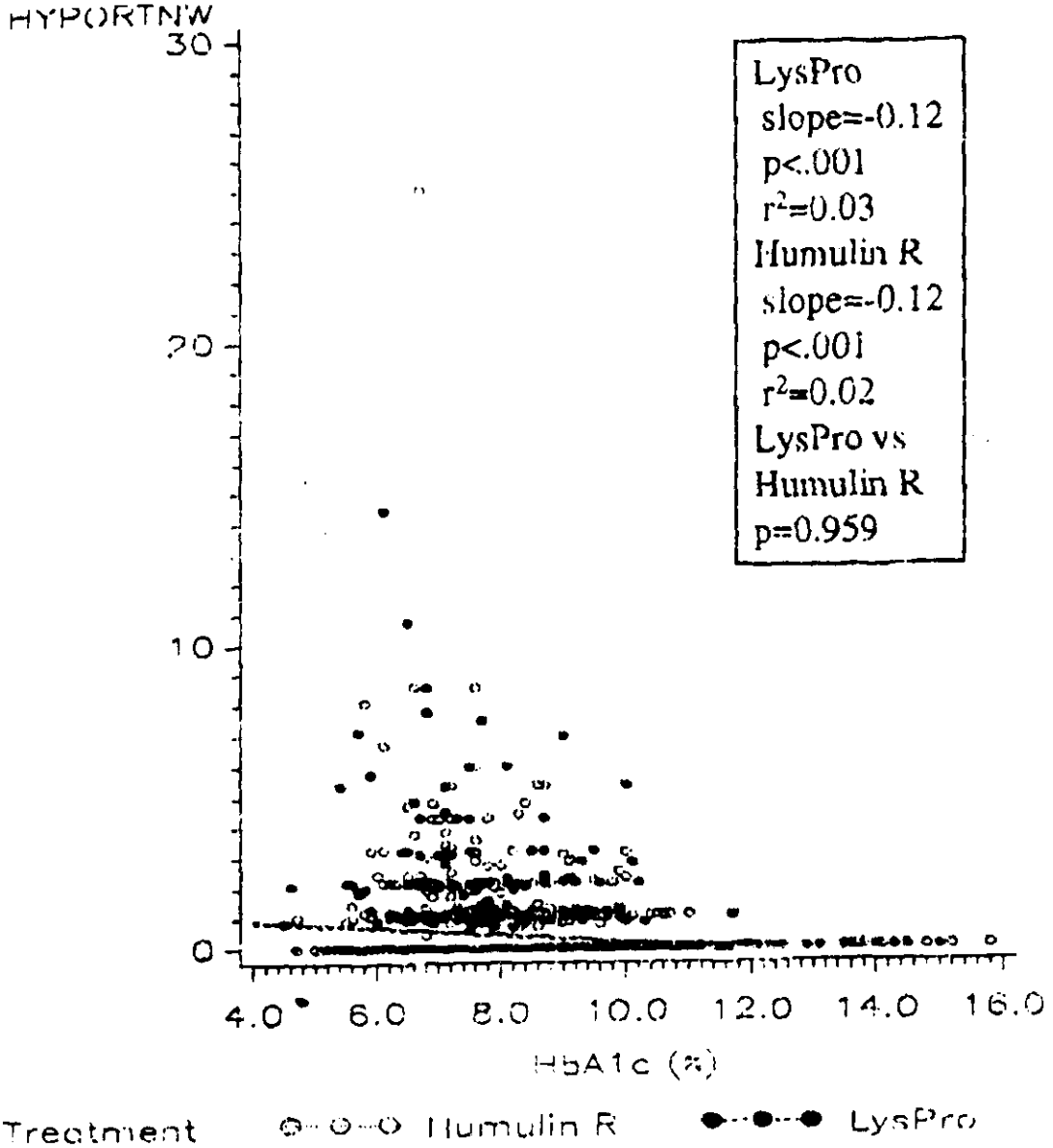
Figure 3: Hypoglycemia Rate New Definition vs. HbA1c
Both Periods Combined



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JUN - 7 1996

PRELIMINARY SAFETY UPDATE FOR NDA #20,563 Lispro
Letter date May 30, Received May 31
Received by medical officer June 3, 1996
Partially reviewed June 7, 1996
3 volumes; 1544 pages
Goal date for NDA June 12, 1996
Sponsor: Lilly Laboratories
Indianapolis, IN

Reportedly the safety data includes information from studies (including IOAA-AH, IOBN, IOAK, IOAM-AO, IOAY, IOBX, IOBP, IOAU, IOBY, IOCM, IODR, and IOBJ) collected-conducted between 4/2/95 through 2/9/96.

Much of the data are from extension studies:
IOAK (for patients from IOAA-AD)
IOAM (for patients from IOAG-AH in UK)
IOAN (for patients from IOAG-AH)
IOAO (for patients from IOAE-AF)
IOAY (for patients from IOAY).

Intepretation of the data is limited because
1) most of the controlled trials were unblinded (and the reporting bias is unknown),
2) there is no denominator (time or actual patient number) for the extension trials,
3) there is selection bias for subjects who entered the extension trials,
4) if adverse events occur with insulin and/or diabetes, but occur at a different rate with Lispro, it is unlikely that they will be detected in short, controlled trials or long uncontrolled trials,
5) it is not clear from the reports whether patients were still in the controlled phase of the trials or in the extension phase when the extension trial carried the same name as the controlled trial,
6) evaluation of diabetic complications was not routinely performed at baseline in the major trials,
7) there were no exit physicals in the major trials
8) investigators often did not manage many of the patients' medical needs so were often unable to obtain good medical records when an adverse event did occur,
9) multiple adverse events were reported on a single adverse event form as addenda (and do not appear to have been codified as discrete AE's by the sponsor in the serial tabulations).

Sponsor Tabulations of Death
During controlled trials

Study	Pt	Tx	Days of Rx	Cause of Death
IOAY	8-218	LP	392	liver disease
IOAY	602-6025	LP	135	sudden death*(in NDA)
IOBM	804-8128	HR	93	hypoglycemic seizure
IOCE	30-484	LP	95	AML

During uncontrolled trials

the end of the controlled phase(s), and whether the endpoint values were taken at 1 year post completion of the controlled phase of the trials. The clinical significance of these changes are difficult to assess because there was no integrated analysis of insulin dose, HgbA1c, and antibody binding level.

Table 6.35. Summary of Baseline, Endpoint, and Change from Baseline to Endpoint for Antibody Tests from Patients in Studies IOAA, IOAB, IOAC, IOAD, IOAG, and IOAH

Antibody	Therapy	N	Baseline Mean (Med)	Endpoint Mean (Med)	Change Mean (Med)	Within-Group p-value	Between-Group p-value[a]
LP-Specific	LP	1806	0.57 (0.10)	0.68 (0.10)	0.12 (0.00)	.011	.880
(% binding)	*Humulin R*	*1814*	*0.55 (0.01)*	*0.61 (0.10)*	*0.05 (0.00)*	.122	
Human Insulin-Specific	LP	1806	0.87 (0.10)	0.84 (0.10)	-0.03 (0.00)	.992	.845
(% binding)	*Humulin R*	*1822*	*0.89 (0.10)*	*0.88 (0.10)*	-0.02 (0.00)	.558	
Cross-Reactive	LP	1811	7.49 (2.90)	8.83 (3.50)	1.34 (0.30)	< .001	< .001
(% binding)	Humulin R	1827	7.54 (2.90)	7.95 (3.18)	0.40 (0.00)	< .001	
Anti-ECP	LP	1917	98.3 (88.0)	96.4 (84.0)	-1.86 (-3.0)	< .001	.841
(RLU)	Humulin R	1931	99.5 (88.0)	97.1 (85.0)	-2.38 (-3.0)	< .001	

Abbreviations: N = number of patients with a baseline and postbaseline measurement, Med = median, LP = insulin lispro, ECP = *Escherichia coli* polypeptides, RLU = relative light units

[a] p-value from the reduced model.

Table 6.36. Summary of Endpoint for Antibody Tests from Patients in Studies IOAE and IOAF

Antibody	Therapy	N	Endpoint Mean (Med)	Between-Group p-value[a]
LP-Specific	LP	228	0.52 (0.2)	.849
(% binding)	Humulin R	227	0.33 (0.3)	
Human Insulin-Specific	LP	228	0.30 (0.1)	.008
(% binding)	Humulin R	227	0.38 (0.2)	
Cross-Reactive	LP	228	11.02 (4.1)	.019
(% binding)	Humulin R	227	9.02 (2.0)	
Anti-ECP	LP	227	102.1 (90.0)	.089
(RLU)	Humulin R	228	112.0 (94.0)	

Abbreviations: N = number of patients with a baseline and postbaseline measurement; Med = median; LP = insulin lispro; ECP = *Escherichia coli* polypeptides; RLU = relative light units.

[a] p-value from the reduced model.

Table 6.41. Summary of Baseline, Endpoint at 1-Year, and Change from Baseline to 1-Year Endpoint for Cross-Reactive Antibodies within Diabetes Type and Basal Insulin from Studies IOAK, IOAM and IOAN

	Subset	N	Baseline Mean (Med)	Endpoint Mean (Med)	Change Mean (Med)	Within-Group p-value	Between-Group p-value
Diabetes Type	Type I	425	13.22 (7.48)	14.09 (7.96)	0.87 (0.59)	.003	.237
	Type II	245	10.15 (3.90)	10.27 (3.50)	0.09 (0.00)	.789	
Basal Insulin	Humulin N	503	11.93 (5.73)	12.43 (6.69)	0.51 (0.16)	.046	.207
	Humulin U	167	12.54 (5.41)	13.42 (5.57)	0.78 (0.32)	.206	
Overall		670	12.11 (5.57)	12.69 (6.37)	0.58 (0.20)	.019	

Abbreviations: N = number of patients with a baseline and postbaseline measurement; Med = median

Reference range for cross-reactive antibody binding is 0% to 2.5%.

Study	Pt	Tx	Days on Rx	Cause of Death
IOAN	248-2604	LP	760	sudden death* (in NDA)
IOAN	517-5333	LP	751	MI-->CHF
IOAO	51-442	LP	58[illegible]	lung CA
IODH	201-3006	LP	45	suicide by DKA
After discontinuation				
IOAH	966-9746	HR		GI CA
IOAY	966-9702	Mixtard 70/30		dead in bed*
IOCC	835-8059	NPH		lung CA
IOCE	700-7010	Insulatard		drowning

Sponsor Tabulations of Discontinuations due to AE's

Table 5.7. Patients Who Discontinued Due to an Adverse Event

Study (Controlled)	Patient	Treatment	Days on Therapy	Adverse Event
E002[a]	241-2408	Insulin Lispro	0.5 hours	Allergic reaction *
IOAY[b]	005-0129	Insulin Lispro	1 year	Unintended pregnancy
	241-2430	Insulin Lispro	324	Myocardial infarct *
	603-6045	Insulin Lispro	344	Unintended pregnancy
IOBJ[c]	307-3143	Insulin Lispro	88	Diabetic acidosis
	803-8043	Insulin Lispro	51	Diabetic acidosis
	969-9798	Humulin R	0	Diabetic acidosis
IOBN	801-8032	Humulin R	31	Hypoglycemic reaction
	802-8048	Humulin R	28	Emotional lability
IOBO	103-0031	Insulin Lispro	19	Myocardial infarct *
	103-0035	Humulin R	62	Psychosis
IOCC[d]	835-8059	Insulin Lispro	229	Pulmonary adenocarcinoma
IOCE[e]	303-3080	Insulin Lispro	165	Kidney function abnormal *
	404-4106	Glybenclamide	64	Gastrointestinal carcinoma
	503-5082	Insulin Lispro	31	Peritonitis
	504-5110	Glybenclamide	21	Myocardial infarct *
	740-7409	Insulin Lispro	127	Myocardial infarct *
	870-8506	Insulin Lispro	64	Prostatic carcinoma
(Uncontrolled)				
IOAN	102-1048	Insulin Lispro	536	Unintended pregnancy
	151-1525	Insulin Lispro	379	Cerebrovascular accident *
	241-2547	Insulin Lispro	546	Hypoglycemia *
	246-2569	Insulin Lispro	740	Hypoglycemia *
	503-5050	Insulin Lispro	592	Allergic reaction *
	740-7442	Insulin Lispro	798	Hepatitis
	722-7301	Insulin Lispro	518	Atrial arrhythmia *
IOAO	022-0221	Insulin Lispro	175	Carcinoma
	075-0604	Insulin Lispro	359	Surgical procedure (quadruple bypass)
IOBV	101-0101	Insulin Lispro	49	Accidental injury
IOCH	701-7015	Insulin Lispro	35	Hypoglycemia *
	702-7035	Insulin Lispro	72	Accidental injury
IOCP[f]	501-5002	Insulin Lispro	94	Endocarditis

[a] This patient discontinued in Oct 92.

[b] Study IOAY became uncontrolled as of 17 Jan 95.

[c] Study IOBJ became uncontrolled as of 30 Nov 95.

[d] A discussion of this patient is in 5.1.2.1.2 Deaths After Study Discontinuation.

[e] Study IOCE became uncontrolled as of 16 Oct 95.

[f] A discussion of this patient is in 5.1.2.2.1 Serious, Unexpected, Possibly Causally Related Adverse Events.

Condition	Study	ID #	Rx	Age	Occurred	Comments	Other Rx
Chest pain	AF	43-382	LP	??	Dec-93	a fib; RCA occlusion; graft to LAD partial occlusion; DVD	Digoxin
Chest pain/SOB	AH	55-1794	HR	68	May-93	elevated CPK, LDH (MB delayed, LDH fractions ND)	
Chest pain	AK	961-9661	LP	69	May-94	outcome ? prior cardiac hx (refer)	
Chest pain (again)	AK	961-9661	LP	70	May-95	outcome ? previous CP during IOAK (refer)	
Chest pain	AM	801-8166	LP	51	Jun-95	DC next day	
Chest pain/SOB-->CHF	AM	801-8171	LP	89	Mar-95	cause ?	Diuretic
Unstable angina-->CABG	AK	11-285	LP	57	Jan-95		
Chest pain	AK	904-9142	LP	49	Mar-95	unknown etiology	
Chest pain (LBBB) on dialysis-->CHF-->DEATH	AK	904-9152	LP	66	Jan-95	retinopathy/neuropathy/RF (what was creat at entry)	Diuretic
Hypotension+a fib-->sinus-->chest pain	AK	905-9041	LP	85	Mar-95	impaired contractility	
Chest pain+palpitations; LVH on EKG	AN	602-6128	LP	?	Nov-95	(+angio LAD and Cirx)	
Chest pain	AN	966-9753	LP	60	Dec-94	no more info	
Recent angina+CHF-->cath	AO	27-268	LP	59	Dec-94	(refer to abnormal EKG)	Digoxin, Diuretic
Probable persistent angina	AO	43-382	LP	79	May-95		Digoxin, K
Chest pain-->complications c angioplasty-->CABG	AO	72-561	LP	83	Jan-95	DC on digoxin	Digoxin
Chest pain-->3 V disease-->emergency CABG	AO	75-612	LP	83	Sep-05	hx a fib	Digoxin
Chest pain/high BP	AY	855-8557	LP	53	Feb-95	no more information	
Recurrent angina (+ on AH on LP, not on HR)	AN	408-4312	LP	65	Apr-94	also wt gain and depression/ angiography 30% occl ? spasm	
Ant MI	AK	920-9201	LP	80	Aug-95	no prior cardiac hx/ Rx c streptokinase	
Post lat MI--> angioplasty	AK	961-9661	LP	58	Nov-93	prior cardiac hx	
MI	AN	248-2804	LP	88	May-95		Diuretic
MI (+angio-->PTCA	AN	418-4566	LP	55	Jan-96	no more info	
MI	AO	28-62	LP	40	Jun-95		
MI (anteroseptal)	AY	904-9011	LP	83	Jan-95	(retinopathy neuropathy, nephropathy)	
MI-->CHF	AY	992-9947	LP	?	Jul-95	(started on lasix)	
CHF	AH	850-8867	LP	75	May-93	etiology not given	Digoxin, Diuretic
CHF/SOB	AH	7-167	LP	71	Dec-94	pos CXR, elevated LDH, episode of flutter	Digoxin, Diuretic
CHF	AM	804-8070	LP	53	Nov-94	cause ? (no cardiac enzymes)/retinopathy/(refer asthma)	Diuretic
CHF/ increased BUN-creat-glucose	AO	912-9145	LP	56	Dec-95	cause ?	Diuretic, K
Dyspnea (viral v cardiac)-->ischemia-->tachycardia-->DIED	AY	752-7521	LP	59	Oct-94	response to lasix initially/ ?PE-->MI	Diuretic
Tachyarrhythmia absolute-->heparin-->digoxin	AN	405-4381	LP	73	Mar-95	(refer to ischemic eye disease, bradycardia)	Digoxin, Diuretic
Bradycardia-->pacemaker	AN	405-4381	LP	73	Sep-95	refer to ischemic eye disease/ dysrhythmias)	Digoxin, Diuretic
Dysrhythmia-->pacemaker	AN	409-4349	LP	75	Jan-95	no more info/ (refer prostate CA)	
EKG changes-->angio-->CAHD	AN	417-4689	LP	65	Oct-95	(refer prostate CA)	
Angio +	AN	421-4721	LP	55	Feb-94	(refer to hyperglycemia)	
Abnormal EKG	AO	27-268	LP	59	Mar-95	(refer to recent angina+CHF)	Digoxin, Diuretic
EKG-ECHO+thallium-->cath	AO	27-270	LP	49	Oct-95	no more info	
Cath-->CABG/ correction of ASD	AO	402-4781	LP	54	Aug-95	(refer to osteotomy)	
Cath-->PTCA	AY	409-4131	LP	55	May-95		
CABG	AK	7-174	LP	61	Apr-94	prior CABG	
DEATH (atheroma and fresh thrombus)	AM	808-8181	LP	57	Dec-94	retinopathy/neuropathy/proteinuria/asthma/(refer to asthma)	
Found DEAD shortly post breakfast	AN	907-9342	LP	50	Aug-94	AM glucose 10 mmol/L, stable angina	Hydrex+lasix
Collapse in front of MD-->MI-->DIED	AO	905-9105	LP	72	Dec-94	V tach noted-->Discharge-->died in sleep/HTN controlled 3 agents	Natrix
MI-->DIED	AY	855-8552	LP	63	Jan-95	cardiogenic shock p Antiat III	
DIED	AY	904-9016	HR	65	Aug-94	Pt received LP x16 d/ unclear why pt DC from study	Diuretic, K
DIED	AY	904-9019	HR	70	Aug-94	NOT RANDOMIZED	
DIED on street	BH	812-8141	LP	58	Sep-94	(post not provided) (retinopathy/neuropathy)	
Fell (reason?)-->head trauma-->neg CT	AO	29-283	LP	72	Jan-95		
CVA	AY	966-9691	LP	44	Dec-95		Digoxin
CVA/hypoesthesia/dizziness	AY	X3-71	LP	71	May-95		Diuretic
CVA/ Dizziness/ R side weakness	AY	X2-44	LP	61	Dec-94		
TIA	AN	961-9726	LP	67	Jan-96	(refer to rectal bleeding) (did bleeding-->syncopal-like event?)	Lasix
Apoplexy+apraxia	AN	421-4722	LP	61	Dec-93	W/u uncertain/ (retinopathy)	
?TIA-->CVA	AN	417-4542	LP	28	Jan-94	(dizziness/"tendency to collapse")	
CVA/SOB/chest pain	AK	20-492	LP	89	Aug-95	outcome-cause ?	Diuretic
CVA(s)	AK	920-9214	LP	?	May-95	2 hospitalizations/prior cardiac hx	Digoxin, Diuretic (fusid)
CVA-->DEATH (irreg heart beat 3 wks prior)	AN	248-2801	LP	81	Feb-94	(a fib 87/TIA 1 mo prior)/ (retinopathy	
CVA	AO	60-489	LP	89	Jul-94	(retinopathy, hx vascular disease)	
CVA (question of hypoglycemia)	AY	406-4087	LP	87	Aug-94		
Tachyarrhythmia-->CVA	AY	504-5084	LP	59	Sep-94	prior hx of CVA, DC on digoxin	Diuretic

Condition	Study	ID #	Rx	Age	Occurred	Comments	Other Rx
Retinal detachment-->	AY	204-2029	[illegible]	[illegible]	[illegible]-95	no more info	
Retinal bleed into vitreous-->surgery	AN	412-4664	LP	72	Dec-95	refer to [illegible] cataracts	
Optic ischemic neuropathy	AN	301-3124	LP	28	Jan-95	no more info	
Optic ischemic neuropathy	AN	405-4381	LP	73	Feb-95	ischemic retinopathy 18 Jan 94//refer dysrhythmias	Digoxin, Diuretic
Elective surgery for retinopathy	BA	41-15	LP	32	Nov-94	present prior to trial entry	
Vestibular nerve damage	AN	419-4643	LP	28	Mar-95		
Cerebellar ataxia	AN	990-9906	LP	49	May-94		
Seizures	AN	904-9189	LP	15	Mar-95		
HA sinusitis	AK	902-9029	LP	27	Mar-95		
Pharyngitis	BJ	44-80	LP	18	Nov-95	unclear if hyperglycemia OKA present	
Tracheitis	BJ	408-4080	LP	14	Apr-95	refer hypoglycemic seizures--as noted on [illegible] report	
Migraine	AF	12-562	HR	37	Feb-94	[illegible] negative	
ASA 2C	AK	5-124	LP	31	Aug-95	self tx for cold sores	
Chest pain--panic attack	AY	802-8042	LP	35	Nov-94		
Chest infection	AM	808-8185	LP	71	Dec-95	no more info	Bumex
Pneumonia	AK	20-501	LP	66	Dec-94		
Bronchitis	AK	800-8002	LP	20	Jan-95	also ORTHOSTATIC HYPOTENSION	
Bronchitis	AK	905-9043	LP	71	Jun-95		
Bronchitis	AY	905-9208	LP	31	Nov-94		
Bronchitis	AY	904-9024	LP	39	Jul-95		
Asthma	AM	804-8070	P	54	Dec-95	refer to CHF	no diuretic listed
Asthma	AM	808-8181	LP	57	Oct-94	refer to death)	
Asthma	BJ	970-9811	LP	18	Aug-95		
Pneumonia	AN	401-4161	LP	35	Aug-95	no more info	
Pneumonia	BA	41-11	LP	19	Mar-95		
Pulmonary fibrosis-->PE-->DEATH	AM	801-8186	LP	72	Nov-94		
Bronchial lung CA	AK	7-178	LP	69	Oct-93	DIED	
Pneumonia--new-->small cell CA	AY	47-186	LP	?	Dec-95	refer SBO)	
Dyspnea-RLL pneumonia	AY	980-9811	LP	53	Jun-95		
Dyspnea	BH	818-8265	LP	43	Jun-95	refer neuro eval)	
Wegeners--renal dz/brain infarcts/pneumonia	AK	905-9048	LP	72	Aug-94	DIED	Nephro
Esophageal varices--hemorrhage	AN	314-3341	LP	67	Apr-94		Lasix
Small bowel obstruction	AF	43-384	HR	44	Feb-94	no surgical intervention - partial SBO	
Abdominal pain	AK	902-8043	LP	21	Nov-94	cause unknown	
Gastroenteritis/C-spine syndrome	AN	413-4588	LP	25	Apr-95		
Gastroenteritis	AK	720-7208	LP	32	Oct-95	refer	
Gastroenteritis	BJ	904-8051	LP	16	May-95	refer cholecystectomy)	
Gastroenteritis no glu or ketones given	BJ	988-9794	LP	14	[illegible]		
Gastroenteritis no glu or ketones given	BJ	989-9798	LP	15	Jun-95	refer to DKA	
Vomiting no glu or ketones given	BJ	918-9121	LP	15	Jul-95		
Abd pain/v diarrhea/dehydration no glu or ketones given	BJ	968-9777	LP	15	Nov-95		
Abd pain/vdiarrhea no glu or ketones given	BJ	970-9815	LP	16	Dec-95		
Abd pain, loaded colon	AM	802-8026	LP	42	Dec-95	refer to Rx	
Fecal impaction	AN	982-9741	LP	?	May-94	on Rx for enema	
Fecal oozing	BJ	915-9048	LP	14	Nov-95	refer sepsis refer DKA)	
Perirectal abscess	AN	986-8921	LP	23	Sep-94		
Abd pain/ketones	AN	721-7285	LP	21	Aug-95		
Abd pain/dehydration no glu or ketones given	BJ	41-11	LP	15	Jan-96	week of prior lower glucose values (50s)	
Diarrhea vomit	BJ	404-4052	LP	13	Mar-95		
Abd pain/sinusitis no glu or ketones given	BJ	404-4048	LP	11	Mar-95	refer to hyperglycemia)	
Rectal bleeding-->polypectomy	AN	981-9726	LP	67	Nov-95	refer to TIA	Lasix
Small bowel obstruction	AY	47-186	LP	?	Dec-95	refer pneumonia)	
Gastric bleed/ hypertensive crisis	AY	720-1008	LP	60	Nov-94		Diuretic
Gastric ulcer	AY	981-9733	LP	58	Sep-95		
Liver bx routine MTX rx	AY	981-9733	LP	58	Sep-95		
Small bowel obstruction? partial	AY	204-2028	LP	54	Mar-95	refer to prior cholecystectomy	
LFTs increased-Anti drug virus	AY	980-9820	LP	46	Apr-95		
Renal fx-->DVT	AM	802-8029	LP	42	Mar-95	dates don't match)	
Asleep at wheel--auto accident--resolved	AM	803-8043	LP	37	Aug-95	MD says not hypoglycemic	
Road accident	BH	810-8108	LP	?	?	Pt withdrew from study prior to accident	
Back problem	AY	204-2028	LP	?	May-95		
Fracture	AY	302-3041	LP	21	Jun-95	(reportedly no hypoglycemia)	
Trauma	AY	555-8542	LP	58	Apr-95		
Multiple fractures	AY	408-4109	LP	52	Jul-95	(reportedly no hypoglycemia)	
Fx vertebrae	AY	981-9721	LP	42	Oct-95		
Renal stone	AY	408-4132	LP	60	Jun-95		
Prostate CA-->XRT	AN	408-4348	LP	75	Feb-95	refer to dysrhythmia)	
Prostate CA	AN	417-4688	LP	65	Oct-95	refer to EKG changes)	
Orchitis	AN	412-4661	LP	52	Aug-95		
Orchitis	AO	907-9002	LP	65	Jun-95		
UTI	AO	912-9142	LP	46	Aug-95	refer to hyperglycemia-UTI)	
Hematuria--bladder CA	AO	10-211	LP	66	Dec-94	refer ulcerative colitis)	
Coumadin OD--hematuria	AK	201-2030	LP	?	Mar-95		
Hematuria--ureter dz	BJ	970-9811	LP	18	Aug-95		
Renal failure--shunt for dialysis	AN	411-4406	LP	58	Jun-95	(retinopathy/neuropathy/nephropathy)	Diuretic
Melanoma	AK	980-9808	LP	70	Mar-95		
Depression	AK	904-9150	LP	54	Jul-95	refer to org emp case)	Diuretic
Depression	AY	400-4002	LP	59	Oct-94		Diuretic
Depression-Suicide	BJ	44-88	LP	17	Dec-95	refer to hypoglycemia-seizure)	
Fever	AZ	46-91	LP	35	Aug-95		
Mononucleosis	BJ	248-2488	LP	14	Feb-95	(presentation with rash tested 3 wk	
CMV few Rx+	AK	8-215	LP	53	Oct-94		
Pyrexia dialysis	AM	907-9183	LP	29	Jan-96	dialysis patients were excluded from trial/when RF start?	
Infected CAB graft site	AN	981-9730	LP	72	Oct-94		
Allergies/rash	AY	988-9884	LP	24	Mar-95		
Sarcoid (blurred vision/leg parvesin LFTs)	AM	808-8181	LP	44	Nov-94	Rx bx/ normal Ca++/ Rx with steroids	
Anemia--barium enema	AN	981-9721	LP	64	Jan-94		Neither
ETOH--vomiting->	AY	980-9803	LP	30	Mar-95	needed glucose	
Neuropathy evaluation	BH	818-8265	LP	43	Jun-95	some dark dyspnea)	
Allergic Rxn	AN	951-9718	LP	53	Jun-95	no problems since resuming tx with LP	
Pancreatitis/peritonitis/related to drug	AO	412-4745	LP	65	Jan-95	rash present during prior insulin study - to other Rx tested but NPH	
Allergic Rxn - itchy/ facial edema 20 min p LP	BH	818-8265	LP	29	Aug-94	changed to actrapid insulin	
Basal cell CA/ DC bx started on oral agents	AN	988-9743	LP	65	Mar-94	retinopathy	
Peripheral vascular disease-angio	AY	980-9811	LP	[redacted]	Dec-95	(refer cellulitis and R ulcer)	
Neuropathy--DC from study	AN	740-7445	LP	76	Mar-94		
Special diet [illegible] for glucose control	AN	205-2151	LP	?	May-95		
Kidney disease--AMP elevated creat 832 mmol	AK	904-9150	LP	53	Mar-95		Diuretic
Cirrhosis	AN	745-7521	LP	?	Sep-95	neuropathy	
Diabetic AMI	AN	518-5421	P	54	Aug-94	no more info	
Amputee--ligation AMP	AN	518-5301	LP	?	Dec-94		
Gangrene--debridement	AY	980-9811	LP	65	Aug-95	complicated by cellulitis (refer)	
Cellulitis/ ulcers	AY	980-9811	LP	65	Dec-95	refer R ulcer)	
Ligation [illegible] AMP [illegible]	AY	408-4103	LP	62	May-95	refer to major hypoglycemia 1 mo earlier)	

heart

Condition	Study	ID #	Rx	Age	Occurred	Comments	Other Rx
Pregnancy	AA	5-123	LP	27	Jun-93	LP OC healthy baby	
Pregnancy	AE	5 Jan	HR	25	Aug-93	healthy baby	
Pregnancy	AG	6-78	LP	38	Aug-93	healthy baby	
Pregnancy	AK	42 27	LP	24	May-94	healthy baby	
Pregnancy	AK	A3 50	P	26	Sep-94	unknown f u	
Pregnancy	AK	907 9191	LP	31	Feb-94	LP OC healthy baby	
Pregnancy	AN	990-9905	LP	18	Nov-93	LP OC baby with dysplastic kidney	
Pregnancy, spontaneous AB	AY	803-8066	LP	32	Nov-95		

Condition	Study	ID #	Rx	Age	Occurred	Comments	Other Hx
Strabismus-->surgery	AY	602-6024	LP	?	Sep-94		
Cataract surgery	AY	602-6031	LP	66	Aug-95		
Cataract surgery	AN	411-4405	LP	59	Apr-95	(nephropathy, retinopathy)	Delix
Max sinus surgery	AK	720-7209	LP	32	Feb-95	(refer)	
Tracheotomy	AH	858-8874	HR	52	Aug-93	(tracheotomy for vocal cord paralysis (etiology ?)	Diuretic, Digoxin
Bronchoscopy to remove inhaled insulin cap	BJ	X5-114	LP	18	Oct-95		
Tonsillectomy (bc of persistent inflammation)	BJ	248-2470	HR	?	Jun-95		
Tonsillectomy	BJ	304-8051	LP	16	Apr-95	(refer to gastroenterist)	
ENT surgery	AC	412-4421	LP	35	Nov-94	(refer to hypoglycemia)	
Septoplasty	AN	990-9902	LP	20	Dec-93		
Septoplasty	BJ	969-9793	LP	16	Sep-95	(refer DKA)	
Esophageal CA-->surgery-->DEATH	AN	316-3383	LP	60	May-94	hx CVD	
Thyroidectomy	AN	418-4565	LP	29	Jun-95		
Pleural effusion-->surgical procedure	AN	421-4727	LP	64	Nov-93	(refer prostate surgery)	
Enderterectomy	AO	71-544	LP	?	Sep-95		
Appendicitis-->surgery	AC	912-9145	LP	55	Nov-94		
Appendicitis suspected-->surgery	BJ	519-5004	LP	?	Sep-95		
Appendectomy	BJ	918-9123	LP	11	Jul-95		
Cholecystectomy	AK	400-4047	LP	67	Dec-94		
Cholecystitis-->lap-->pentonitis	AN	412-4664	LP	72	May-94	(reonopathy, neuropathy)/PVD (refer eye surgery)	
Cholecystectomy	AY	45-124	LP	67	Feb-95		
Cholecystectomy	AY	204-2026	LP	54	Feb-95	(refer subsequent SBO)	
Hernia repair	AK	854-8542	LP	51	Feb-94		
Carpal tunnel surgery	AK	600-6005	LP	30	Oct-94		
Carpal tunnel surgery	AY	964-9675	LP	46	Jan-95		
Knee replacement	AK	907-9170	LP	72	Jun-95		3 BP Rx
Joint mouse-->knee surgery	AN	416-4528	LP	23	Apr-94		
Knee surgery	AN	417-4544	LP	29	May-95		
Knee surgery	AN	420-4708	LP	57	May-95		
Synovitis-->knee surgery	AN	907-9343	LP	49	Mar-95		
Knee replacement	AO	83-704	LP	71	Apr-95		
Knee surgery for sports injury	BJ	754-7564	HR	15	?		
Lumbar stenosis-->laminectomy	AN	412-4670	LP	68	Aug-94	(neuropathy)	
Neuro sx-->back surgery	AN	417-4686	LP	59	Dec-94		
Trauma-->spinal fusion	AO	83-706	LP	46	Feb-95		
Gonarthrosis-->surgery-->FALL	AN	403-4283	LP	70	Jan-95	no more info	
Osteotomy/gonarthrosis	AO	402-4781	LP	54	Sep-94	(refer to CABG)	
Pin for fx	AY	964-9662	LP	67	Jun-94		
Fall (? cause)-->fx-->surgical reduction	BJ	987-9754	LP	13	Aug-95		
Renal stone-->surgery	AK	905-9020	LP	60	May-95		Natrilix
Prostate surgery	AM	802-8201	LP	71	Nov-95	(manic depression)	
Prostate surgery	AN	421-4727	LP	64	Aug-95	(refer pleural effusion)	
Penile implant	AY	962-9841	LP	49	May-95		
Vancocystotomy	BJ	608-6093	LP	?	Jun-95		
? surgical procedure	AN	602-6127	LP	?	?	no more info	
Elective Surgery	BH	817-8249	LP	x40	Jun-95		
Benign breast lesion--> surgery	AK	301-3022	LP	45	Oct-93		
Breast lesion-->bx-->lymphoma	AN	722-7207	LP	61	Oct-95		Digoxin
Breast CA-->surgery-->chemo	AN	517-5328	LP	?	Jan-96		
Cervical polyp-->surgery	AN	913-9383	LP	51	Jul-95		
Oophorectomy	AN	966-9741	LP	40	Apr-95		
Hysterectomy	AY	723-7232	LP	41	Mar-95		
Tubal ligation	AN	417-4543	LP	38	May-95		
Endometroablation	AY	966-9695	LP	45	Nov-94		

Condition	Study	ID #	Rx	Age	Occurred	Comments	Other Rx
Hyperglycemia/Bulimic/depression	AK	11 282	LP	50	Mar 95		Diuretic
Hyperglycemia	AF	402 4788	HR	58	Jun 93	obese with aberrant insulin needs	
Hyperglycemia	AK	20 501	LP	46	Mar 95	underlying pneumonia (refer to with reg ins while in hosp	Diuretic
Hyperglycemia c DKA (abcess)	AA	621 4068	LP	61	Nov 95	(also retinopathy)	
Hyperglycemia c ETOH	AA	720 7218	LP	28	Nov 94		
Hyperglycemia/ Severe HTN	AK	904 9144	LP	59	May 94	(refer)	Diuretic
Hyperglycemia/ Confusion	AK	904 9144	LP	69	Jan 95	(refer)	Diuretic
Hyperglycemia (presumably)	AK	900 8008	LP	65	Dec 94	event not described, no underlying infection	
Hyperglycemia (+ketones & acidosis) (severe laryngitis)	AN	902 9161	LP	20	Oct 94	allergic rxn to antibiotics (refer another hyperglycemia episode)	
Hyperglycemia (+ketones/ abd discomfort/ sore throat	AN	902 9161	LP	21	May 95	(refer to prior episode of hyperglycemia)	
Hyperglycemia c DKA (gastroenteritis)	AM	800 8008	LP	46	Nov 95	(refer to other hyperglycemia)	
Hyperglycemia c DKA (lung infection/asthma)	AM	801 8162	LP		Dec 95		
DKA (2nd hospitalization)	AM	805 8087	LP	24	Dec 94	cause ?	
DKA	AM	807 8145	LP	42	Jan 95	cause ?	
DKA (2nd hospitalization/DC from study)	AN	203 2107	LP	70	Aug-94	cause ?	
Hyperglycemia ?	AN	421 4721	LP	55	Jan-95	(refer to + angio)	
DKA (abd pain) (sore throat)	AN	905 9205	LP	17	Jun-95	no more info	
Hyperglycemia (otitis externa)	AN	907 9348	LP	51	Apr 95		
Hyperglycemia (?DKA) (->ARDS-->DEATH (but pt NrCOM)	AN	913 9361	LP	45	Oct 94	HCO3<5-->Na+ 75+ for days >K+5 &/ No dz/ No autopsy	
Hyperglycemia (infectious mono with hepatic involvement)	AN	984-9667	LP	43	Sep-95	(refer to hypoglycemic seizure)	
Hyperglycemia (ulcerative colitis->steroids)	AO	10-211	LP	66	Feb 95	(refer to bladder CA)	
Hyperglycemia (?resp infection) (+ketones)	AO	62-121	LP	19	Nov 94	(refer to hyperglycemia)	
Hyperglycemia (ran out of LP) (vomiting)	AO	62-121	LP	79	Nov 95	another episode) -->ER (refer to hyperglycemia)	
Hyperglycemia (UTI)	AO	912-9142	LP	46	Jan-95	(refer UTI)	
Hyperglycemia (glu 13 mmol/L urine 6+ pH 7.42 ketones-)	BJ	915-9043	LP	11	Aug-95	abd pain and vomiting	
Hyperglycemia (pneumonia)	BJ	916-9127	LP	12	Jul-95	ESR normal	
urine +for glucose and ketones	BA	X1-4	LP	[illegible]	Oct 94	(?GI and URI sx)	
Hyperglycemia (glu 300 mg/dl/abd pain/NL urine ketones+	BJ	404-4048	LP	11	Jan 95		
Ketonuria/ N/V (glu not tested/ ?food poisoning in Bangladesh	BJ	754-7569	LP	17	Apr 95		
DKA	BA	X1-11	LP	18	Jan 95	(refer pneumonia)	
DKA (glu 418 acetone 1 8 abd pain V dehydration)	BJ	X1-4	HR	12	May 95	(obese 68 kg/prior episode-reported where?)	
DKA (glu 392 acetone 1 8 pH 7 2 V abd pain)	BJ	X1-4	LP	12	Jul-95	(refer to prior and subsequent episodes)	
DKA (glu 621 acetone 1 2 V)	BJ	X1-4	LP	12	Jul-95	(refer to prior and subsequent episodes)	
DKA (acetone 1 2 V)	BJ	X1-4	LP	12	Sep-95	(refer to prior and subsequent episodes)	
DKA (N V)	BJ	X4-77	LP	15	Jan 96		
DKA (difficulty seeing->DC insulin)	BJ	X5-108	LP	13	Aug-95	(gluc 397 urine ket large) (prior hx of same)	
DKA	BJ	405-4082	LP	15	Dec 95	(question of non-compliance	
DKA (gluc 340 ketones mild GI sx hyperventilation)	BJ	409-4121	LP	16	Aug-95	(questio[illegible] non-compliance (refer to DKA) unclear RE insulin type	
DKA (gluc 800)	BJ	409-4121	HR	16	Jan 96	(question of non-compliance (refer to DKA) unclear RE insulin type	
DKA (glu 23 mmol/l HCO3 15 mmol/L)	BJ	701-7008	HR	19	Jun 95		
DKA (glucose 34 8 mmol/L) (subsequent pharyngitis)	BJ	703-7032	HR	17	May 95		
DKA	BJ	803-8081	LP	16	Sep-95	(refer to DKA)	
DKA	BJ	803 8081	LP	16	Sep-95	? relationship to PID (refer to DKA)	
DKA (glu 34 3 mmol 4+ketonuria)	BJ	862-8505	LP	17	Sep-95		
DKA (gluc ? pH 6 95 ketones 3+/URI sx)	BJ	915-9004	HR	12	Jul-95	(refer to Hyperglycemia)	
Hyperglycemia-->hospitalization for stabilization +ketones	BJ	915-9004	LP	12	Nov-95	(refer DKA) gluc 28 8 mmol/l	
DKA (glu 25 mmol/l pH 7 12 ketones 2+) (GI sx pharyngitis)	BJ	915-9008	HR	16	May-95		
DKA (glu 12 5 mmol/l pH ? 27 ketones trace) no infection	BJ	915-9030	LP	13	Apr-95	(? bc of reduced Nx/refer DKA)	
DKA (glu 6+ ketones 4+) (back pain V)	BJ	915-9030	HR	14	Jun-95	(refer DKA) (pt in hosp 21 7 June and then readmitted 1 day later)	
DKA (glu 36 7 pH 8 99 ketones 3+)	BJ	915-9037	LP	17	Nov-95		
DKA (GI sx)	BJ	915 9004	LP	12	Mar-95		
DKA (gluc 15 4 ketones++ pH 7 28/GI sx)	BJ	915-9048	LP	14	Dec-95	(refer ketosis refer fecal loading)	
DKA (gluc 12 mmol/l pH 7 3* BE 4 8 urine +ketoglu)	BJ	915-908	LP	14	Jan-96	abd pain/V/dehydration (refer fecal loading ketosis DKA)	
DKA (change in habits)	BJ	987 9758	LP	16	Apr 95		
DKA (URI) (unable to manage at home)	BJ	988-9775	LP	17	May 95		
DKA (?compliance)	BJ	988-9744	LP	14	Jul 95	(refer septoplasty)	
DKA blamed on reduced effect ? bc of storage)	BJ	989-9789	LP	15	Dec 95	(refer to gastroenteritis)	
Ketosis (glu 10 2 mmol ketones+ GI sx) (? ate old food)	BJ	915-9048	LP	13	Apr 95	(refer fecal loading refer DKA)	
Hyperglycemia (gave LP instead of U bc of cap color change)	BJ	X4-78	LP	13	Aug 95		
Hyperglycemia (gave LP instead of N in evening-high am FBG	BJ	984-9485	LP	15	Jul-95	(no hypoglycemia reported)	
Hyperglycemia-esophagitis-->hosp for control	AO	56-103	LP	19	Aug-95		
Poor glucose control-->hospitalization	AY	409-4125	LP	68	Feb-95		
Erratic glucoses-->hospitalization	AY	986-9702	LP	46	Oct-94		
Seizures	AN	802-8022	LP	24	Apr 94	limited wlu	
TIA vs hypoglycemia (blurred vision/speech disorder/fall)	AN	800-8181	LP	70	Nov 94	limited w	
Hypoglycemia-->fall-->fracture	AK	720-7202	LP	51	Oct 93	no glucose tested/no syncope w/u (retinopathy)	
Hypoglycemia-->LOC-->burns-->grafts-->infection	AK	900-9004	LP	28	Oct 94	while cooking/glucose p episode 4 3 mmol/ no syncope w/u	
Hypoglycemia (unexpected/no warning)	AM	802-8104	LP	?	May-95	rx oral glucose	
? Hypoglycemia	AN	308-3182	LP	38	Mar 94	rx glucose injection/ no more info	
Hypoglycemia	AN	407-4784	LP	33	May-95	fell asleep after noon meal-->Rx c IV glucose	
Hypoglycemia-->LOC	AN	800-8071	LP	22	Sep-94	missed food-->Rx c IV glucose	
? Hypoglycemia/p LP-->lunch-->then glucose labs-->seizure	AN	984-9667	LP	43	Mar 95	no more info (refer to hyperglycemia-mono)	
Hypoglycemic coma/ vomiting-->hematemesis	AN	990-9814	LP	29	Aug-94	(had seizure witnessed by EMTs)	
Hypoglycemia-->LOC 2 hr p LP-->Rx with IV glucose	AO	412-4421	LP	35	Nov-94	(refer ENT surgery) (prior hypoglycemia ?OAE)	
Hypoglycemia (evening-post LP)-->coma	AY	240-2403	LP	34	Aug-95	rx c IV glucose	
Hypoglycemia-->neuro findings	AY	203-2010	LP	29	Jun-95		
Hypoglycemia (sc glu 3 3mmol-->eat to eat-->LOC x6 hr	AY	986-97 3	LP	42	Mar 95		
Hypoglycemic seizure (Was dressing Mr Dew 8x9 eaten)	BJ	X4-86	LP	17	Jul 95	(unclear when event occurred if ate lunch if gave noon LP	
Hypoglycemia-->LOC (glucose 3 2 mmol in hospital)	BJ	248-2485	LP	?	Aug-95	(eventually responded to IV glucose)	
Hypoglycemic seizure (2 8 mmol) shortly p eating and LP inj	BJ	408-4080	LP	14	Apr 95	had LOC+had+urinary incontinence (refer tracheitis hypo coma)	
Hypoglycemic seizure-coma (glucose 1 05 mmol)	BJ	408-4080	LP	14	Jun-95	(refer tracheitis and prior probable hypoglycemic seizure)	
Hypoglycemia-->coma	BJ	408-4109	HR	13	Mar 95	last severe hypoglycemia 7/95	
Hypoglycemia	BJ	520-5023	HR	?	Jul-95	(refer to hypoglycemia/ no more info	
Hypoglycemia	BJ	520-5023	HR	?	Aug-95	rx c IV glucose/ (refer to hypoglycemia)	
Hypoglycemia-->seizure ~5 AM	BJ	701 7008	LP	14	Jun-95	to bed early BG 10-15 mmol/l no other habit change Rx c glucagon	
Hypoglycemia-->glucagon-->IV glucose+hospitalization	BJ	753-7544	LP	15	Oct 95		
Hypoglycemia (2 1 mmol/L)-->coma after bruing	BL	970-9814	LP	15	Jan-96	rx c IV glucose	
Gave LP instead of U	AK	7-179	LP	69	Oct-95	self-monitoring	Diuretic
Gave LP by accident	AM	804-8088	LP	36	Apr 94	extra food-->no hypoglycemia	
Loss of consciousness	AK	7 164	LP	58	Apr 94	substituted LP for U neuropathy	Diuretic
Hypoglycemia (problems with pen-wrong dose given)	AY	409-4132	LP	60	Jun-95	(refer renal stone)	
Hypoglycemia (wrong dose given)	BH	811-8127	Actra	25	Nov-94		
Hypoglycemia (wrong dose)	BH	813-8167	LP	56	Aug-94		
?Wrong dose given when using pen instead of vial	BH	814-8184	Actra	45	Jun-94	sequelae ?	
Hypoglycemia (skipped snack/ebstrix glu 70-->HA V)	BJ	X2 35	HR	12	Apr 95	rx c IV glucose	
Hypoglycemia (gave LP instead of N)	BJ	X4 82	LP	13	Aug-95	self tx c carbohydrate	
Hypoglycemic coma (gave R instead of N)	BJ	144-1442	HR	16	May 95	(responded to IV glucose	
Hypoglycemia (used N instead of LP at 6 pm) (9 pm glu 2 4)	BJ	803-8037	LP	11	Apr 95	(why did hypoglycemia occur so relatively early ?)	
Hypoglycemia (used S instead of U)	BJ	803-8041	HR		Jan-95	rx c carbohydrate	
Hypoglycemia (used R instead of N at bedtime) Rx glucagon	BJ	987 9755	HR	14	Aug-95		

The abstracts and articles presented were reviewed. Ann Reb was provided with a copy as requested. Relevant articles were reviewed by Mike Fossler.

Major points were discussed with Drs. Sobel and Fleming.

6/7/96
Elizabeth Koller, M.D.

CC: HFD 510 Misbin/Koller/Fleming/Sobel

6/7/96

FEB 28 1996

NDA 20-563 23 February 1996

Eli Lily and Company
Lily Corporate Center
Indianapolis, Indiana 46285

Submission: 13,14 Mar 95

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary

Humalog (insulin lispro, recombinant DNA origin)

Synthetic (recombinant DNA origin, E. coli derived) Analog of Human Insulin [Lys (B28)-Pro (B29)]

Indicated Use: Control of blood glucose; treatment of diabetes mellitus.

Dosage: Individualized by the physician.

Related: IND

Form: Humalog is a sterile solution for subcutaneous injection. It should not be used intramuscularly. The concentration of Humalog is 100 units/mL (U-100).

Table of Contents

IND - Original Review of IND dtd. 12,13 Jul 90 (attached).
2,3 etc. - This review.

cc: Original NDA 20-563; HFD-345; HFD-502 JDeGeorge;
HFD-510 NDA 20-563; HFD-510 AJordan; HFD-510 DHertig

David H. Hertig
Pharmacologist

AJordan 2/28

Foreign Studies: None

Preclinical Studies: LysPro = LY275585
Pharmacology. See also Original Review IND dtd. 12,13 July 1990 (attached).

Cardiovascular and Respiratory Effects in Anesthetized Dogs: (Report 1) (See also IND , review p.3)

When anesthetized male beagles received 0.1 U/kg LysPro or Humulin BR Diluent by i.v. bolus injection (to maximize exposure) it is reported that no toxicologically important changes in cardiovascular or respiratory parameters were observed. However, there were slight prolongations of the QRS duration (max. 9% at 10 min) and Q-T_c interval (max. 10% at 5 min). The increases in QRS duration and Q-T_c interval were reported to be similar to that seen after administration of 0.1 U/kg Humulin R.

Cardiovascular Effects in Conscious Rats: (Report 3)

As a single s.c. injection of 1, 3, or 10 U/kg LysPro had no significant effects upon mean arterial blood pressure or heart rate in conscious male Sprague-Dawley rats.

Effects on Renal Function and Electrolyte Excretion in Fischer 344 Rats: (Report 2)

A single s.c. dose of 1, 3, 6 U/kg LysPro followed by oral saline caused an increase in urine electrolyte excretion resulting in elevated osmol excretion and osmolal clearance. Rats in all treatment groups maintained serum electrolyte (sodium) and osmol balance and thus the sponsor did not consider these changes to represent an adverse renal effect.

Gastrointestinal Effects in Mice: (Report 4)

Gastrointestinal motility, as evidenced by charcoal meal transit, was not affected by s.c. doses up to 3 U/kg in male mice.

Pharmacological Evaluation in Isolated Smooth and Cardiac Muscle Preparations In Vitro: (Report 5)

Agonist as well as antagonist activity was evaluated against standard agonists at concentrations of $1x10^{-9}$ to $1x10^{-5}$ M. (Molar concentrations equivalent to 5.81 ng/ml to 58.1 µg/ml LysPro.)

LysPro did not significantly contract or relax the guinea pig ileum, estrogen-primed rat uterus, or rat vas deferens, nor did it significantly inhibit or potentiate the twitch height response induced by field stimulation of the rat vas deferens. No significant effects were seen on the inotropic or chronotropic activity of the spontaneously beating guinea pig atria. The twitch height response to field stimulation in the guinea pig ileum was significantly decreased at concentrations of $\geq 1x20^{-7}$ M.

$1x10^{-5}$ M mildly antagonized the response of the ileum to acetylcholine, the field-stimulated guinea pig ileum response to angiotensin I, and slightly antagonized the inotropic response of the atria to isoproterenol; the chronotropic response of the atria to isoproterenol was not affected. $1x10^{-5}$ M mildly antagonized the response of the vas deferens to norepinephrine and mildly potentiated the response of the estrogen-primed uterus to oxytocin.

Thus, studies with LysPro at $\leq 1x10^{-5}$ M did not exhibit agonist activity in the ileum, atria, estrogen-primed uterus, or vas deferens. Only the highest concentration tested, $1x10^{-5}$ M (10 micromolar) may slightly antagonize cholinergic, adrenergic, and angiotensin receptors, and may potentiate oxytocic

receptors. [It is reported that most clinically relevant agents are active in smooth muscle in vitro at nanomolar concentrations and thus, effects seen at higher micromolar concentrations are not considered clinically relevant.]

Acute Behavioral Effects in Mice: (Report 6)

LysPro did not alter pain thresholds or interfere with autonomic responsiveness in CD-1 male mice tested with s.c. doses of 0, 0.03, 0.3, and 3 U/kg. Dose dependent reductions were seen in spontaneous ambulatory and non-ambulatory activity. At the high dose hexobarbital-induced sleep times were increased and sensorimotor responsiveness decreased. Electroshock or pentylenetetrazol evaluation showed no changes in convulsive thresholds. There was, however, a dose-related trend toward increased seizure thresholds. Body temperature and neuromuscular function were unaffected. [The sponsor reports that based on this information, 3 U/kg LysPro may produce sedation or CNS depression and decrease sensorimotor responsiveness; and that single therapeutic doses of LysPro would not be expected to adversely affect the other CNS functions evaluated.]

Studies in the Conscious Female Pig: (Report 10)

LysPro was compared with a soluble human insulin formulation, Humulin BR in conscious female pigs. LysPro was more rapidly absorbed from subcutaneous tissues and was more rapid acting than the soluble human insulin formulation. There was a decrease in LysPro arterial concentrations in the last hour of infusion, possibly indicating an increase in metabolic clearance at this time. Hepatic removal of LysPro however, remained nearly constant during the infusion. Except for a decrease in the intestinal uptake of LysPro, splanchnic handling of both insulin and LysPro are reported to be near-equivalent. Disposal of glucose by peripheral tissues as well as the splanchnic bed was nearly equivalent during the infusion of either LysPro or insulin.

The time course of suppression of glucose production in the liver was similar for both compounds. Removal of insulin or LysPro by the liver, corresponding to a 50% extraction, suggests that the liver is the principal site of insulin action. However, at the hindlimb muscle, the principal site of action, the kinetics of LysPro and insulin show a significant deviation. The action of both substances with respect to glucose remains very similar, however, human insulin is removed in hindlimb muscle with an extraction rate of ca. 25-30% (maintained throughout the infusion period) while LysPro shows a lower rate of removal averaging 10-15% near the beginning of infusion and then rapidly decreasing to an average uptake near zero. There appears to be a dissociation of insulin action on glucose removal from its extraction out of the circulation; i.e. glucose stimulated removal by the two compounds is parallel and reaches a level of ca. 30% in 2 hrs. in the hindlimb while their extraction varies widely in this muscle.

Comparisons of rates of subcutaneous absorption in the pig model of three LysPro formulations differing slightly in zinc and preservative compositions showed the formulations to be almost identical and to exhibit more rapid absorption than the soluble human insulin formulation. Equivalent bioeffectiveness was demonstrated by nearly identical rates of glucose infusion (reported to be actual and cumulative).

In vitro Analysis of Lys(28), Pro(B29) Human Insulin (LY275585): (Report 9)

Human insulin and LY275585 were equipotent [ED_{50}: 21 ± 12 vs 26 ± 5.2 pM respectively (n=3, p=NS)] in terms of potency (81%) at stimulating glucose transport into isolated human adipocytes. LY275585 was reported not to appear different than human insulin in binding (differences did exist) to the insulin receptor in human liver [membranes (potency rel. to Ins 68%) and solubilized receptor (92%)], skeletal muscle (63%) and adipocytes (75%) (low numbers precluded statistical analysis). Comparison of LY275585 and insulin in terms of affinity for human skeletal muscle IGF-I receptor in a sole experiment reportedly showed no apparent difference. Both insulins were ca 400-fold less potent than IGF-I itself.

In vitro analysis - Stimulation of Growth of Human Mammary Epithelial Cells (HMECs) and Binding to the HMEC IGF-I Receptor: (Report 8)

In vitro studies generally indicated that LysPro was essentially equivalent to human insulin with respect to insulin receptor binding and glucose transport into adipocytes. LysPro showed a greater binding affinity to the IGF-I receptor although this was not manifested in a greater mitogenic effect in a functional-type assay such as stimulation of growth of human mammary epithelial cells (HMEC) in culture by insulin and insulin analogs. The ED_{50} was 16.0 ± 3.0 for human insulin vs 18.6 ± 4.0 nM for LY275585 and 4.84 ± 0.69 for Asp(B_{10}) insulin. LY275585 was approximately 1.4 times more potent than insulin, but ca 2.5 x less potent than Asp(B_{10}) insulin in terms of binding to the HMEC IGF-I receptor. [A 12 mo. toxicity study performed by on Asp(B_{10}) insulin showed an increased incidence of breast tumors in rats associated with treatment with Asp(B_{10})-insulin, but not normal insulin (Drejer, K., Diabetes/Metabolism Reviews 8, 259-286, 1992.).]

ADME Studies: Lilly Research Laboratories. Lot:
Pharmacokinetics, Disposition, and Metabolism of LY275585:

The pharmacokinetics of LY275585 were studied in rats and dogs.

Rats: When Fischer rats were given single s.c. injections of 2 and 4 units/kg LY275585, the peak concentration (C_{max}) of insulin-like immunoreactivity (IRI) was 7.07 (at 10 min) and 19.9 nmol/L (at 20 min), respectively. The area under the plasma concentration curve for 2 U/kg was 4.49 nmol·h/L (AUC_{0-4h}) and that for 4 U/kg was 12.3 nmol·h/L (AUC_{0-4h}). For the low dose the concentration of IRI fell from the peak with a half-life of 17.76 min and was below detectable limits by 150 min after administration. Half-life for the high dose was 19.0 min. and IRI was below detectable limits at 180 min after injection.

Maximum glucose suppression with 2 U/kg was 55% of controls at 45 min (68% of controls at 10 min), and 53% of controls at 75 min (73% of controls at 20 min) with the high dose. Plasma glucose returned to control levels by 120 min for the low dose and by 240 min for the high dose.

Male Fischer 344 rats received ^{125}I-A14-LY275585 (Lot intravenously (24.4 ng/kg, 1.48 µCi/animal) and the levels and chemical nature or ^{125}I-radioactivity were determined in plasma, liver and kidney.

Radioactivity was cleared rapidly from the plasma. Compared to 1 min post-injection levels ca 15% of the radioactivity was present at the 3 min time-point. Following a rapid distribution phase, plasma radioactivity was slowly eliminated over the next 3 hrs. Liver and kidney quickly took up radioactivity with peak levels 5 min after injection. For the kidney the per gram of radioactivity was 3-4 times higher than that of the liver. Both tissues (major organs involved in the clearance of human insulin) showed a rapid clearance with ≤10% of peak levels remaining at 3 hrs.

Radioactivity in liver and kidney was predominantly in the form of ^{125}I-peptides/MIT(monoiodotyrosine) or inorganic iodide. It is reported that the findings are consistent with the rapid proteolytic metabolism of ^{125}I-LY275585 in the liver and kidney to the ultimate metabolite ^{125}I-MIT, with subsequent deiodination to yield inorganic iodide.

In another study ^{125}I-(A14)-LY275585 (Lot was given to male Fischer 344 rats subcutaneously (44 ng/kg, 2.09, 2.11 µCi/animal). Radioactivity in plasma was detectable 5 min after dosing. Plasma radioactivity reached a plateau at 90 min (C_{max} was 0.94% of dose/ml plasma at 3 hrs.) where it remained over the 4 hrs examined.

Trichloroacetic acid (TCA) and silver nitrate were used to examine the degradation of ^{125}I-(A14)-LY275585 to small peptide intermediates and the subsequent metabolism of these intermediates to inorganic iodide. Anion exchange was also used to determine metabolic profiles of protein-associated radioactivity in plasma.

However, it is reported that although the data provide insight into the rates of catabolism of ^{125}I-(A14)-LY275585, the plasma kinetics of ^{125}I-radioactivity does not accurately represent the kinetics of native LY275585.

A single daily 2 U/kg (59.6 µg/kg) dose of LY275585 was given subcutaneously to male Fischer 344 rats for 7 consecutive days. LY275585 plasma concentrations were obtained from the rats after a single injection of LY275585 on Days 1, 4, and 7. Plasma insulin-like immunoreactivity (IRI) concentration was ascertained by

Peak plasma concentrations Days 1, 4, and 7 were 5.50, 5.94, and 5.96 nmol/L respectively, after 15 min. The IRI plasma concentration decreased on these days from the peak level with a t½ of 12.7, 15.7, and 18.0 min, respectively; IRI levels were below detection after 90 min. AUCs on these days were 2.79, 3.45, and 3.63 nmol·h/L, respectively. LY275585 did not accumulate over the time-course of study.

Urine and feces were collected over a 72 hr period following subcutaneous administration of ^{125}I-(A14)-LY275585 (45 ng/kg, 1.57 µCi/animal) to male Fischer rats. Animals were then sacrificed and residual ^{125}I-(A14)-LY275585 was determined in whole blood, plasma, lung, thyroid, heart, skin, skeletal muscle and duodenum.

Urine contained the majority of administered radioactivity [(78.7%) 72.5% in first 24 hrs], with a minor amount in the feces (3.77%). The thyroid glands contained the majority of tissue radioactivity (3.07%). Overall recovery of radioactivity was 87.3%. The majority of urinary radioactivity (81.3%) was soluble in 15% trichloroacetic acid indicating an association with small peptides, and monoiodotyrosine or presence as free ^{125}I-iodide. It is reported that high levels of radioactivity in the thyroid that persist beyond 72 hrs are consistent with the degradation of ^{125}I-(A14)-LY275585 to small ^{125}I-peptide fragments and ultimately inorganic ^{125}Iodide. The process probably represents uptake of free iodide into the thyroid with subsequent incorporation into thyroglobulin.

Following s.c. administration of 4 U/kg (119.2 µg/kg) LY275585 to male Fischer 344 rats, anion chromatography of plasma at 10 and 45 min showed the presence of a single immunoreactive peak (≥99%) with retention characteristics of LY275585. Recovery of insulin-like immunoreactivity from plasma ranged from 60-70%.

Dogs: Vehicle - Sterile diluent for Humulin BR

1 U/kg (29.8 µg/kg) LY275585 was administered subcutaneously to male beagle dogs and the plasma concentration was determined by along with plasma glucose levels.

The IRI peak plasma concentration was 1.70 nmol/L and the C_{max} was reached 45 min after injection. IRI plasma concentrations declined after peak with a t½ of about 1.15 hr. The $AUC_{0\text{-}6h}$ was 3.80 nmol·h/L. At 6 hrs after injection IRI was detectable (0.05 nmol/L) at about the same levels as in untreated animals.

Plasma glucose was decreased to 73% of controls at 20 min and by 75 min maximum depression was 66% of control. By 180 min plasma glucose had returned to control levels.

A 1-Day Blood Level Study in Fischer 344 Rats Given a single Subcutaneous Injection of LY275585: Lilly Research Laboratories Study R43393. Report 26 May 1994. Lot: Q.A.: Present.

Groups of 30/sex Fischer 344 rats received a single s.c. dose of 0, 20, 200 U/kg LY275585 and blood was collected over 6 hours (5/sex/time period).

All rats survived and serum concentration showed considerable variability. LY275585 was rapidly absorbed with maximum serum concentrations being achieved by 0.5 hr. Elimination was rapid with a terminal half-life of 0.5 hr. or less. Compared to males, females had a greater clearance (56.0 vs 34.8 ml/min/kg F vs M low dose clearance and 29.0 vs 23.5 ml/min/kg F vs M high dose clearance) and volume of distribution (2.70 vs 1.36 L/kg F vs M low dose and 0.67 vs 0.57 L/kg F vs M high dose) with the difference being more pronounced for the lower dose.

However, both sexes had consistent differences in distribution. The ten-fold increase in dose resulted in increases in C_{max} greater than 10-fold (M;F combined 210.3 vs 2535 ng/ml and AUC 266.1 vs 4512 ng-hr/ml). LY275585 disposition was saturated between doses and clearance was reduced by 30% or more as the dose was increased.

Through 2 hours after administration the magnitude and duration of the decrease in mean blood glucose were similar (ca 50%) for both dose groups suggesting saturation of the insulin receptor sites. The return of mean blood glucose to predose values at 4 to 6 hrs. after dosing was delayed (a longer duration of action) for the 200 U/kg group and remained slightly below control values (ca 7%) at 6 hrs.

Acute Toxicity Studies with LysPro: See also IND Review dtd. 12 Jul 90. New Formulation with increased m-cresol preservative. TR 20. Study R30493.
Bulk Lot Formulated Lot . [Each ml contained glycerin, 16 mg; m-cresol, 1.6 mg: phenol, 0.65 mg; sodium phosphate dibasic, 2 mg in water for injection. Sterile Diluent for Humulin was also used.]
Rat: Fischer 344
Neither Vehicle control nor 10 U/kg LY275585 s.c. produced any deaths in 5/sex/group. No signs of toxicity were observed and thus no adverse toxicity was associated with the change in formulation.
Thus S.C. - Median Lethal dose = > 10 U/kg

6-Month Subcutaneous Toxicity Study of LY275585 (Human Insulin Analog) in Fischer 344 Rats: Lilly Research Laboratories. May 1993. Study R15792. TR 17. Lot: assume 100 U/ml (Bulk lot . Start: Mar 92. Q.A. - Present.

Dose: 0, 5, 20 U/kg for 6 months
Vehicle vol. 2 ml/kg

No. Animals: 15M;15F per group.
Males 149.0 ± 7.5 g Females 113.1 ± 5.0 g Age - 7 weeks

Note: Test article decreased in potency by ca. 5% (103.86 initial - 98.73% final) throughout duration of study.
Average dose received ca. 4.6 U/kg and 19.3 U/kg.
Buffered Vehicle - 16 mg Glycerin, ACS and 2 mg Sodium Phosphate Dibasic, ACS per ml in purified water. - Control solution = commercially available Sterile Diluent for Humulin diluted with vehicle to achieve a conc. of 0.109 mg phenol/ml.

Results:

One male in each dose group died unrelated to treatment [low dose - mononuclear cell leukemia; high dose - hypoglycemic shock due to lack of food (feeder malfunction) post dose].

Clinical observations showed no apparent treatment related findings.

Body weight gain increased significantly during the first 3 months in treated males (similar to controls at termination) and sporadically throughout treatment in females (increased at termination by 12.5% low and 11.2% high dose).

Food consumption was statistically significantly increased in high dose females during the last 3 months of treatment. Mean efficiency of food utilization was significantly increased during the first 3 months in treated males of both doses and sporadically in females of both doses.

Ophthalmologic exams revealed no treatment-related effects. The incidence of retinal degeneration seen in all groups was less in the high dose group.

Hematological examination revealed several statistically significant findings, however, they were indicated as not being apparently treatment-related

changes since the magnitude was negligible, they were not consistent and not in a dose related pattern.

Clinical chemistry showed cholesterol and/or triglyceride values that were mildly decreased in both doses of males and/or females (possibly a pharmacological effect of the compound). Other changes of a small magnitude included mildly decreased albumin in high dose females at 3 months. At 6 months high dose females showed decreased total protein attributable to decreased albumin (ca.0.9 fold) and globulin (ca. 0.9 fold). AST and ALT were minimally decreased (ca 0.8 and 0.7 fold, respectively in low and high dose males and females. Total bilirubin was mildly decreased (ca. 0.7 fold) at 3 and 6 months in high dose males. CPK which showed a dose related reduction in females (high dose significant) at 91 days and a dose related increase in males (high dose significant) showed a non significant high dose (only) increase at 6 mos. in females and males. Other significant changes were reported to be of a small magnitude and not consistent. [The sponsor indicates that many of the findings at 3 months in the males were due to artifacts in specimen processing.]

Urinalysis showed no consistent treatment-related changes. The statistically significant urinalysis findings were generally of a small magnitude and not in a dose related pattern.

Organ weights, absolute or relative, showed some statistically significant changes, however, they were considered by the sponsor to be inconsistent and reveal no apparent toxicologically important changes.

Pathology was reported to show no compound-related gross or microscopic lesions. However, histologically there were a number of lesions associated with slight grades of severity or associated with aging rats. Incidental lesions included multi-organ inflammation and congestion, hepatocellular necrosis and focal cellular atypia, urinary bladder calculi, hypospermatogenesis, adrenal gland vacuolization, colonic nematodiasis, thyroid follicular hyperplasia, cataract, retinal degeneration and chronic iritis. Possible aging associated lesions were present in the kidney (renal tubular cast formation, mineralization or regeneration, and interstitial inflammation), heart (small inflammatory or necrotic foci) and bone marrow (prominent aggregates of lymphocytes - only in females).

Blood glucose determined ca. 24 hours after the last insulin dose was within normal range.

1-Year Subcutaneous Toxicity Study of LY275585 in Fischer 344 Rats: Lilly Research Laboratories. Study R07792 TR 24. Report dtd. March 1994. Study Dates Jun 92 - Jul 93. Lots (Bulk Lot ; Lot - 30 May 93 to end): Q.A.: Present.

Dose: 3, 20, 200 U/kg

No. Animals: 30M;30F per dose group. 35M;35F vehicle controls. Age 7-8 wks. Males 153.0 ± 11.0 g. Females 111.7 ± 6.0 g.

Stability: Both Lots were stable thru the live-phase of study. Mean concentration 98.4%.

NOTE: It is reported that as shown in a blood level study (R43393) doses of 20 and 200 U/kg of LY275585 produced a maximal drop in blood glucose concentration of ca. 55%. This change reportedly only slightly exceeded the drop of 40-50% in blood glucose concentration determined in rats given doses up to 3 U/kg (R24589) and thus doses of LY275585 20 U/kg induced a maximal pharmacological effect based on blood glucose depression.

Results:

Three males and two 200 U/kg females, and one 20 U/kg male and one control female died. One high dose died (hypoglycemic shock!) when a feeder malfunctioned and it could not access food after dosing. Of the other four high

dose that died one died due to obstruction by a urinary bladder calculus, one from a pituitary adenoma and no cause of death was determined for the remaining two. A low dose animal had urinary obstruction secondary to bladder calculus formation and the control rat had a severe gastric ulcer.

Clinical observations were reported as not being treatment-related.

Significant increases in mean body weight, body weight gain, food consumption and efficiency of food utilization (EFU; also for 20 U/kg females) were seen for both sexes of the high dose. By the end of treatment high dose body weight gain for males was 13% and that for females 17% greater than controls. Increases at 20 U/kg were slight (<10%) and not sustained. At the end of treatment food consumption for the high dose was 8% greater than controls for males and 5% for females. 20 U/kg males had increased food consumption the 2nd-5th month which were slight (<4%) and not sustained. Values for 20 U/kg females were similar to controls. Mean Effi ency of Food Utilization (EFU) was significantly increased for both sexes at 2 U/kg and 20 U/kg females. EFU at termination for the high dose was 4% greater than controls for males and 13% for females. EFU was increased in 20 U/kg females months 1-11; males at this dose showed no effect.

Ophthalmoscopic examination revealed no apparent treatment-related ocular effects based on pretreatment, interim and final examinations.

Hematology on 10 rats/sex/group at ca. the mid-point and end of study revealed no important compound-related changes according to the sponsor. Apparently minor compound-related changes (relative to controls) seen at termination (some also at 6 mos.) included some increase in mean Hb (ca 5%), PCV (ca 5%), MCV and MCH (ca 5%) mainly in high dose males, platelet count (ca 16%) of high and low dose males and females; and prothrombin time (ca 5%) of high and low dose females. There were also mean lymphocyte count increases in high dose males (ca 22%) and high and low dose females (ca 41%).

Clinical chemistry also on 10 rats/sex/group at similar time periods produced several treatment-related changes reported to be mostly related to pharmacologic activity. There was a slight increase in high dose male and female mean serum glucose (ca. 35%) and female low and high dose inorganic phosphorus (14%); slight decreases in low and high dose female serum triglycerides (ca. 19%) and low and high dose male and female cholesterol (ca. 22%). Various other significant differences were transitory in nature or of a small magnitude with lack of dose-response or consistency between the sexes. These included decreases in total protein, BUN, total bilirubin, ALT and AST.

Urinalysis at the end and mid-study produced no apparent important treatment-related changes. However compared to controls there was a slight increase in mean urine volume of high dose males and females which was associated with a corresponding increase in total excretion of electrolytes in the females.

Organ weights showed no toxicologically significant changes as reported by the sponsor. It appeared that most of the changes in mean organ weights of both males and females of the high dose were due to increases in mean body weights of that group. Relative to body weights significant high dose increases included male adrenals, and female, parathyroids/thyroids and uterus; decreases included male spleen, testes, and brain and female liver, pituitary and brain.

Necropsy showed a non dose-related enhancement of the degree and incidence of inflammation at the subcutaneous injection sites compared to controls (also had mild inflammation). The low incidences of mammary gland adenoma and fibroadenoma noted in this study were reported to be consistent with historical data from other 1-year studies conducted in their laboratory with Fischer 344 rats. Male rats showed no significant difference from male control rats with respect to an increase in tubuloalveolar morphology indicative of an enhanced endocrine effect attributed to prolactin. Minimal chronic focal cortical inflammation of the kidney was increased in females of both treated groups compared to controls. The incidence of slight dilation of the uterus showed a slight dose related increase. The incidence of slight progressive cardiomyopathy in high dose males was greater than that of controls however, males and females of all groups including controls had a high incidence of minimal progressive cardiomyopathy.

Immunotoxicity determination of anti-LY275585 IgG and IgM levels showed no statistically significant effects.

1-Year Subcutaneous Study of LY275585 in Beagle Dogs: Lilly Research Laboratories. Study D03592. TR 22. December 1993. Bulk Lot Formulated Lot Start: Mar 92. Q.A.: Present.

Dose. 0, 1, 2 U/kg s.c. (controls 0.1 ml/kg sterile diluent for Humulin)

No. Animals: 4M;4F per group. 7-8 months of age
Males 8.3 ± 0.7 kg; Females 8.0 ± 0.8 kg.

NOTE: Dogs are to be dosed after having eaten a portion of the food ration. Dogs that do not eat will not be dosed on that day.

Results:

There were no deaths.

One control and one 1 U/kg dog were not dosed once and 2M;3F dogs were not dosed 2-9 times.

Clinical signs included three high dose dogs with one or four occurrences of hypoglycemia, characterized by hypoactivity and lateral recumbency which required clinical intervention of dextrose administration. Other hypoglycemic observations included emesis, tremors, and hyperactivity. Low dose dogs did not have any incidents of hypoglycemia requiring food supplementation or dextrose administration. The incidence and frequency of abnormal stools was low being seen in 1M;1F low dose and 3M;1F high dose. Other findings frequently noted in dog colonies were not reported to be treatment related.

Compared to controls, body weights of the 1 and 2 U/kg males and 1 U/kg females were increased during the last 6 months. [Due to low number of animals and high variability the increase was not statistically significant.]

Food consumption which fluctuated due to manipulations to prevent hypoglycemia, was reported to show no treatment-related changes.

Terminal physical examinations reportedly showed no treatment related clinical findings.

No apparent compound-related ocular effects were found.

Electrocardiograms showed a modest increase in HR 2 hrs. after dosing in both groups (Low Dose Non-Sig.) on Day 184 and 0.5 and 2 hrs. after dosing on Day 366 in the 2 U/kg group. [Hypoglycemia, is reported to produce an increase in circulating levels of catecholamines (Liang et al., JClin. Invest. 69, 1321-1336, 1982).] Non-significant increases were seen in dosed animals at various other time periods. QTc intervals (combined sexes) showed some increases over controls 2 hrs. after injection of 2 U/kg on Days 268 and 365 (females also Day 183 and in general greater than males). The changes in QTc interval were associated with T wave morphology alterations which were reported to be likely due to effects known to occur during insulin-induced hypoglycemia [Mudge and Weiner in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th ed. pp. 682-707, 1990.].

Hematology showed no apparent treatment related findings. The few statistically significant findings appeared to be sporadic. Bone marrow smears prepared at the end of treatment were not evaluated due to the lack of hematological findings.

Clinical Chemistry included serial evaluations of blood glucose which showed moderate dose-related decreases by 15 minutes postinjection. In general decreases of the 1 U/kg group were ca 35% and for the 2 U/kg group ca. 47%. Both dose groups showed further blood glucose decreases by 1 and 2 hrs after dosing after which they began to rise being comparable to pretreatment values by 6 hrs in the 1 U/kg group. For the 2 U/kg group recovery was slower and by 6 hrs after dosing values occasionally remained below pretreatment values (ca 25%). Observed changes in blood glucose lowering after 1 month were fairly consistent throughout the dosing period. Additional treatment-related changes, compared to control and pretreatment, included slight increases in mean serum cholesterol and triglycerides at the end of treatment. Compared to controls K+

levels showed no statistically significant changes.

Urinalysis revealed no apparent treatment related changes.
Organ weights were variable without any apparent treatment related effects.
Necropsy and microscopic examination did not reveal any apparent treatment related findings.

Reproduction Studies:

Male Fertility Study of LY275585 Administered Subcutaneously to Fischer 344 Rats: Lilly Research Laboratories. Study R21192. TR 18 dtd Aug 93.
Lot: Bulk Formulated Live Phase of Study R21192: Aug-Sep 92.
Q.A.: Present.

Male Fischer 344/Tac rats were given daily subcutaneous injections of 0, 5, or 20 units LY275585/kg as part of a 6-month chronic study (R15792 above). LY275585 was given to 15 male rats/group for about 5 months prior to and during cohabitation with sexually receptive untreated Fischer 344 female rats. At the time of mating females were ca 13 weeks of age and weighed 147.8 ± 9.0 g (mean±SD). Females were killed 13 days after separation from the males for study of reproductive parameters.

Fifteen control, 14 each low and high dose males alive after 5 months of treatment were cohabited with untreated females. 3, 0, and 3 males (control-high dose) failed to mate during the first overnight cohabitation and were each cohabited with a second female. One male of the high dose group mated with the second female. Mating indices were 80 (12/15), 100 and 86 (12/14)% control thru high dose and fertility indices were 83 (10/12), 100 and 100% for males control thru high dose. No significant differences were noted in pre- and post implantation losses, numbers of corpora lutea, implantations, or dead implantations (early resorptions). However, although not reported as significant the low dose preimplantation loss and high dose post implantation loss were greater than that of controls.

There were no significant differences reported for testicular or prostate weights and there were no microscopic testicular changes indicative of a treatment-related effect on sperm production.

The reproductive performance no-effect level was given as 20 units/kg/day for male rats.

A 6-Month Fertility, Perinatal, and Postnatal Study, Including Behavioral and Reproductive Assessment of the F Generation, in CD Rats Administered LY275585 by Subcutaneous Injection: Lilly Research Laboratories. Studies R36492, R36592, R36692, R37392. TR 23. dtd. Feb 94. Lot: Q.A.: Present.

Effects on reproductive performance of F_0 CD rats [Crl:CD (SD) Charles River] and on the development, behavior, and reproductive performance of their F_1 offspring were evaluated in rats given 0, 1, 5, or 20 U/kg LY275585 (1 ml/kg).

Male rats (20/group) were treated beginning 2 weeks prior to cohabitation and throughout the mating period (R36492).

Females (20/group) in the delivery component (R36592) were treated 2-weeks prior to a maximum 2-week cohabitation period with males throughout Postpartum Day 20. Dams were permitted to deliver and maintain their young through a 21-day lactation period.

Females (20/group) in the teratology component (R36692) were treated 2 weeks prior to cohabitation through Gestation Day 19 and killed on Day 20.

After weaning 1 pup/sex/litter was assigned to the F_1 generation (R37392). The F_1 generation 0, 1, 5, 20 U/kg treatment-derived groups consisted of 20, 18, 15 and 17 rats/sex, respectively. They received no treatment. Behavioral testing (30-60 days) was conducted and a reproduction trial was conducted.

F_1 dams were allowed to deliver and maintain F_2 progeny through Postpartum Day 1. F_1 were necropsied at ca. 18 weeks of age.

Results:

F_0 Deaths - 1 male and four 20 U/kg females and one 5 U/kg F died with the causative factor appearing to be hypoglycemia.

F_0 - Slight increases in body weights, body weight gains and/or food consumption were noted in high dose males throughout treatment and during pretreatment for females of the teratology portion of study. No alterations of these parameters were seen for females in either study segment. Compared to controls, dams from all treated groups gained less weight and showed reduced efficiency of food utilization during the first week postpartum, however, during the lactation period there were no significant changes in body weights or food consumption.

F_0 mating and fertility were not affected by treatment. Males showed signs of mating and fertility with at least one female. The slightly lengthened mean gestation lengths for treated females were not considered to be biologically relevant by the sponsor. Live birth index, litter size (slightly smaller than controls for 1 and 5 U/kg groups), offspring growth and survival to Postpartum Day 21 were not effected by treatment.

Treatment during the teratology portion showed little or no effect on implantations (per dam increase in the high dose), live litter size or resorption rates. The apparent preimplantation loss at 1 and 5 U/kg were not statistically significant and were reported to be due to individual animal increases. Effects that may have been treatment related suggesting a marginal effect on in utero growth were decreased fetal body weights (ca 7%) and increased incidence of fetal runts/litter in the high dose group.

There was no teratogenicity.

All F_1 rats survived to termination. F_1 efficacy of food utilization decreased during the growth phase in 5 and 20 U/kg males and 5 and 20 U/kg females weighed less during the beginning of the growth phase. High dose rats were more reactive than controls in the startle test (hyperreactive to eliciting auditory stimuli). No effects were seen on mating, fertility, or reproductive end-points such as gestation length, live birth index, litter size, progeny survival, progeny body weight, and percent males. F_1 rats had no apparent treatment-related lesions.

According to the sponsor, 5 U/kg/day was considered to be a no-adverse-effect level for developmental toxicity.

Subcutaneous Teratology Study of LY275585 in New Zealand White Rabbits: Lilly Research Laboratories. Study B00793. TR 25. dtd. April 1994. Lot: Bulk Lot Q.A.: Present. Study Dates: Nov-Dec 1993.

Dose Determinations: Reported that dose selection was based on two preliminary studies. In nonpregnant rabbits (Study B07192) single, s.c. doses of 0.5 and 0.75 U/kg LY275585 produced ca 55 and 68% reductions in serum glucose concentrations, respectively. A pilot study in pregnant rabbits (Study B02893) at doses of 0, 0.13, 0.25 and 0.5 U/kg gestation Days 6-18 produced serum glucose concentration depressions of ca 40-44% in all treated groups. There was a dose related normalization of glucose response with treatment groups returning to control levels by 6 hours after dosing. There were no adverse effects on maternal body weight gain, food consumption or fetal viability, weight or external morphology.

0, 0.1, 0.25, 0.75 U/kg/day LY275585 were administered subcutaneously in Sterile Diluent for Humulin 3R at a volume of 0.1 ml/kg to 20 female New Zealand white rabbits per group Days 7-19 of gestation. To minimize risk of hypoglycemic shock, food availability was modified so that food was available Days 0-19 from at least 1 hr. prior to dosing until at least 6 hrs. after dosing. Days 20-27 food was available ad libitum. Sacrifice was on Day 28.

There were no deaths or clinical signs of toxicity reported. 17, 16, 17 and 18 (85, 80, 85, 90%) pregnant rabbits (control thru high dose) were examined on Gestation Day 28.

Although LY275585 reportedly did not adversely affect body weight, body weight gain or food consumption, marginal increases in body weight gain and food consumption occurring in the 0.25 and 0.75 U/kg groups were reported to appear to be compensatory and consistent with the pharmacologic effects of insulins.

Treatment groups showed similar values for corpora lutea, implantations and percent preimplantation loss (the early resorptions per litter were slightly greater for the two higher dose groups).

LY275585 did not adversely affect fetal viability, fetal weight, sex ratios, incidence of fetal runts (number per litter slightly greater for the low and high dose groups), or morphology. However, fetuses with variations per litter were slightly greater for treated than for controls. Variations included some increases in mid and high dose extra or rudimentary ribs and incomplete ossification at the high dose. Deviations for the high dose included an increased incidence of bipartite sternebra and incomplete ossification of the pelvic girdle.

Treated showed no increase in malformations over that of controls.

The sponsor reports the NOAEL for LY275585 in this study to be 0.75 U/kg, the highest dose tested; the LOAEL for developmental toxicity was not determined.

Mutagenicity Studies:

The Effect of LY275585 on the Induction of Reverse Mutations in Salmonella Typhimurium and Escherichia Coli Using the Ames Test: Lilly Research Laboratories. Study 911112AMS3249. TR 10. dtd. Jan 1992. Initiation: Nov 91. Lot: Q.A.: Present.

Salmonella typhimurium strains TA1535, TA1537, TA98 and TA100; and Escherichia coli strain WP2uvrA were tested with and without metabolic activation using an S9 fraction prepared from the livers of Aroclor 1254-induced rats according to the method of Ames, et al. N-ethyl-N'-nitro-N-nitroso-guanidine (ENNG), 2-nitrofluorene (2NF), and 9-aminoacridine (9AmAc) served as positive controls for the nonactivated assay, and 2-aminoanthracene (2AA) served as the positive control for the activated assay.

LY275585 treatment did not result in the induction of S. typhimurium and E. coli revertants when tested at concentrations of 312.5, 625, 1250, 2500, and 5000 µg/plate in either nonactivated or activated tests and thus it was concluded that LY275585 was not mutagenic in the Ames Salmonella/E.coli microsome test for bacterial mutation.

Effect of LY275585 on the Induction of Reverse Mutations in Salmonella typhimurium and Escherichia coli Using the Ames Test: Lilly Research Laboratories. Study 930713AMS3249. TR 21. dtd. Oct 1993. Initiated Jul 1993. Lot: Q.A.: Present.

This study appears to be a repeat of Study 911112AMS3249, TR 10 above using a different lot of LY275585.

Concentrations ranged from 312.5 to 5000 µg/plate as in the previous study, and it was concluded that LY275585 was not mutagenic in the Ames Salmonella/E.coli microsome test for bacterial mutation.

The Effect of LY275585 on the Induction of Forward Mutation at the Thymidine Kinase Locus of L5178Y Mouse Lymphoma Cells: Lilly Research Laboratories. Study 920311MLA3249. TR 11. dtd. Sep 1992. Initiated Mar 1992. Lot: Q.A.: Present.

The L5178Y TK$^{+/-}$ mouse lymphoma cell assay was used to test the potential of LY275585 to induce mammalian cell mutation. This test was carried out both with and without metabolic activation using an S9 liver fraction from Aroclor 1254-treated rats. Positive controls were ethylmethane sulfonate (EMS) for the nonactivated and 3-methylcholanthrene (3MC) for the activated assay.

Treatment with LY275585 did not induce mutation at concentrations ranging from 10, 25, 50, 100, 250, 500, 750, and 1000 µg/ml with or without metabolic activation. No concentration-dependent cytotoxic response was observed and slight variations in mutation frequency noted in LY275585-treated cultures were similar to those of the controls and were not concentration-dependent.

Thus, the conclusion was that LY275585 is not mutagenic in L5178Y mouse lymphoma cells with or without metabolic activation.

The Effect of LY275585 on the In Vitro Induction of Chromosome Aberrations in Chinese Hamster Ovary Cells: Lilly Research Laboratories. Study 920624CAB3249. TR 13. dtd. Dec 1992. Initiated Jun 1992. Lot: Q.A.: Present.

Chinese hamster ovary (CHO) cells were used to investigate the potential of LY275585 to induce chromosome aberrations. This test was carried out both with and without metabolic activation using an S9 liver fraction from Aroclor 1254-treated rats. CHO cells were exposed for 4 hours to concentrations of 1000, 1500, or 2000 µg/ml LY275585 with and without metabolic activation followed by evaluation of chromosomal aberrations. The positive control in the nonactivated assay was Mitomycin C and that for the activated assay was cyclophosphamide.

There was no increase in chromosomal aberrations with or without metabolic activation following treatment with LY275585. Thus the conclusion was that LY275585 does not induce chromosomal aberrations in vitro in Chinese hamster ovary cells.

The Effect of a Single Subcutaneous Injection of LY275585 on the Induction of Micronuclei in Bone Marrow of ICR Mice: Lilly Research Laboratories. Study 920316MNT3249. TR 12. dtd. Sep 1992. Bulk Lot: Q.A.: Present.

Male and female mice (5/sex) ca 7 weeks of age received a single subcutaneous injection of either vehicle or 2.5, 5.0 or 10.0 U/kg LY275585 (vol. 10 ml/kg), or the positive control, 25 mg/kg of the promutagen cyclophosphamide. Bone marrow was collected ca 24, 48, and 72 hours after LY275585 treatment (24 hrs. only for cyclophosphamide) and the frequency of micronucleated polychromatic erythrocytes was determined. The incidence of micronucleated polychromatic erythrocytes (MPCE) of LY275585 treated and control were not different. The test system was sensitive to a chemical clastogen as indicated by the positive control.

The conclusion was that LY275585 did not induce micronuclei in vivo in bone marrow of ICR mice; it was not clastogenic and did not interact with the mitotic spindle.

Hyperimmunogenicity Study With LY275585 Administered Intramuscularly in Freund's Adjuvant to Rhesus Monkeys for 6 Weeks. Lilly Research Laboratories. Studies P03692 (Treatment Jul-Sep 1992) and P01493 (Treatment Apr 93). TR 19. Lot: · RS0118; LY041001 - RS0133; Cpd 165744 - RS0100. Q A.: Present Study P03692 - Intramuscular - 52 Days: P01493 - Intravenous challenge - 2 Days (for IgE antibody). [Reported that since the primary structure of monkey insulin is identical to that of human insulin, the inferences made in this study should be directly applicable to man.]

Male rhesus monkeys (4 per group) were used to investigate the development of insulin antibodies after weekly immunization in Freund's adjuvant with 1) LY275585, 2) LY041001, biosynthetic human insulin and 3) compound 165744, purified porcine insulin.

Monkeys were immunized over a 6-week period with increasing doses of insulin, ranging from 10 to 100 µg/monkey. Serum collected prior to immunization and 5, 10 and 16 days after the final immunization was analyzed for IgG insulin antibodies. Prior to immunization serum and serum 10 days after final immunization were analyzed for IgE (class associated with allergy) insulin antibodies. [IgG antibody was detected in one LY275585 monkey pretreatment. It developed a higher antibody titer which reached a peak of 20.0 µg/ml 5 days after final immunization (this concentration of antibody was 20 to 100-fold lower than that reached with other proteins using an identical protocol). Other monkeys did not show any insulin antibody responses. [Two LY041001 and one 165744 monkeys exhibited hypoglycemia and unconsciousness Test Day 29 and were revived with dextrose solution.]

No IgE antibodies were detected in any of the monkeys.

The conclusion is that according to this study all three insulin forms have an extremely weak immunogenic potential in rhesus monkeys.

Literature:

Several volumes of reprints and abstracts were submitted with this NDA. Few of the articles were specific for LysPro. The majority of articles and abstracts concerned the physiology, pharmacology and toxicology of insulin and other analogs as well as various preclinical test methods, principles and techniques of teratology and statistical principles, methods and analysis. Also covered were various effects of insulin in normal and diabetic subjects.

Labeling: See Comment Section below.

Comments and Conclusion:

Humalog (LysPro), which is produced by means of a strain of Escherichia coli bacteria that has been genetically altered, is structurally similar to natural insulin with the exception that the amino acids at B_{28} (Pro) and B_{29} (Lys) in the C-terminal portion of the B-chain of insulin are inverted to Lys B_{28}, Pro B_{29} in Humalog.

The C-terminal portion of the B-chains of both insulin and IGF-I have considerable related structural homology and similar hydrophobic character. The one key difference is at B_{28-29} where the Pro-Lys sequence of insulin is Lys-Pro in the like region of IGF-I. Since IGF-I does not self-associate, the sponsor reasoned that by inverting the sequence of regular insulin from Pro-Lys to Lys-Pro the self-association characteristics of insulin might be more like those of IGF-I and thus provide a monomeric-type of insulin that would provide an ultra-fast time action. (Commercial formulation insulin exists in a hexameric state in solution, which delays onset of hypoglycemic action. After s.c. administration regular insulin undergoes a process of dissociation to form dimers and monomers, so as to be able to diffuse through capillary membranes

towards the circulatory flow.) Thus, the rate of absorption of "monomeric" LysPro (also less readily joined to a zinc ion) from subcutaneous injection sites is greater than that of regular human insulin. By producing more rapid and higher serum insulin concentrations with a shorter duration of activity, a rapid acting analog should decrease glucose excursion during and after meals and improve glucose control with less chance for late hypoglycemia. [The time course of action of any insulin, however, may vary considerably in different individuals or at different times in the same individual. As with all insulin preparations, the duration of action of Humalog is dependent on dose, site of injection, blood supply, temperature, and physical activity.]

The pharmacokinetic and pharmacodynamic profiles of LysPro point towards a more rapid acting, and therefore a more physiological mealtime insulin, than regular insulin. Initial clinical pharmacology studies reported the onset of activity of LysPro to be within 15 minutes of administration; that for regular human insulin is 30 to 45 minutes. LysPro serum levels peak at about 1 hr. compared to 2-3 hrs. for regular human insulin. LysPro pharmacokinetics showed a duration of action ca. 3.5 to 4.5 hrs. compared to ca. 5.5 to 7.5 hrs. for regular insulin. It is reported that clinical pharmacology studies in patients with type I and type II diabetes showed that optimal glycemic control can be obtained with LysPro administered 0-15 min before a meal vs 30-45 minutes for regular human insulin.

In general LysPro appears to be biologically equivalent to standard human insulin with regard to its hypoglycemic activity in animals. LysPro appears to be equivalent to insulin in several in vitro tests including insulin receptor binding in cultured lymphocytes, glucose transport in adipocytes and for IGF-I receptors in porcine aortic smooth muscle cells. In vitro studies showed LysPro to be equipotent in terms of binding to the human placental (92%) and IM9 lymphocyte (106%) insulin receptor and in stimulating ^{14}C glucose uptake into rat adipocytes.

LysPro was about 1.5x more potent than insulin at binding to the placental IGF-I receptor, and about 4x more potent at binding to the placental-IGF receptor and also more potent at stimulating [^{3}H] thymidine incorporation into human vascular smooth muscle cells. [According to C. Reviriego and E. Bolanos (Endocrinologia, Vol. 41, No. 9, 1994), the affinity of LysPro for the receptor of IGF-I in human placental membranes is significantly lower than IGF-I and AspB10]

The greater binding affinity for the IGF-I receptor by LysPro was not manifested in a greater mitogenic effect in a functional-type assay such as stimulation of growth of human mammary epithelial cells in culture.

Additional studies conducted under limited circumstances (low receptor or n-numbers) which did not receive a formal review showed insulin receptor preparations derived from human liver, human skeletal muscle, and human adipose tissue to have binding from 63-92% relative to human insulin.

Preclinically there appears to be a dissociation of insulin action on glucose removal from its extraction out of the circulation; i.e. glucose stimulated removal by the two compounds in the hindlimb muscle of pigs is equivalent, while their extraction varies widely in this muscle. The significance of this finding is uncertain.

Pharmacokinetics were investigated in rats and dogs (See p. 4). For rats the half-life following single s.c. injections of LY275585 of 2 and 4 U/kg was ca. 18 and 19 min with a C_{max} of 7.07 and 19.9 nmol/L and T_{max} of 10 and 20 min respectively. Maximum glucose suppression was reached at ca. 45 and 75 min for the two doses. LY275585 did not show accumulation following 7 days continuous dosing in the rat.

When larger doses (20, 200 U/kg) were given to rats, elimination was rapid with a terminal half-life of ca 1/2 hr. Females had a greater clearance and volume of distribution than males with the difference being more pronounced for

the lower dose. The ten-fold increase in dose resulted in C_{max} increases greater than 10 fold. LY275585 disposition was saturated between doses and clearance was reduced by 30% or more as the dose was increased. For 2 hours after administration the magnitude and duration of the decrease in mean blood glucose were similar for both dose groups suggesting saturation of the insulin receptor sites. The higher dose had a longer duration of action.

Following a 1 U/kg s.c. dose in dogs the t½ was 1.15 hrs. with a C_{max} of 1.70 nmol/L seen at 45 minutes. Maximum glucose suppression was seen at 1.15 hours.

The drug was rapidly cleared from plasma and degraded into small peptide fragments in both rats and dogs.

Plasma kinetic profiles with ^{125}I-LY275585 for the rat are reported to not accurately represent the kinetics of native LY275585.

Acute toxicity studies produced no deaths or signs of toxicity when male and female rats were given a single i.v. or s.c. dose of 10 U/kg LysPro. Dogs tolerated a single i.v. dose of 0.1 U/kg or a single s.c. dose of 2.0 U/kg. These doses, considered to be maximally tolerated doses, decreased blood glucose ca. 50% without causing significant signs of toxicity.

The maximum tolerated dose of LysPro (3.0 U/kg reported as based on depression of blood glucose concentrations in a pilot study) administered s.c. to rats daily for 1 month caused no apparent biologically important changes.

2.0 U/kg LysPro, reported to cause approximately a 50% reduction in glucose levels in dogs in a pilot study, was considered the maximum tolerated dose for repeated administration to dogs. In the 1-month s.c. dog study transient changes in T wave morphology, prolongation of the QT interval and increased heart rate were slight and considered by the sponsor to be the result of hypoglycemia and lowering of potassium levels produced by the drug. [However, at the time of clinical chemistry measurement (pre-test, and Days 7, 13, 21 and 29) potassium levels were not significantly different from controls.] Effects possibly associated with hypoglycemia included a slight (significant) increase over controls in heart rates at the 2 hr. time point on Day 29. Slight prolongations of the QRS duration (maximum 9% at 10 min) and Q-T$_c$ interval (maximum 10% at 5 min) as related in the Pharmacology section of the IND review were reported to have been previously observed following Humulin R. (See also next page of this review regarding effects in 1 year dog study.)

When rats were given 0, 5, 20 U/kg s.c. for 6 months, body weight gains were increased in males and females at both doses and food was increased in high dose females with the efficiency of food utilization being increased in both sexes at both doses. Triglyceride and cholesterol decreases were noted for males and females of both doses. Various other clinical chemistry values were variable and of a small magnitude. There were no treatment-related ophthalmologic findings and blood glucose values 24 hrs. after the last dose were within normal range.

The 1-year rat s.c. study at doses of 0, 20, 200 U/kg/day again showed increased body weights, body weight gain, food consumption and efficiency of food utilization for both sexes. Treatment-related changes were mostly related to pharmacologic activity. Some apparently minor changes were seen in hematology. Decreases were noted in triglycerides and cholesterol. The slight increase in glucose of male and female high dose animals at termination (ca 24 hrs after dosing) was attributed by the sponsor to the rebound in glucose concentration that follows hypoglycemia. There was a nondose-related enhancement of the degree and incidence of inflammation at injection sites.

Increases in body weights, weight gains, food consumption and efficiency of food utilization appeared to be due to enhanced physiological/pharmacological effects produced by large, repeated doses of insulin with respect to promoting fatty acid synthesis, storage of triglycerides in adipose tissue and protein synthesis.

Because the development, function, and morphology of the mammary glands are influenced by the endocrine system and in view of the fact that dose dependent mammary gland fibroadenomas and adenocarcinomas had developed with the rapid-acting insulin $AspB_{10}$, mammary glands were examined periodically for alterations in size and development of nodules as well as receiving multiple section histological examination. LY275585 did not influence the incidence of mammary neoplasms. In addition there were no morphologic changes in the mammary gland indicative of an enhanced prolactin endocrine effect.

Although the incidence of slight cardiomyopathy was slightly increased in high dose males, males and females of all groups including controls had a high incidence of minimal progressive cardiomyopathy.

No significant antibody levels were detected when serum was analyzed for the presence of specific IgG or IgM antibodies focused towards LY275585.

There were no apparent ocular effects.

Dogs received 0, 1, 2 U/kg LY275585 s.c. for 1 year. Blood glucose was decreased (also occurrences of hypoglycemia) in both males and females at 2 U/kg, triglyceride and cholesterol were increased and there was an increase in heart rate and T wave alteration. Heart rate alterations may have been affected by hypoglycemia which is reported to produce an increase in circulating levels of catecholamines (Liang et al., JClin. Invest. 69, 1321-1336, 1982). In addition it is reported [Mudge and Weiner in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th ed. pp. 682-707, 1990.] that changes in QTc interval associated with T wave morphology alterations may occur following insulin administration. These initially healty dogs showed no significant changes in potassium measurements.

Further insight into this area will have to rely on clinical data.

No apparent compound related ocular effects were found.

When male rats were given daily s.c. doses of 0, 5, or 20 Units (as part of the 6 mo. chronic study) and mated with untreated females the reproductive performance no-effect level was given as 20 U/kg/day.

Effects on reproductive performance of F_0 rats and on the development, behavior, and reproductive performance of their F_1 offspring were studied in M & F rats given 0, 1, 5, or 20 U/kg LY275585. The few parenteral deaths were attributed to hypoglycemia and some effects were seen on body weights and food consumption. F_0 mating and fertility were not affected by treatment and there was no teratogenicity. All F_1 rats survived to termination with no apparent treatment-related lesions, however, high dose rats were more reactive than controls in the startle test (hyperreactive to eliciting auditory stimuli). Mating and reproductive end-points did not seem to be affected. According to the sponsor, 5 U/kg/day was considered to be a no-adverse-effect level for developmental toxicity.

Doses of 0, 0.1, 0.25, 0.75 U/kg/day in the rabbit teratology study (based on production of ca 55% and 68% reductions in serum glucose with doses of 0.5 and 0.75 U/kg LY275585, respectively) showed no increase in malformations over that of controls.

LY275585 was not mutagenic as tested in a number of mutagenicity tests including: Ames Salmonella/E. coli microsome tests; Induction of forward mutation at the thymidine kinase locus of LB178Y mouse lymphoma cells; In vitro induction of chromosome aberrations in Chinese hamster ovary cells; or Induction of micronuclei in bone marrow of ICR mice; and Induction of unscheduled DNA synthesis in primary cultures of adult rat hepatocytes.

According to the hyperimmunogenicity study with LY275585, biosynthetic human insulin and porcine insulin, all three insulin forms have an extremely weak immunogenic potential in rhesus monkeys.

Carcinogenicity studies were deemed not necessary for this insulin analog.

Labeling was developed as Information for the Patient in accordance with 21 CFR 429 and is very similar to that approved for Humulin R (insulin human injection, USP [recombinant DNA origin]), Eli Lilly and Company (NDA 18-780).

We recommend Physician labeling - to be worked out among the various disciplines.

Pharmacology recommends approval of Humalog (insulin lispro) for control of blood glucose; treatment of diabetes mellitus however, we suggest Physician rather than Patient labeling.

David H. Hertig
Pharmacologist

cc:
Original NDA 20-563; IND
HFD-24 JDeGeorge
HFD-345
HFD-510 NDA 20-563; IND
HFD-510 AJordan
HFD-510 DHertig

Clinical Pharmacology & Biopharmaceutics Review

NDA: 20-563

Insulin lispro (100 U/mL)
(Humalog®)

FEB 22 1996

Submisson Date: 3/13/95
9/6/95
10/23/95
12/18/95

Sponsor: Eli Lilly
Indianapolis, IN

Type of Submission: New Drug Application (1S-NME)

Reviewer: Michael J. Fossler, Pharm. D., Ph. D.

Synopsis

Eli Lilly has submitted NDA 20-563 for insulin lispro, an analog of human insulin. The proposed indication is for the treatment of diabetes mellitus. Insulin lispro (Humalog) has a quick onset of action and a short duration of activity, and is intended to be given within 15 minutes of a meal.

Most of the studies submitted to the pharmacokinetics portion of the NDA were performed in normal volunteers. The absolute bioavailability after subcutaneous injection ranges from 55-77%. In normal volunteers, subcutaneous injections of insulin lispro are absorbed more quickly than regular human insulin. Zinc (added to enhance stability) does tend to attenuate the rate of absorption of insulin lispro, but it is still absorbed faster than regular human insulin. The to-be-marketed formulation was shown to be bioequivalent to the clinical trials formulation in 16 normal male volunteers. Mixing insulin lispro with NPH insulin significantly reduces the rate but not the extent of absorption, but it appears that ultralente has no effect on either rate or extent. Insulin lispro is absorbed faster than regular human insulin at all of the usual insulin injection sites (abdomen, thigh, deltoid).

The pharmacokinetics and pharmacodynamics of insulin lispro were studied in 18 normal volunteers using a partial crossover design. After intravenous administration, the clearance of insulin lispro is identical to human insulin. In addition the kinetics of both compounds is non-linear with dose, as clearance drops by 50% as the dose is increased from 0.1 U/kg to 0.2 U/kg. After sc

Non-linearity is also seen after subcutaneous injection. Using the glucose infusion rate as a pharmacodynamic measure in subjects on a glucose clamp, onset of action was slightly faster and duration of action shorter with insulin lispro as compared with regular insulin.

One PK/PD study was performed in 10 Type I diabetic patients. The patients were dosed with either regular insulin or insulin lispro before a standardized test meal high in carbohydrates. Concentrations of insulin and blood glucose were measured over time. Insulin lispro peaked higher and earlier than regular insulin and significantly attenuated the post-prandial glucose peak as compared with regular insulin.

No metabolism or drug interaction studies were performed. Non-diabetic patients with varying degrees of renal failure showed no significant decrease in the clearance of insulin lispro. A population analysis was performed, but due to analytical and experimental difficulties yielded no useful information on the pharmacokinetics of insulin lispro in the diabetic population. No information exists on the effect of age or gender on the pharmacokinetics/pharmacodynamics of insulin lispro. Although children as young as three have been treated with the compound, no information exists on the disposition or pharmacodynamics of insulin lispro in the pediatric population.

Recommendation

The Division of Pharmaceutical Evaluation II (HFD-870) has reviewed the NDA 20-563 for insulin lispro and has determined that although the NDA is adequate for approval, critical information is lacking in the submission. The additional information necessary could be obtained as Phase IV studies if the compound is approved for marketing. Please forward the text under **X. General Comments (to be sent to sponsor)** to the sponsor as appropriate.

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Appendix I: Study Summaries (available from DPE-II upon request)

Background

Eli Lilly has submitted NDA 20-563 for insulin lispro, an analog of human insulin. Insulin lispro (28^{B}-L-lysine-29^{B}-L-proline insulin (human)) is identical in structure to human insulin except that at positions

This reversal allows the compound to exist as a monomer in solution. This is in contrast to human insulin, which even in solution exists as a mixture of dimeric and hexameric forms. Thus the altered compound is absorbed more rapidly after subcutaneous injection, which may help control post-prandial glucose levels.

Insulin lispro is a 2-chain peptide containing 51 amino acids. Its molecular formula, weight and pI (5.6) are identical to those of human insulin. The primary structure is shown in Figure 1.

Figure 1: Primary structure of insulin lispro.

Summary of Bioavailability/Pharmacokinetics/Pharmacodynamics

I. Bioavailability/Bioequivalence

A. Absolute Bioavailability

The absolute bioavailability of insulin lispro was found to range between 55-77% at doses of 0.1-0.2 U/kg. This absolute bioavailability is similar to regular human insulin, which in the same study was found to have an absolute bioavailability of 48-89%.

B. Bioequivalence

Effect of Formulation

Early Phase I studies of insulin lispro used a lyophilized formulation without zinc. This formulation did not have a practical shelf-life. To determine whether the addition of Zn^{2+} had a significant effect on the absorption rate of insulin lispro, a four-way, randomized cross-over trial was performed in ten young healthy males using the glucose clamp technique to maintain euglycemia. Each subject received either sc insulin lispro, sc insulin lispro with Zn^{2+}, sc human insulin or intravenous human insulin. The results are shown in Table 1. Although Zn^{2+} does attenuate the rate of absorption (as estimated by Cmax) by 20-40%, the absorption rate is still significantly faster for insulin lispro than for human insulin.

To enhance stability, the to-be-marketed formulation has a different preservative system than the clinical formulation, consisting of 3.15 mg/ml m-cresol. The clinical formulation had a mixed preservative system consisting of 1.09 mg/ml phenol and 1.25 m-cresol. As both phenol and m-cresol are known to promote self-association of insulin, a bioequivalency study was carried out in 16 healthy male volunteers in a randomized crossover study. The dose used was 10 units of either the clinical formulation or the to-be-marketed formulation. Based on the two one-sided tests procedure on AUC and Cmax (Table 2), the two formulations are bioequivalent. Figure 2 shows that the mean concentration vs. time curves are superimposable for the two formulations.

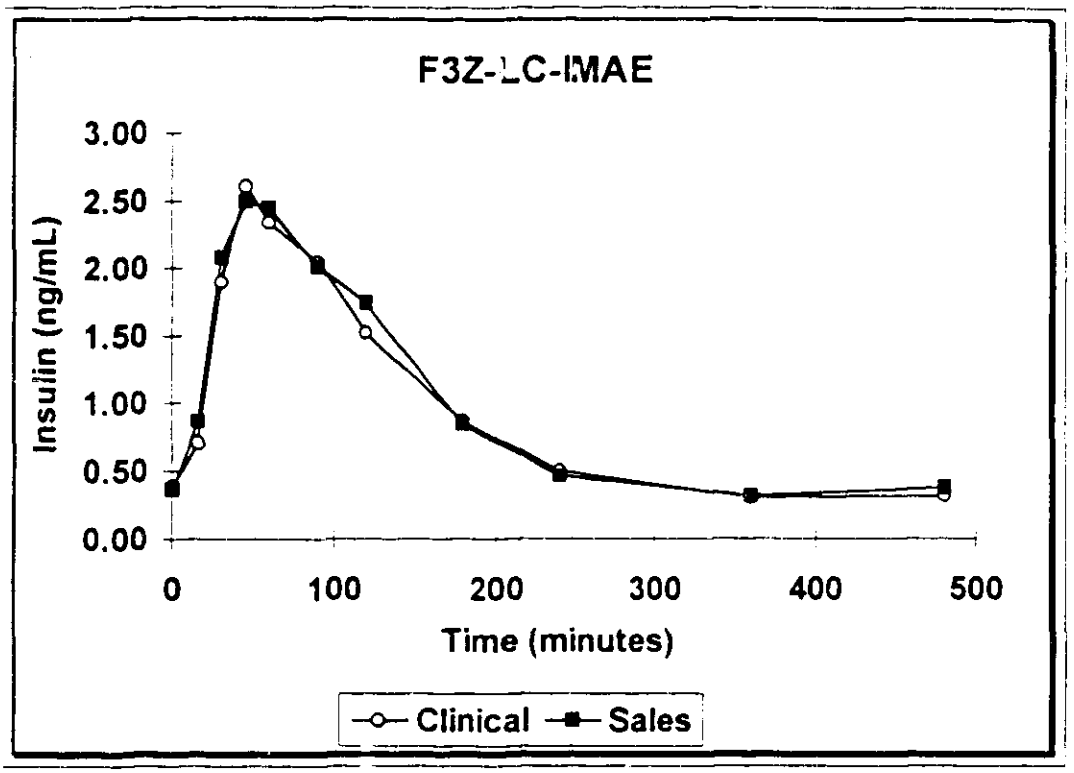
*Table 1: Back-transformed means and 90% confidence intervals for the log-ratios of $AUC_{(0\text{-}720\ min)}$ and Cmax after administration of 10 units of human insulin and two formulations of insulin lispro. Mean (90% CI's) n = 10. Reference formulation indicated by *.*

	Lyophilized insulin lispro vs. regular insulin*	Zn insulin lispro vs. regular insulin*	Zn insulin lispro vs. lyophilized insulin lispro*
$AUC_{(0\text{-}720\ min)}$ (µg*min/L)	109.6 (97.0, 123.9)	103.2 (91.3, 116.6)	94.1 (83.3, 106.4)
Cmax (ng/mL)	215.4 (169.2, 274.2)	171.1 (134.4, 217.8)	79.4 (62.4, 101.1)

Table 2: Results of the two one-sided tests procedure comparing the to-be-marketed formulation with the clinical formulation, using the clinical formulation as the reference. N = 16 (Study F3Z-LC-IMAE)

	To-be-marketed formulation vs. Clinical formulation
$AUC_{(0\text{-}480\ min)}$ (µg*min/L)	103.7 (99.1, 108.5)
Cmax (ng/mL)	103.1 (87.9, 121.1)

Figure 2: Insulin plasma concentration vs. time curves for the clinical and the to-be-marketed (sales) formulation. The curves are nearly superimposable. Each point represents the mean of 16 subjects.



As most diabetics also take a long-acting insulin (e.g., NPH or Ultralente) in addition to a short-acting insulin,many times it is more convenient for the patient to mix the long and short-acting insulins in the same syringe and inject them together. To determine whether the quick absorption of insulin lispro is preserved when mixed with long-acting insulins such as NPH or ultralente, 13 male volunteers were given insulin lispro along with either NPH or ultralente either as separate injections or as a single injection. The two insulins were mixed immediately before the single injection. The results show that mixing with NPH (but not ultralente) attenuates the rate of absorption (as measured by Cmax) by 20-50%. The tmax for mixed insulin lispro/NPH is also increased as compared to separate injections (0.75 hr separate vs 1.27 hr mixed), but the tmax for mixed insulin lispro/ultralente shows little change from the separate injections (0.85 hr separate vs. 0.73 hr mixed). These data suggest that insulin lispro should not be mixed with NPH insulin.

Table 3: Back-transformed means and 90% confidence intervals for the log-ratios of $AUC_{(0-12\ hr)}$ and Cmax after administration of 0.2 units/kg of insulin lispro and two formulations of long-acting human insulin as separate injections or mixed in one syringe. Mixing with NPH greatly attenuates the rate of absorption. Mean (90% CI) n = 13.

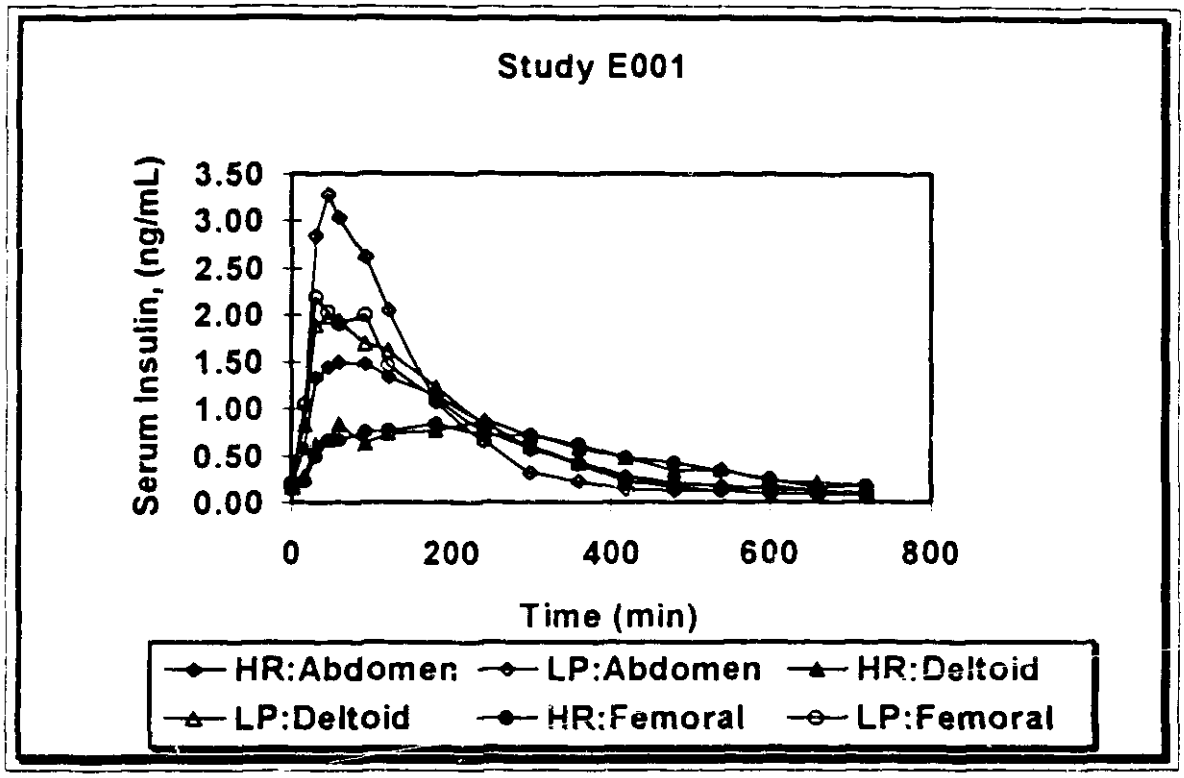
	Mixed vs. Separate* (NPH)	Mixed vs. Separate** (Ultralente)
AUC(0-12 hrs)	106 (90.4, 124.3)	100.1 (85.3, 117.3)
Cmax	69.9 (58.8, 83.0)	105.1 (88.4, 125)

*mean tmax for separate injection is 0.75 hr. vs. 1.27 hr. mixed
**mean tmax for separate injection is 0.85 hr. vs. 0.73 hr. mixed

Effect of Injection Sites

The subcutaneous site where the dose of insulin is injected has a profound effect on the rate of its absorption. It is generally accepted that the rate of absorption of insulin is fastest from the abdomen, intermediate from the arm and is slowest from the thigh. To determine what effect the site of injection has on the rate of absorption of insulin lispro, a study was performed in 12 healthy male volunteers. Each volunteer was given either human insulin or insulin lispro (0.2 U/kg) in either the abdominal, deltoid or femoral region in a randomized crossover fashion. The results (Figure 3) show that insulin lispro is consistently absorbed at a higher rate than regular human insulin at all three injection sites, with the Cmax after abdominal administration about 50% higher than those resulting after deltoid or thigh injection.

Figure 3: Serum concentration vs. time profiles for human insulin (HR) and insulin lispro (LP) after injection of 0.2 U/kg in the abdomen, deltiod, or femoral regions. (N = 12)



II. Pharmacokinetics

Normal Volunteers

The pharmacokinetics of insulin lispro and human insulin after both intravenous and subcutaneous injections in 18 healthy male volunteers were studied using a rising single-dose randomized partial-crossover design. Results are shown in Table 4. As shown previously, subcutaneously administered insulin lispro is absorbed faster (as shown by increased Cmax and decreased tmax) than regular human insulin at all four sc doses. Human regular insulin also displays a longer half-life than insulin lispro at all sc doses. This most likely reflects the rate-limited absorption of human insulin, as intravenous doses of both compounds have nearly identical half-lives. Clearance values for the intravenous doses of the two

compounds are nearly identical within-dose; however, clearance drops by more than 50% for both insulins when the dose is increased from 0.1 to 0.2 U/kg. There is some evidence as well of nonlinearity at sc doses > 0.2 U/kg for the subcutaneous administrations of both compounds, as the AUC values increase more than proportionally with increasing sc dose.

Type I Diabetic Patients

Two studies examined the pharmacokinetics of sc insulin lispro and human insulin in diabetics. The first study (Study IOAJ) was performed in eight Type I diabetics. Each patient was given 0.15 U/kg of either regular insulin or insulin lispro followed by a 600 kcal test meal. Samples for insulin and glucose measurements were measured over eight hours. Each treatment was repeated three times to get a estimate of both intra- and inter-patient variability. It was discovered later that all of the subjects had antibodies to insulin, and that one of the subjects (Subject 8) had very high insulin antibody levels. This patient also had measured insulin concentrations many times higher than the other, indicating that the antibodies were interfering with the , which makes the data unreliable.

Because the insulin antibodies interfere with the or insulin, the Agency requested additional data in patients using an appropriate extraction method for autoantibodies. The firm submitted Study IOAT on 12/18/95. This single-dose, randomized double-blind crossover study compared the PK/PD of regular insulin and insulin lispro in 10 C-peptide negative patients after ingestion of a meal high in carbohydrates. Eac subject was begun on an insulin infusion (0.2mU/kg/min) which was maintained throughout the study, and served as a "basal" insulin. Blood glucose was clamped at 120 mg/dL prior to the start of the study. A subcutaneous injection of either regular human insulin or insulin lispro was given immediately before the ingestion of a meal of pizza, Coca-Cola®, and tirami-su. The dose of insulin was individualized for each patient, but was kept constant within-patient across the two arms of the study. Concentrations of blood glucose and serum insulin[1] were followed for 8 hours post-injection.

The results are shown in Table 5 and Figure 4. The data show that insulin lispro is absorbed faster (by roughly 45 minutes) than regular human insulin in these patients, as peak concentrations are higher and earlier in the lispro arm. Both insulins are absorbed to a similar extent, as seen in normal volunteers.

[1] The assay used in this study included a which has been shown to remove insulin autoantibodies from human serum. This assay was performed at the clinical study site.

Table 4: Pharmacokinetics of human and lispro insulin after subcutaneous and intravenous administration to healthy male volunteers. Mean (SD,CV%). (Study IMAC)

Dose, Route	Type	AUC(0-t')[a] (ng*hr/mL)	Cmax (ng/mL)	tmax (hr)	$t_{1/2}$ (hr)	CL/F (mL/min/kg)
0.1 U/kg,sc	LP (n = 9)	3.90 (1.71, 43.9)	2.04 (0.85, 41.6)	0.60 (0.11, 19.8)	1.27 (0.68, 53.6)	17.8 (8.84, 49.8)
	HR (n = 9)	3.78 (2.41, 63.8)	1.23 (0.59, 47.9)	0.9 (0.52, 60.0)	2.72 (2.0, 73.4)	25.0 (16.1, 64.3)
0.2 U/kg sc	LP (n = 9)	7.24 (2.93, 40.4)	3.71 (1.37, 37.0)	1.0 (0.31, 31.0)	1.14 (0.52, 45.5)	17.7 (7.2, 40.6)
	HR (n = 9)	7.98 (4.01, 50.3)	1.72 (0.9, 52.5)	1.5 (0.48, 32.3)	4.4 (4.8, 110)	19.8 (9.64, 48.7)
0.3 U/kg,sc	LP (n = 3)	16.1 (2.57, 16.0)	7.90 (0.68, 8.7)	0.8 (0.29, 34.6)	0.87 (0.22, 24.7)	10.6 (1.77, 16.6)
	HR (n = 9)	10.5 (4.66, 44.4)	2.3 (1.12, 48.7)	2.1 (1.04, 50 8)	2.39 (1.18, 49.3)	22.5 (11.3, 50.5)
0.4 U/kg,sc	LP (n = 3)	21.8 (5.10, 23.4)	8.50 (2.53, 29.7)	1.6 (0.72, 45.6)	1.52 (1.22, 80.4)	10.4 (2.22, 21.3)
	HR (n = 3)	21.4 (5.27, 24.7)	4.43 (0.52, 11.7)	2.8 (1.26, 44.4)	2.03 (1.24, 61.2)	12.3 (3.8, 30.7)
0.1 U/kg,iv	LP (n = 12)	3.34 (1.2, 36.1)	na	na	0.76 (0.57, 75.2)	20.3 (10.9, 53.5)
	HR (n = 12)	3.41 (1.4, 40.9)	na	na	0.76 (0.65, 85.2)	20.6 (5.6, 27.2)
0.2 U/kg,iv (n = 6)	LP (n = 12)	13.0 (2.99,23.0)	na	na	1.04 (0.63, 60.8)	8.8 (2.3, 26.0)
	HR (n = 6)	14.7 (4.8, 32.4)	na	na	1.43 (0.8, 56.3)	9.48 (4.3, 44.9

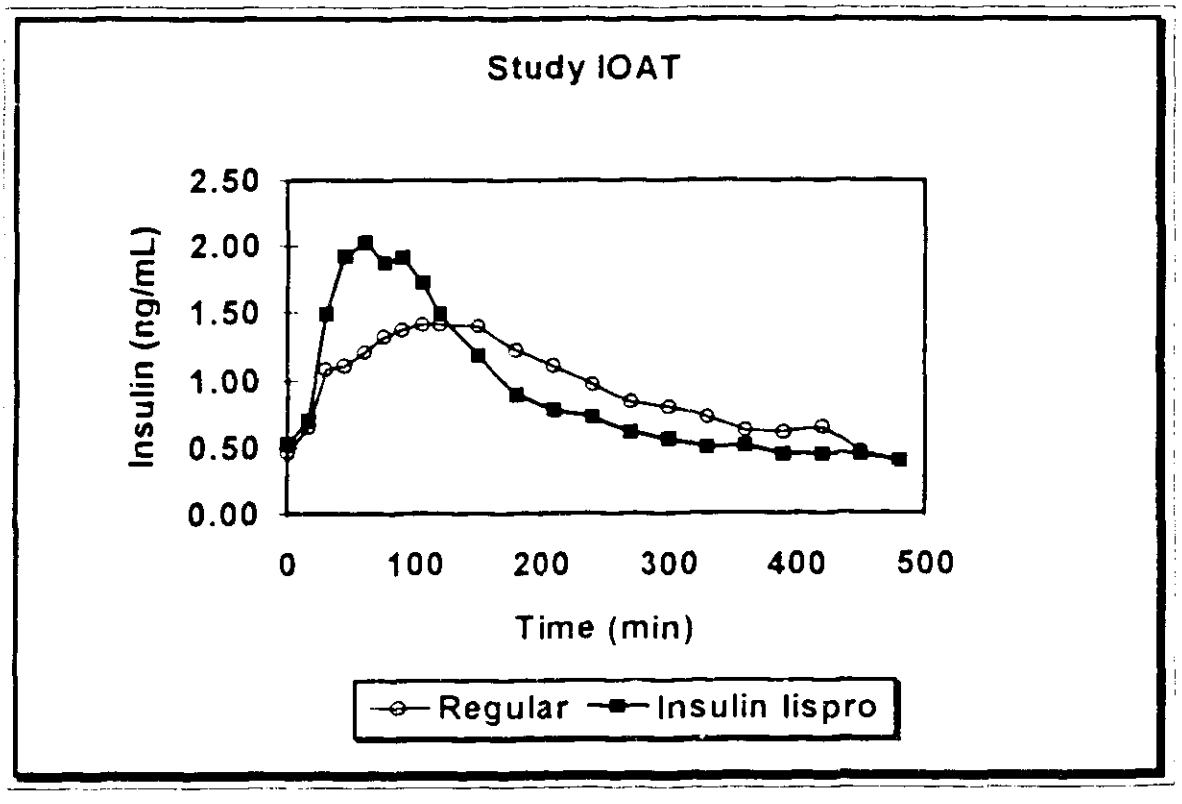
na-not applicable [a]from time zero until insulin concentrations reached baseline levels

Table 5: Pharmacokinetic parameters of human insulin and insulin lispro after a single sc dose in 10 Type I diabetics. Values in the table are mean ± SD. (Study IOAT)

Treatment	Cmax (ng/mL)	*NCmax (ng/mL/U)	tmax (hr)	**AUC(0-∞) (ng*hr/mL)	*NAUC(0-∞) (ng*hr/mL/U)
Lispro (n = 10)	1.66 ±0.42	0.11 ±0.03	1.13 ± 0.29	3.64 ± 0.88	0.24 ± 0.06
Human Insulin (n = 10)	1.07 ± 0.3	0.07 ±0.03	1.9 ±0.46	4.05 ±0.75	0.27 ±0.05
p-value (ANOVA)	<0.001	<0.001	<0.001	0.205	0.249

*adjusted for dose
**corrected for basal insulin infusion

Figure 4: Mean serum insulin concentration after a sc dose of regular human insulin or insulin lispro in Type I diabetic patients. Each point represents the mean of 10 patients.



III. Metabolism

No metabolism studies were performed. It is likely that insulin lispro undergoes similar metabolism to human insulin.

IV. Dose and Dosage Form Proportionality

The dose of insulin lispro to be given to each patient must be individualized based on the patient's current disease state, degree of control, and other patient-related variables. Insulin lispro will be marketed in only one strength (100 units/mL).

V. Special Populations

Renal

No significant difference in insulin lispro pharmacokinetics was observed between non-diabetic patients with renal impairment (ranging from slight impairment to anephric) and normal controls.

Age, Gender, Pediatric

No information on the effect of age or gender on the pharmacokinetics/pharmacodynamics of insulin lispro is available. A population analysis was performed on a large sub-set of the patients used in the clinical efficacy trials. The results of the analysis showed that clearance of insulin lispro is reduced in subjects >69 years of age and that bioavailability is decreased in hypertensives and smokers. However, the reliability of this analysis is in question due to several questionable assumptions which had to be made concerning the absorption and bioavailability of the concomitantly-administered basal insulins. In addition, there are potential analytical difficulties, as no extraction of insulin antibodies was performed in these patient samples, which can interfere with the assay.

The compound has been used in patients as young as 3 years old; however, no information exists on the disposition of insulin lispro in the pediatric population.

VI. Drug Interactions

No drug interaction studies were performed.

VII. Pharmacokinetic/Pharmacodynamic Relationships

Normal Volunteers

The PK/PD of insulin lispro was studied in normal volunteers using the glucose clamp procedure. The PD measurement used in all of these studies was the glucose infusion rate (GIR) required to maintain euglycemia. Table 6 displays a summary of the data obtained from Study IMAC. From Table 6, it is noted that maximum glucose infusion rate (Rmax) for the insulin lispro is higher and occurs earlier at all four doses. Onset of action is slightly faster and duration of action slightly shorter for insulin lispro as compared with regular insulin, although these parameters show significant variability. Figure 5 shows the the mean GIR curves over time for the two treatments. From Figure 5, it is noted that, although in general the GIR curves resulting from insulin lispro administration peak higher and earlier than those from regular insulin, the differences are not large.

Type I diabetics

Study IOAT was performed in 10 Type I diabetic patients. Each patient was maintained on a basal insulin infusion (0.2 mU/kg/min) and serum glucose was clamped at 120 mg/dL prior to the study.A sc dose of either insulin lispro or regular human insulin was given, followed immediately by a carbohydrate-rich meal. Figure 6 shows the mean blood glucose over time curves for the study. It can be readily seen that insulin lispro attenuates the post-prandial rise in blood glucose as compared to regular insulin. The secondary peak seen in the lispro curve (also seen in most of the individual patient plots) is most likely due to more slowly-absorbed carbohydrates. The rise in blood sugar at this time in the lispro group indicates that the sc lispro insulin has been largely eliminated. This secondary peak is not seen in the regular insulin plot, due to its longer duration of action.

Table 6: Mean pharmacodynamic parameters from 18 healthy males given 0.1-0.4 U/kg insulin lispro or regular human insulin and maintained on a glucose clamp. Values in the table are mean ± sd (range). Rmax: maximum glucose infusion rate, TRmax: time of Rmax (Study IMAC).

Treatment	Dose	Rmax (mg/min)	TRmax (min)	Onset* (min)	Duration** (min)
Insulin lispro	0.1 U/kg (n = 9)	539 ± 193 (275-846)	93 ± 25 (45-120)	35 ± 10 (20-45)	297 ± 124 (120-495)
	0.2 U/kg (n = 9)	748 ± 219 (546-1178)	146 ± 112 (45-420)	30 ± 11 (10-45)	353 ± 183 (180-795)
	0.3 U/kg (n = 3)	850 ± 108 (737-951)	85 ± 9 (75-90)	28 ± 3 (25-30)	312 ± 68 (270-390)
	0.4 U/kg (n = 3)	843 ± 197 (693-1067)	130 ± 75 (60-210)	32 ± 12 (25-45)	458 ± 60 (395-515)
Regular Human	0.1 U/kg (n = 9)	389 ± 179 (110-684)	145 ± 112 (20-390)	39 ± 19 (10-75)	304 ± 164 (140-645)
	0.2 U/kg (n = 9)	520 ± 203 (228-726)	185 ± 94 (75-360)	49 ± 18 (25-75)	541 ± 196 (275-795)
	0.3 U/kg (n = 9)	628 ± 158 (428-928)	180 ± 51 (105-270)	43 ± 9 (30-60)	312 ± 68 (270-390)
	0.4 U/kg (n = 3)	701 ± 55 (638-739)	195 ± 65 (150-270)	43 ± 18 (25-60)	627 ± 93 (540-725)

* defined as the first of at least 3 consecutive times that GIR > 10% Rmax.

** defined as the first of at least 3 consecutive times that GIR < 10% Rmax post-Rmax.

Figure 5: Mean GIR vs. time plots for 4 doses of insulin lispro and regular human insulin given to normal male volunteers. For ease of examination, all insulin lispro markers are solid; all regular insulin markers are clear. (Study IMAC).

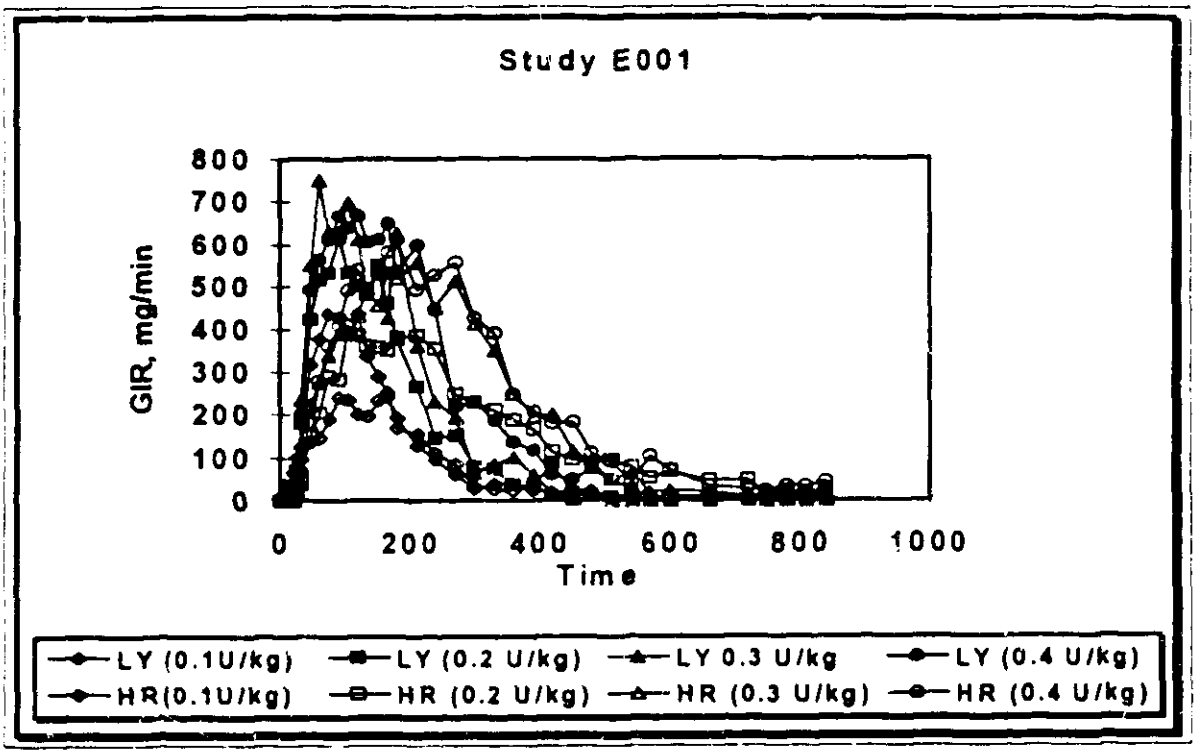
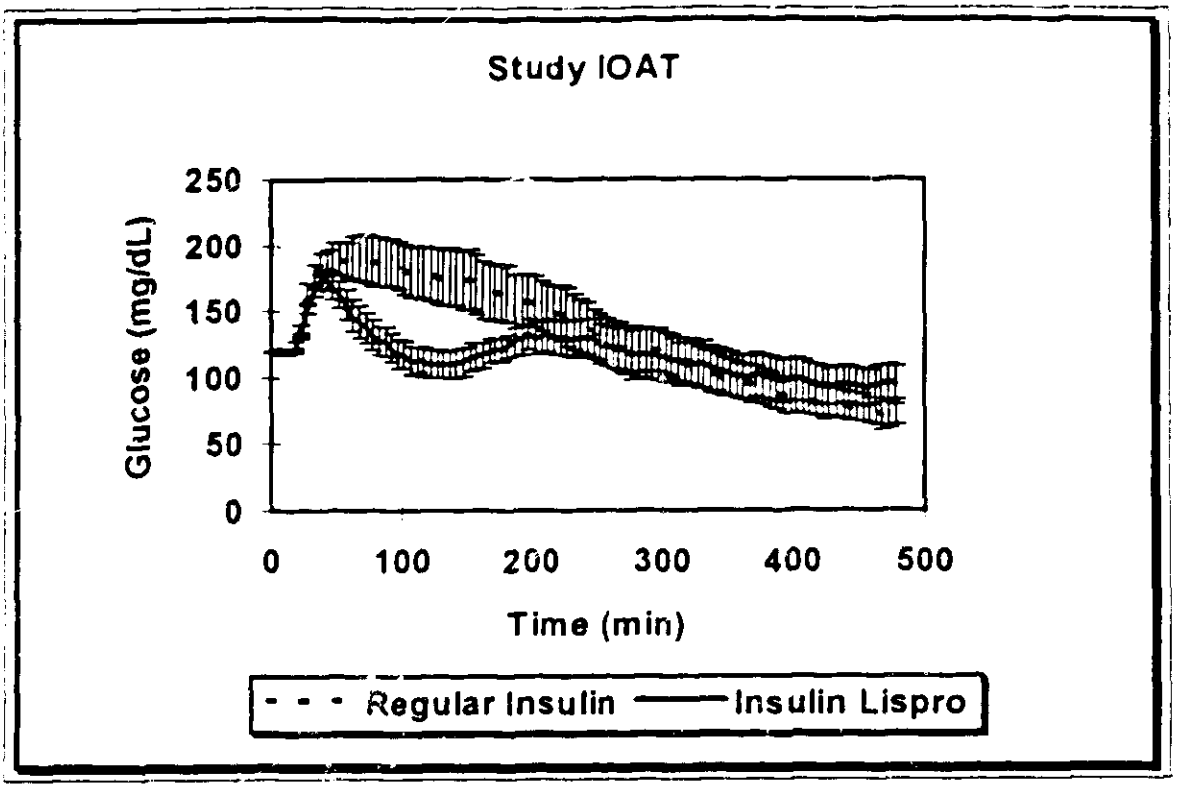


Figure 6: Overall mean blood glucose levels over time in 10 Type I diabetic patients given either regular insulin or insulin lispro immediatly before a carbohydrate-rich meal. Error bars denote ± one standard error. (Study IOAT)



VIII. Formulation

The to-be-marketed formulation is listed in Table 7.

Table 7: To-be-marketed formulation of insulin lispro. Batch sizes and lot numbers of all clinical batches are located in the Appendix.

Ingredient	Quantity/mL	Allowable Variation	Function
Insulin lispro	**100 units		Active
Glycerin, USP	16 mg		Tonicity modifier
m-Cresol	3.15 mg		Preservative
*Zn**	19.7 µg		Stabilizer
Dibasic Sodium Phosphate, USP	1.88 mg		Buffer
10% HCl	qs		pH adjustment
10% NaOH	qs		pH adjustment
Water for injection	qs 1 mL		vehicle

* added as zinc oxide, USP
**100 units = 3.5 mg

IX. Assays

The assay used for both insulin lispro and human insulin (except for Study IOAT)

. The assay was validated by Lilly in-house as shown in Table 8.

The package insert of the assay states the following:

> *The application of insulin [redacted] to patients already undergoing insulin therapy is complicated by the fact that such therapy typically leads to the formation of anti-insulin antibodies capable of interfering with the assay.*

Because of this, the plasma insulin/insulin lispro levels in patients are suspect, since no antibody levels were determined. It is for this reason, (as well as additional reasons detailed above) that the population PK study is not considered to be of much utility. In Study IOAJ, it was stated in the report that anti-insulin antibodies were measured and found to be zero for all eight patients. However, the raw data were not supplied to the Division. The Division requested these data in a teleconference with the firm on 8/29/95. On 9/26/95, the reviewer spoke to Jim Woodworth, Ph.D., of Lilly who stated that the antibody data were lost to retrieval, but the samples had been located and were being re-run. On 10/24/95, the reviewer received the antibody data. It was immediately obvious that all subjects in the study had insulin-binding antibodies, with Subject 8 having particularly high titers, so it is unclear why it was stated in the submission that no antibodies were seen. Because of the presence of antibodies, these data are not considered reliable.

As normal volunteers do not normally have antibodies to insulin, the assay is considered reliable for them. The volunteers also received insulin lispro, which

is a foreign protein capable of eliciting an immune response. Generally, the subjects received only one dose of the product, so it is considered unlikely that any anti-insulin antibodies were formed in these subjects.

A different kit was used for Study IOAT, which is the pivotal PK/PD study in patients. The kit used was from and was performed at the study site. step was performed to rid the patient samples of any insulin antibodies prior to analysis. Validation data for this assay are shown in Table 9. Although the assay appears sufficiently precise, it is noted from the table that accuracy is poor at concentrations above 0.68 ng/mL. This is most likely due to loss of insulin from the sample due to the Therefore, it may be that the higher insulin/insulin lispro concentrations are underestimated in this study, and that the most emphasis should be placed on the glucodynamic data.

Table 9: ***Insulin assay validation summary, used in Study IOAT.***

1 page
purged

XI. Labeling Comments (to be sent to Sponsor)

1. The text under CLINICAL PHARMACOLOGY in the draft physician labeling should be modified as follows:

CLINICAL PHARMACOLOGY

The primary activity of insulin is the regulation of glucose metabolism. In addition, all insulins have several anabolic and anti-catabolic actions on many tissues in the body. In muscle and other tissues (except the brain), insulin causes rapid transport of glucose and amino acids intracellularly, promotes anabolism and inhibits protein catabolism. In the liver, insulin promotes the uptake and storage of glucose in the form of glycogen, inhibits gluconeogenesis, and promotes the conversion of excess glucose into fat.

Humalog has been shown to be equipotent to human insulin on a molar basis.

Absorption

Humalog is as bioavailable as regular human insulin, with absolute bioavailablity ranging between 55%-77% at doses of 0.1-0.2 U/kg.

Studies in both normal volunteers and Type I diabetics demonstrate that Humalog is absorbed faster than regular insulin. In normal volunteers given subcutaneous doses of Humalog ranging from 0.1-0.4 U/kg, peak serum levels were seen 30-90 minutes after injection. In contrast, volunteers given equivalent amounts of regular human insulin reached peak levels anywhere from 50-120 minutes after dosing. In Type I diabetics, similar results were seen (see figure below). Humalog is absorbed faster than regular human insulin at all three of the common injection sites used by diabetics (e.g., abdomen, thigh, deltoid).

A study was performed to determine whether Humalog may be mixed in the same syringe with long-acting insulins such as NPH or Ultralente. When mixed with NPH just before injection, the rate of absorption of Humalog (as estimated by Cmax) is decreased by 30%, and the mean time to peak increased from 45 minutes to 76 minutes. No effect was seen when Humalog was mixed with Ultralente. ***These results suggest that mixing Humalog with NPH insulin will significantly decrease its rate of absorption.***

A study was performed in 12 healthy male volunteers to determine what effect the site of injection has on the absorption rate of Humalog. Each volunteer was given either human insulin or insulin lispro (0.2 U/kg) in either the abdominal, deltoid or femoral region in a randomized crossover fashion. The results show that insulin lispro is consistently absorbed at a higher rate than regular human insulin at

all three injection sites, with peak insulin lispro concentrations after abdominal administration about 50% higher than those resulting from deltoid or thigh injection.

Distribution

The volume of distribution for Humalog is identical to human insulin, ranging from 0.26-0.36 L/kg.

Metabolism

No metabolism studies were conducted. It is assumed that the metabolism of Humalog is identical to human insulin.

Elimination

When given intravenously, both Humalog and human insulin show identical dose-dependent elimination, with a $t_{1/2}$ of 26 minutes at 0.1 U/kg, and a $t_{1/2}$ of 52 minutes at 0.2 U/kg. Given subcutaneously, the $t_{1/2}$ values observed for Humalog are longer (about 1 hour) due to rate-limiting absorption.

Special Populations

Renal

No significant difference in insulin lispro pharmacokinetics was observed between non-diabetic patients with renal impairment (ranging from slight impairment to anephric) and normal controls.

Age, Gender, Pediatric

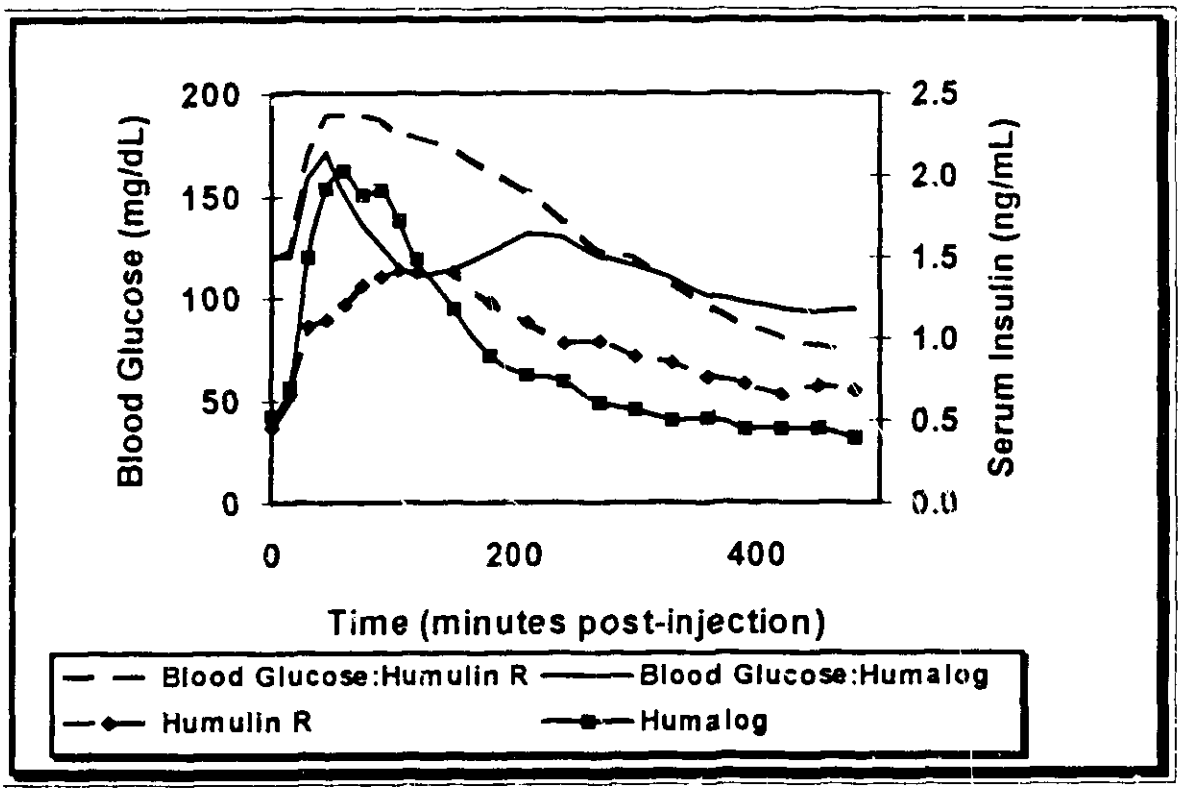
No information on the effect of age or gender on the pharmacokinetics/pharmacodynamics of insulin lispro is available.

Drug-Drug Interactions

No studies were performed.

Pharmacokinetics/Pharmacodynamics of Humalog in Type I Diabetics

Serum insulin, serum Humalog and blood glucose levels after subcutaneous injection of either regular human insulin or Humalog immediately before consumption of a meal high in carbohydrates in 10 Type I diabetics



2. On page 9 under **DOSAGE AND ADMINISTRATION**, the first sentence of the third paragraph should be changed to the following:

"Humalog is absorbed rapidly (with peak concentrations being reached 30-90 minutes post-injection, as compared with 50-120 minutes for regular insulin) and would be expected to have a faster onset of activity and a shorter duration of action than regular insulin."

3. On page 9 under **Mixing Humalog with longer-acting insulins**, a statement should be added warning of the decrease in absorption rate seen when Humalog is mixed with NPH insulin.

2/22/96

Michael J. Fossler, Pharm. D., Ph. D.

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 2/7/96

FT initialed by Hae-Young Ahn, Ph.D., Team Leader 2/22/96

Biopharm day held 2/16/96 11:00 AM. Present: Lesko, M. Chen, Lazor, Ahn, Koller (HFD-510), Misbin (HFD-510), Fossler

version: final

cc: NDA 20-563 (orig., 1 copy), HFD-510(Koller, Misbin, Weber), HFD-880(Fleischer), HFD-870(M. Chen, Fossler, Ahn), HFD-860(Malinowski), HFD-850(Drug file, Chron. file, Reviewer), HFD-205(FOI) HFD-340 (Vish)

APR 16 1996

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA #: 20-563
CHEMISTRY REVIEW #: 1 DATE REVIEWED: 04-16-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	03-13-95	03-14-95	03-16-95
AMENDMENT	07-21-95	07-25-95	
	11-06-95	11-07-95	
	04-01-96	04-02-96	

NAME & ADDRESS OF APPLICANT: Eli Lilly and Co.
Lilly Technology Center
Indianapolis, IN 46285

DRUG PRODUCT NAME

Proprietary:	Humalog
Nonproprietary/Established/USAN:	Insulin Lispro
Code Name/#:	LY275585
Chem Type/Ther Class:	1 S

ANDA Suitability Petition / DESI / Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION: Insulin

DOSAGE FORM:	Injectable (solution)
STRENGTHS:	100 U/mL (10 ml vials and 1.5 ml cartridges)
ROUTE OF ADMINISTRATION:	Injection
DISPENSED:	_X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Lispro;

SUPPORTING DOCUMENTS:

IND , Lispro Insulin (rDNA origin), Ely Lilly.

DMFs

RELATED DOCUMENTS (If applicable): NDA 18-780, Humulin R, Human Insulin (rDNA origin), Ely Lilly; IND Human Proinsulin, Ely Lilly.

CONSULTS: Environmental Assessment; Microbiology; CDER Labeling and Nomenclature Committee.

REMARKS/COMMENTS:

This NDA describes Insulin Lispro, a recombinant analogue of human insulin. In Lispro, the order of the amino acids at the B-28 (proline) and B-29 (lysine) positions have been reversed, resulting in B^{28}-lysine-B^{29}-proline human insulin.

In the clinical studies performed to date, there were fewer incidents of hypoglycemia associated with Humalog than with Humulin R reported. With respect to area under the curve (AUC), Lispro has been shown to be equivalent to human insulin in terms of potency per unit weight of protein.

Lispro drug substance is produced by recombinant DNA methods in *E. coli*, and is produced by a form of Lispro insulin. are performed at Lilly's Dista facility in the UK followed by operations at the Lilly Technology center in Indianapolis. The isolation of the Drug Substance follows essentially the same steps used in the production of derived human insulin. Lispro has the same molecular weight, pI, and amino acid composition as human insulin. Lispro can be distinguished from human (and beef and pork insulins) insulin by The sponsor has performed extensive studies of the secondary, tertiary, and quaternary structures of Lispro, and with the exception of the conformation of the , it is essentially equivalent to human insulin.

The Drug Product will be marketed under the trade name, Humalog™, for both 10 mL vials and 1.5 ml cartridges. Drug Product vials will be manufactured in the firm's facilities in Indianapolis, whereas the cartridges will be manufactured in the firm's Fegersheim, France facilities. Cartridges are for use with the B-D Pen and B-D Ultra Pen.

Amendment 07-21-95 provides the following: 1) for the drug substance: updated stability data; revised tests and specifications to include tightened specifications for , analytical data for 16 commercial-size batches; and, 2) for the drug product: batch histones for three representative full-scale batches of 10 ml vials manufactured at the Indianapolis, Indiana facility and three representative full-scale batches of 1.5 ml cartridges manufactured at Fegersheim, France facility; revised tests and specifications to include tightened specifications for analytical data for three commercial-size lots each of vials and cartridges; stability data for four full-scale lots of vials manufactured at the Indianapolis, Indiana facility; stability data for three full-scale lots of cartridges manufactured at the Fegersheim, France facility; updated stability data for those lots previously submitted; the results of simulated in-use stability of cartridges manufactured at the Indianapolis, Indiana facility; the results of a dosing accuracy studies to support the use of the B-D Pen and B-D Pen Ultra; and, analytical results for methods validation samples.

Amendment 11-06-95 provides the results of validation studies to demonstrate the stability of various in-process intermediates in order to support holding times of more than Also provided are the results of simulated in-use stability studies) of 1.5 ml cartridges manufactured at the Fegersheim, France facility.

Amendment 04-01-96 provides a draft labeling for the Physician's Package Insert, revised Patient's Package Insert, cartridge label, cartridges carton, vial label, and vial carton.

CONCLUSIONS & RECOMMENDATIONS:

The chemistry, manufacturing and controls (CMC) information is not satisfactory. The Microbiology information for sterilization process validation was found to be satisfactory (see consultive Microbiology Review #2, dated 1-22-96). The Environmental Assessment (EA) documentation was found to be adequate and a FONSI was recommended (see consultive EA Review, dated 2-19-96). The CGMP status of all of the facilities utilized by the firm were found to be acceptable as of 11-27-95, however, the Lilly France Fegersheim facility, which is utilized for cartridge manufacture, was found to be unacceptable. The results of a re-inspection of the firm's Fegersheim facility are pending. Additional CMC deficiencies are detailed in the Chemist's Draft Letter. Issue a chemistry information request letter.

cc:
Org. NDA 20-563
HFD-510/Division File
HFD-510/W.Berlin/S.Moore/Y.Chiu/J.Weber(CSO)

William K. Berlin, Review Chemist

Stephen K. Moore, Team Leader Chemist

Filename: N20563o.lsp

MAY 2 9 1996

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA #: 20-563

CHEMISTRY REVIEW #: 2 DATE REVIEWED: 05-29-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	03-13-95	03-14-95	03-16-95
AMENDMENT	04-22-96	04-23-96	
	05-14-96	05-15-96	
	05-28-96	05-29-96 (1 of 2)	
	05-28-96	05-29-96 (2 of 2)	

NAME & ADDRESS OF APPLICANT: Eli Lilly and Co.
Lilly Technology Center
Indianapolis, IN 46285

DRUG PRODUCT NAME

Proprietary:	Humalog
Nonproprietary/Established/USAN:	Insulin Lispro
Code Name/#:	LY275585, LysPro
Chem Type/Ther Class:	1 S

ANDA Suitability Petition / DESI / Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION: Insulin

DOSAGE FORM:	Injectable (solution)
STRENGTHS:	100 U/mL (10 ml vials and 1.5 ml cartridges)
ROUTE OF ADMINISTRATION:	Injection
DISPENSED:	_X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Lispro;

SUPPORTING DOCUMENTS:

IND Lispro Insulin (rDNA origin), Ely Lilly.

DMFs

RELATED DOCUMENTS (if applicable): NDA 18-780, Humulin R, Human Insulin (rDNA origin), Ely Lilly; IND Human Proinsulin, Ely Lilly.

CONSULTS: Environmental Assessment; Microbiology; CDER Labeling and Nomenclature Committee.

REMARKS/COMMENTS:

This review covers the responses to a chemistry information request letter issued to the firm on the basis of Chemistry Review #1, dated 4-16-96 (see FDA letter, dated 4-30-96).

Amendment 4-22-96 provides revised labeling for the physician's package insert, patient information for vials and patient information for cartridges, cartons, and labels.

Amendment 5-14-96 provides the responses to requests for chemistry information on the 1) drug substance, including

structural and biological characterization . reference standard /. and
2) drug product, including sampling plan and labeling

Amendment 5-28-96 (1 of 2) provides a Phase 4 commitment to

Amendment 5-28-96 (2 of 2) provides a revised physician's package insert, patient information for vials and patient information for cartridges. The submission is stated to be the same as a 5-24-96 FAX.

The firm makes the following Phase 4 chemistry commitments.

CONCLUSIONS & RECOMMENDATIONS:

From a Chemistry point of view, this application may now be approved. The chemistry, manufacturing and controls (CMC) information is satisfactory. The Microbiology information for sterilization process validation was found to be satisfactory (see consultive Microbiology Review #2, dated 1-22-96). The Environmental Assessment (EA) documentation was found to be satisfactory (see consultive EA Review and FONSI, dated 2-19-96). The CGMP status of all of the facilities utilized by the firm were found to be acceptable as of 5-22-96 (see EER dated 4-25-95 and Follow-up EER, dated 4-14-96)

cc:
Org. NDA 20-563
HFD-510/Division File
HFD-510/W.Berlin/S.Moore/Y.Chiu/J.Weber(C.

5/29/96
William K. Berlin, Review Chemist

Stephen Moore 5/29/96
Stephen K. Moore, Team Leader Chemist

Filename: N20563o2 lsp

Consult #342

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Ms. Yana Mille, Chair, (HFD-611) MPN II

FROM: Division of Metabolism & Endocrine Drug Products HFD- 510
Attention: Dr. Stephen Moore Phone 443-3510

DATE: 8-17-94

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Humalog™ IND # ~~NDA/ANDA#~~ (Pre-NDA stage)

Company Name: Eli Lilly and Company

Established name, including dosage form: Lispro (dosage form: injectable)

Other trademarks by the same firm for companion products: Humulin® (for human insulin products R, N, L and U)

Indications for Use (may be a summary if proposed statement is lengthy):

Treatment of diabetes (proposed).

Initial comments from the submitter: (concerns, observations, etc.)

1) Lispro is a Lys(B28), Pro(B29) analogue of human insulin.

2) The NDA for this new molecular entity will be submitted in the near future. Therefore the firm has requested a tradename review at this time.

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev May.94

COMPLETED

Consult #342 (HFD-510)

HUMALOG Lispro Injection

The Committee noted the similarity between the proposed name and the human insulin, Humulin. However, the Committee believes they are sufficiently different, and with adequately different packaging there should be not significant risk of medication error involving the proposed proprietary name with Humulin.

The Committee has no reason to find the proposed name unacceptable.

CDER Labeling and Nomenclature Committee

Ilene Mills, Chair 10/11/94

J. Short

AUG 7 1995

Consultative Review to HFD-510
DIVISION OF MEDICAL IMAGING, SURGICAL,
and DENTAL DRUG PRODUCTS; HFD-160

Microbiologist's Review #1
31 July 1995

A. 1. NDA 20-563
APPLICANT: Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

2. PRODUCT NAMES: Humalog® (insulin lispro)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is an injectable for subcutaneous injection. Strength is 100 U/mL.

4. METHODS OF STERILIZATION:
The drug product is

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The drug product is used to control blood glucose levels in the treatment of diabetes mellitus.

B. 1. DATE OF INITIAL SUBMISSION: 13 March 1995

2. DATE OF AMENDMENT: 5 June 1995 (Amended with Microbiology Information.)

3. RELATED DOCUMENTS:

IND	DMF	
DMF	DMF	DMF
DMF	DMF	DMF
DMF	DMF	DMF
DMF	DMF	

4. ASSIGNED FOR REVIEW: 4 April 1995

C. REMARKS: The NDA provides for the manufacture of two product container configurations at different facilities. Vials (10 mL fill) will be manufactured at: Eli Lilly and Company, Lilly Technology Center, 1200 - 1555 Kentucky Avenue, Indianapolis, IN. Cartridges (1.5 mL fill) will be manufactured at: Eli Lilly France S.A., rue du Colonel Lilly, 67640 Fegersheim, France.

D. CONCLUSIONS: The application is approvable upon resolution of microbiology concerns.

31 July 1995

Paul Stinavage, Ph.D.

PAC 8/7/95

cc: Original NDA 20-563
HFD-160/Stinavage/Consult File
HFD-510/Div File/J. Short
Drafted by: P. Stinavage
R/D initialed by P. Cooney

Short

JAN 22 1996

REVIEW FOR HFD-510
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #2 OF NDA 20-563
18 January 1996

A. 1. NDA 20-563
APPLICANT: Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

2. PRODUCT NAMES: Humalog® (insulin lispro)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is an injectable for subcutaneous injection. Strength is 100 U/mL.

4. METHODS OF STERILIZATION:
The drug product is

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The drug product is used to control blood glucose levels in the treatment of diabetes mellitus.

B. 1. DATE OF INITIAL SUBMISSION: 13 March 1995

2. DATE OF AMENDMENT: 13 December 1995

3. RELATED DOCUMENTS:

IND	DMF	
DMF	DMF	DMF
DMF	DMF	DMF
DMF	DMF	DMF
DMF	DMF	

4. ASSIGNED FOR REVIEW: 4 April 1995

C. REMARKS: The amendment is a response to deficiencies found in the 31 July 1995 review of the New Drug Application.

D. CONCLUSIONS: The application is recommended for approval on the basis of the information supplied.

18 January 1996
Paul Stinavage, Ph.D.

DNR 1/22/96

cc: Original NDA 20-563
HFD-805/Stinavage/Consult File
HFD-510/Div File/J. Short

Drafted by: P. Stinavage, 18 January 1996
R/D initialed by P. Cooney, 18 January 1996

Short

CONSULTATIVE REVIEW TO HFD-510
DIVISION OF MEDICAL IMAGING, SURGICAL, and DENTAL DRUG PRODUCTS; HFD-160

Microbiologist's Comments for Filing Meeting
3 April 1995

A. 1. NDA 20-563

SPONSOR Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, Indiana 46285

2. PRODUCT NAMES: HUMALOG™ (insulin lispro, recombinant DNA origin)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: A sterile solution of 100 units per mL for subcutaneous injection. The dosage form consists of multi-dose cartridges of 1.5 mL of 100 units per mL (for use in injector pen devices) or in 10 mL multi-dose vials. The solution is preserved with *m*-cresol (3.15 mg/mL).

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Insulin

6. DRUG PRIORITY CLASSIFICATION: 1S

B. 1. DATE OF INITIAL SUBMISSION: 13 March 1995

2. DATE OF AMENDMENT: (none)

3. RELATED DOCUMENTS: DMF

were various DMFs

C. REMARKS. The applicant has provided a copy of the "complete drug product section" (CMC volume 1.59A) as well as introductory and summary volumes (1.1 and 1.1A) of the submission in white jackets for microbiology review. Type I DMF references are provided for manufacturing procedures.

The product is manufactured at 2 sites. The 1.5 mL cartridge presentation is manufactured at Lilly S.A. at rue de Colonel Lilly in Fegersheim, France, and the 10 mL vial presentation is manufactured at the Eli Lilly Technology Center at 1200 - 1555

Kentucky Avenue in Indianapolis, Indiana. Other approved insulin products are manufactured by Eli Lilly at these facilities.

The drug product composition was described (v. 1.59a, P. 12) and is shown in Table 1, below.

Table 1. Composition of the drug solution.

Component	Amount per mL
LysPro	100 units
Glycerin, USP	16 mg
m-Cresol	3.15 mg
Zinc Oxide, USP	q.s. to Zn^{++} of 0.0197 mg
Dibasic Sodium Phosphate, USP	1.88 mg
Water for Injection, USP	q.s. to 1 mL

Specific process information for product registration batches was provided. Representative batch (registration batch) histories were concisely summarized, including sterilization parameters and data. Substantive information for microbiology review of sterility issues was not provided, including:

is recommended and methods for should be described.

As a general guide to the applicant, the FDA "*Guideline for Submitting Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*" (Federal Register *58*(231): 63996-64001, 3 December 1993) will be provided.

D. CONCLUSIONS: The submission is not recommended for filing on the basis of sterility assurance issues. A knowledgeable conclusion concerning the sterilization methods and their validation cannot be made upon review of the material submitted. Should the Division decide to file the application as submitted, a review may be completed by the end of July 1995.

4-4-95
David Hussong, Ph.D.

4/4/95

cc:

Original NDA 20-563
HFD-510/Division File
HFD-160/Consult File
HFD-510/CSO
HFD-510/Chemist/S. Moore
HFD-160/D. Hussong

drafted by: D. Hussong, 04/03/95
R/D initialed by: P. Cooney, 04/04/95

NDA 20-563

APR 30 1996

Lilly Research Laboratories
Attention: Timothy R. Franson, M.D.
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Franson:

Please refer to your pending March 13, 1995, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Humalog™, [insulin lispro, (rDNA origin) Injection].

We also refer to your amendments dated April 1, July 21, and November 6, 1995.

We have completed our review of the Chemistry, Manufacturing and Controls section of your submission and have identified the following deficiencies:

Drug Substance

1. Please provide a table showing the identity of the Lispro lots that were used in the as described in volumes 1.2 and 1.6. Also, please include information on whether these were clinical lots, commercial-scale lots or reference standard lots.

2. Please supply information on the volume of the culture, number of vials and amount per vial for the

3.

4. Contingency plans for the action to be taken in the event of the exhaustive utilization, or loss of the should be submitted.

5. The results of a validation study to demonstrate stability of the copy number of the should be provided.

6. Please commit to perform in the post-approval period, a validation study of the

7. Please provide brief details of the preparation of the Lispro primary reference standard.

8. A current and fully-characterized Lispro primary reference standard must be maintained. The characterization should include the full modified

analysis should be capable of distinguishing Lispro from human insulin.

9. Please provide a test and specifications sheet for the qualification of current and future Lispro primary reference standards.

10. Please indicate whether or not a Lispro working reference standard will be utilized. If so, a brief description of its preparation and the criteria for qualification need to be furnished.

11. Regarding the the following should be provided:

1

2.

Drug Product

1. Please provide a brief description of the sampling plan used for the drug product.

2. A 24-month expiration dating period is granted on the basis of the stability data submitted.

Labeling

1. Whereas phenol is an integral and important functional component of the drug substance, the list of ingredients and their quantitative amounts in the Description section of the Physician's Insert should include phenol and the amount.

2. A second paragraph should be added to the Description section of the Physician's Insert to state that the cartridges are for use only in B-D Pen and B-D Pen Ultra.

3. Since there are two different Patient's Package Inserts, one for vials and the other for cartridges, the one for vials should include the word "Vial" in the title.

4. The following sentence in the Description section of the Patient's Package Inserts for both vials and cartridges: "Humalog has had nothing added to change the speed or length of its action." is the first statement made in this section concerning the rate and effect of Lispro action. The sentence is potentially confusing in the context presented and therefore it should either be deleted or revised with more detail and moved to a position of lesser prominence in the text.

5. The color burgundy (on the aluminum crimp seals and plastic flip-off seals for vials, and aluminum crimp seals for cartridges, should not appear on the labeling or be referred to as a color code for Lispro in either the labeling or advertising until the current proposed color-coding scheme for insulins becomes finalized.

Establishment Inspection

The establishment evaluation of the Lilly France Fegersheim facility was found unacceptable, the results of the re-inspection are pending.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Ms. Jena Weber at 301-443-3510.

Sincerely yours,

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Original NDA 20-563
HFD-510
HFD-510/WBerlin/SMoore/YYChiu
HFD-511/JWeber/04/25/96/Lispro.chm

Concurrences:SShen for Wberlin 4/26/SMoore 4/26/EGalliers 4/29/96

Final:JWeber 5/3/96

INFORMATION REQUEST

~~SHORT~~
Weber

IND
NDA 20-563

MAR - 7 1996

Lilly Research Laboratories
Attention: Timothy R. Franson, M.D.
Executive Director, North American Regulatory Affairs
Lilly Corporate Center
INDIANAPOLIS IN 46285

Dear Dr. Franson:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for Humalog [insulin lispro (rDNA origin)].

Reference is also made to your amendment February 28, 1994, requesting a waiver of the requirement for the submission of paper copies of the case report forms for your Computer-Assisted NDA (20-563) subsequently submitted on March 13, 1995, for Humalog [insulin lispro (rDNA origin)] Injection, 100 units/mL.

We have completed the review of your amendment and have concluded that under 21 CFR 314.90(b)(2) your proposed alternative electronic submission justifies waiver of the "hard copy" requirements of 21 CFR 314.50(f). Consequently, your waiver request is granted.

Should future retrieval be deemed necessary, and as a condition of granting this waiver, you are required to maintain the paper copies of the case report forms in a reviewable format.

If you have any questions, please contact:

John R. Short, R.Ph.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,

/S JWoodcock

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

cc: Original NDA 20-563
Original IND
HFD-510/Div. Files (one each for NDA and IND)
DISTRICT OFFICE
HFD-001/JWoodcock
HFD-005/JAxelrad
HFD-323/PMotise
HFD-510/CSO/J.R.Short
HFD-510/EKoller, RMisbin, AFleming

drafted: JShort/12/10/95 \N20563AD.4JS
r/d Initials: EGalliers 12/12, AFleming 12/28, SSobel 1/3/96
final: JShort 1/29/96
redrafted: JShort 2/21/96
r/d Initials:
final:

ADVICE LETTER

NDA 20-563

Lilly Research Laboratories
Attention: Timothy R. Franson, M.D.
Executive Director, North American Regulatory Affairs
Lilly Corporate Center
INDIANAPOLIS IN 46285

FEB 26 1996

Dear Dr. Franson:

We acknowledge receipt on December 19, 1995, of your December 18, 1995 amendment to your new drug application for Humalog [insulin lispro (rDNA origin)] Injection, 100 units/mL.

We consider this a major amendment received by the agency within three months of the user fee due date. Therefore, the user fee clock is extended three months. The new due date is June 14, 1996.

If you have any questions, please contact:

Jena Weber
Consumer Safety Officer
(301) 443-3510

Sincerely yours,

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Original NDA 20-563
HFD-510/Div. Files
DISTRICT OFFICE
HFD-005/RHassall, NSager
HFD-40/AReb
HFD-870/MFossler, HAhn
HFD-715/BTaneja, DMarticello
HFD-510/CSO/J.R.Short
HFD-510/EKoller, RMisbin, AFleming, SMoore, DHertig, AJordan

drafted: JShort/2/11/96 \N20563RV.JRS
r/d Initials: EGalliers 2/23/96
final: JShort 2/25/96

REVIEW EXTENSION (Goal Date 6/14/96)

2/25/96

Short
W.Ben

DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date JAN 30 1996

From Solomon Sobel, M.D. 1/29/96
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

Subject Waiver of Paper Copies of Case Report Forms for NDA 20-563

To Director
Center for Drug Evaluation and Research

Through James Bilstad, M.D.
Director
Office of Drug Evaluation II
Jane Axelrad
Associate Director for Policy, CDER

2/27/96
3/1/96

On July 11, 1994, the Division sent a letter (under IND to Lilly informing them that we granted their request to replace paper copies of case report forms with electronic case report forms in the format of a CANDA. Later we learned that such a waiver may only be granted by the Center director. This prompted two telephone conversations with Lilly (October 13 and November 7, 1995) to discuss the situation. During the later one, Ms. Axelrad informed Lilly that the required submission of paper copies of case report forms could be waived, but the Division must be able to obtain all needed information from the electronic case report forms. The Division believes that the contents of the electronic case report forms are adequate. Attached is a letter to Lilly granting their waiver request. If you agree with this action, please sign and return to Mr. John Short of this Division.

Lilly subsequently decided to submit the paper copies of the case report forms and these were received on December 12, 1995 (submission dated December 11, 1995). Lilly still wishes to receive this letter confirming our decision to issue the waiver because they foresee the same issue arising with a future NDA.

Thank you.

Attachments (3)
IND Letter Dated 7/11/94
NDA 20-563 Memo of Teleconference (draft) held 10/13/95
NDA 20-563 Memo of Teleconference (final) held 11/7/95

cc: Original NDA 20-563
HFD-510/Div. Files
HFD-001/JWoodcock
HFD-005/JAxelrad
HFD-323/PMotise
HFD-510/CSO/J.R.Short
HFD-510/EKoller, RMisbin, AFleming

drafted: JShort/12/10/95 \N20563AD.4JS
r/d Initials: EGalliers 12/12, AFleming 12/28, SSobel 1/3/96
final: JShort 1/29/96

NDA 20-563
Humalog (insulin lispro) Injection
Lilly Research Laboratories

December 6, 1995

MEMORANDUM OF TELECONFERENCE

Lilly Representatives:

Gregory Davis, Ph.D., Director, Regulatory Affairs CM&C
Bruce Frank, Ph.D., Research Advisor, Biopharmaceutical Development
Paul Hines, Development Projects Management
Ervin Kattelman, Ph.D., Research Scientist, Biosynthetic Technical Services
Barbara Mallett, Senior Regulatory Representative, Regulatory Affairs CM&C
William Muth, Ph.D., Natural Products Research and Development
Mary Sitckelmeyer, Ph.D., Biopharmaceutical Product Development

FDA Staff:

Dr. Moore
Dr. Berlin
Mr. Short (CSO)

Purpose: Lilly requested the meeting to discuss 1) a proposed site change for and initial recovery of the lispro bulk drug substance (BDS), and 2) See information appended to the attached correspondence dated November 20, 1995, for details of Lilly's presentation.

Discussion and Conclusions: Dr. Davis noted that Lilly wants to discuss these changes at this time not as a change in the pending NDA, but as a supplement to the NDA following approval (assuming that the NDA will be approved).

After Mr. Short introduced the people on our end of the teleconference, Dr. Davis questioned why Dr. Chiu was not present. Mr. Short explained how she no longer is involved in the day-to-day decision making of the chemists in this Division since October 1, 1995, when she became the acting Director, Division of New Drug Chemistry II, within the newly created Office of New Drug Chemistry (ONDC). Mr. Short explained that the day-to-day operations are now overseen by two acting Team Leaders, Dr. Stephen Moore and Dr. Helen Davies.

Site Change

Dr. Muth explained how Lilly plans to move the , in the production of the BDS will be moved from the Biotech Center at Dista (in the UK) to Lilly's Indianapolis facilities. All other steps in the production of the BDS will be performed at the

Indianapolis facility, as currently described in the NDA. Dr. Davis noted that the process is essentially the same but all new equipment will be used. See page 5 of attachments for minor site differences.

Mr. Hines described the timeline for implementation of this change, culminating with a NDA supplement submission in September 1996. He then went on to describe the proposed contents of the supplement (see attachments). Lilly will provide accelerated and 3-month, real-time stability data for the BDS produced in the new facility. Dr. Moore requested that a commitment be provided that long-term stability results will be included in subsequent annual reports. Lilly also will provide batch-release data on drug product produced from the BDS totally produced at the Lilly facility for the following drug products:

2 lots of U100 Vials
2 lots of U100 1.5 mL Cartridges
*1 lot of U40 Vials
*1 lot of U100 Vials

*These three lots will be manufactured primarily for European registration, but the release data will provide further support for this supplement.

No stability data will be provided in the supplement on the drug product produced from the new BDS. Dr. Moore requested that a commitment be made to provide this data in subsequent annual reports.

Other Issues (regarding pending NDA)

Dr. Davis noted that answers are being generated for the microbiology and environmental assessment (information request letter dated 9/6/95) and will soon be submitted to the NDA.

Regarding the inspection of the manufacturing facilities, Dr. Moore told the Lilly representatives that all received a satisfactory inspection except the Fegersheim, France facility, which was found "unacceptable". Dr. Moore asked Dr. Davis to let him know when this facility would be ready for re-inspection and then Dr. Moore would initiate a new EER (Establishment Evaluation Request). Dr. Davis said he would do this as soon as the facility was ready for inspection.

Conclusion

FDA staff had no objections to the proposed content of the two supplements discussed.

ACTION ITEMS:

1. Lilly to provide supplements as provided above.

2. Dr. Davis to inform Dr. Moore when the Fegersheim, France facility is ready for re-inspection.

3. Lilly to provide responses to our IR letter dated 9/6/95 re: microbiology and EA deficiencies.

John R. Short, CSO

Attachments

Background Material (correspondence dated 11/20/95)

NDA 20-563
Humalog (insulin lispro) Injection
Lilly Research Laboratories

November 7, 1995

MEMORANDUM OF TELECONFERENCE

Lilly Representatives:

Timothy Franson, M.D., Executive Director, North American Regulatory Affairs
Robert Hizer, Systems Informatics Advisor
Diana McKenzie, Manager, Regulatory Systems
Philip Reid, M.D., Vice President, Lilly Research Laboratories
Jeffrey Winn, D.D.S., Regulatory Scientist, North American Regulatory Affairs

FDA Staff:

Mr. Short
Ms. Axelrad (HFD-005)
Mr. Motise (HFD-323)

Purpose: FDA requested the teleconference as a follow-up to our previous teleconference held October 13, 1995, to discuss the possibility of FDA waiving the requirement of submitting paper copies of case report forms (CRFs).

Logistics Information: Each of the FDA representatives was in his/her respective office to be part of the call.

Background: See Memo of Teleconference dated October 13, 1995, wherein Lilly explained to Mr. Motise their procedure for obtaining electronic information and their electronic auditing procedure. Ms. Axelrad was not part of the first conversation.

Discussion and Conclusions: Ms. Axelrad told Lilly that she had discussed the results of the October 13, 1995, teleconference with various CDER staffers, including Dr. Woodcock, and that the conclusion had been reached that we have no problem granting Lilly a waiver from submitting paper copies of CRFs. She noted, however, that HFD-510 is having difficultly reviewing the data in the CANDA because the data are scattered throughout the CANDA and are not organized on a per-patient basis as they would be in a paper CRF. Ms. Axelrad said that waiving the paper requirement will not relieve Lilly of the responsibility of providing the HFD-510 staff with data in a reviewable format.

Ms. Axelrad said that based upon what Mr. Motise learned from the October 13 discussion, he is concerned about whether the reliability of the data generated can be demonstrated (because of the method by which it was collected), whether reported electronically or on paper, but Ms. Axelrad

said FDA agrees that we should be able to handle the problem through our DSI audits of the pivotal clinical trials.

Ms. Axelrad said she was aware of Lilly's concern during the October 13 teleconference that we were applying 1995 standards for data integrity to data which were generated in 1991. She said CDER needs to address this problem for future applications and will do so in the final electronic signature/records rule.

Mr. Motise noted that it is of utmost importance that anyone be able to see changes made in CRFs. He said his greatest concern about Lilly's electronic CRFs is that such changes (which should be detectable via an audit trail) are available only in a separate file. In other words, only if one is looking at the separate file would it be possible to know if and what changes are made in the CRF. Mr. Hizer said that the paper copies of files for patients in the audits Dr. Turner will be performing (submitted November 3, 1995 to IND . show the changes made, i.e., there is a paper audit trail. Mr. Short noted that Mr. Motise may want to look at the desk copy forwarded by Lilly to Dr. Turner's office.

Mr. Motise noted that he had one other concern: that the auditors should be able to examine the electronic trail of change, not just a paper trail, because the records were collected electronically and the paper representations may not reflect all changes. Mr. Hizer noted that although all computers were removed from each site at the time the data collection was completed, he said the computers could be re-installed with all the data and Lilly personnel available on short notice. Mr. Motise liked this idea because then the audit could be done on data in its native form. Mr. Motise said that it also would be good to do the audit with both paper and electronic data available for comparison. Mr. Motise suggested that Lilly set up the computers at each site to be audited, but Mr. Hizer said that Dr. Turner had agreed (prior to his departure on a current audit trip) that Lilly could produce the electronic capability at the site if requested by Dr. Turner. It was agreed that if this could be done within 1 or 2 days (2 days at the most) of Dr. Turner's request, that would be satisfactory.

Mr. Short agreed that he would generate the waiver letter to be signed by Dr. Woodcock.

ACTION ITEMS:

1) Mr. Short to generate the waiver letter to be signed by Dr. Woodcock.

2) Lilly to be prepared to delivery computer equipment and electronic data to whatever site Dr. Turner requests (during his audit of the site) within 2 days of the request.

John R. Short, CSO

Short

DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date OCT 17 1995

From Solomon Sobel, M.D.
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)

Subject Request for Clinical Study Audits for NDA 20-563, Humalaog (lispro insulin) Injection

To Director, Division of Scientific Investigations, HFD-340

We have identified the following studies as being pivotal to the approval of this application. We recommend that the indicated sites be audited.

Besides the Moscow site, we have selected several other pivotal trial sites for audit. The sites were selected with several criteria in mind: a) the number of patients, b) the location was a site for more than one study, c) there were perceived problems at the site, and/or d) there was some geographic proximity between locations. Although there are some problems with the South African sites, we realize that an audit there would present some logistical problems and have not included them in this request.

Study #	# pts	Investigator #	Name	Address
Moscow Site:				
IOAJ	8	101	I. Dedov	Nat. Center for Endocrinology, Moscow, Russia
First Tier:				
IOAA	22	003	H.P. Chase	U of Colorado, 4200 E. 9th Ave, Denver, CO
IOAF	11	005	M.L. Spencer	Park Nicollet, 5000 W. 39th St., Minneapolis, MN
IOAF	14	024	T. Blevins	ADCCR, 911 W. 38th St., Austin, TX
IOAF	11	029	V. Calamia	201 Forest Ave Staten Island, NY
IOAF	11	064	N.G. Soler	SDEC, 2528 Farragut, Springfield, IL
IOAF	18	072	P. Lodewick	700 18th St., S. Birmingham, AL
IOAF	10	080	E. Ritchey	IDC, 3655 Lutheran Pky., Wheat Ridge, CO

IOAA	9	300	B. Charbonnel	Hotel-Dieu Pavillion, Mere Et Enfant, Place Alexis
IOAF	7	"	"	Ricordeau, France
IOAA	10	600	A. Jara	Hospital Gregorio Maranon, Madrid, Spain

Second Tier:

IOAF	6	079	D. Bloomfield	St. Vincent's, 355 Bard St., Staten Island, NY
IOAF	11	082	M.A. Charles	DMRC, 1000 S. Anaheim, Anaheim, CA

Most of the above investigators also conducted extension trials.

For your assistance, attached is a complete list of investigators by study number.

The reviewing medical officer for this application is Dr. Elizabeth Koller, phone 443-3490. In her absence, you may contact Dr. Robert Misbin, phone 443-3510.

The responsible project manager is Mr. John Short, phone 443-3510.

The User Fee goal date is March 14, 1996.
The Division's action goal date is January 12, 1996.

[NOTE: We are more than half way in the 12-month review process because initially it was decided that a DSI investigation was not necessary as this is an insulin product (for which investigations are not generally done), but it was decided during the review process that an investigation is necessary.]

cc: NDA Arch
HFD-510
HFD-344/GTurner
HFD-510/EKoller, RMisbin, AFleming
HFD-511/JShort 10/14/95/FT/JS/10/17/95 \N20563M.DSI
Concurrence: EGalliers, EKoller 10/14, AFleming for RMisbin, AFleming 10/16/95

10/17/95 10/17/95

Short

OCT 24 1995

MEMORANDUM OF TELECON

DATE October 10, 1995

APPLICATION NUMBER: NDA 20-563

BETWEEN:

Name: Jeff Winn, DDS
Phone: 317-276-2098
Representing: Lilly Research Laboratories

AND

Name: John R Short, CSO
Division of Metabolism and Endocrine Drug Products, HFD-510

SUBJECT: Physician PI and Advisory Committee Meeting

As an Action Item from our internal STATUS meeting for Humalog on September 19 & 21, 1995, I called Dr Winn and informed him that we would like Lilly to submit a physician's version of the PI for this drug (Lilly assumed it would be an OTC item like all other insulins and, therefore, only provided the patient version in the NDA). Dr. Winn said that it was quite a shock to know that we are thinking of making is product an Rx item, and that he would check into providing us a physician's PI.

changed to 2/29/95

I also informed Dr. Winn that we would be taking this NDA to our Endocrinologic and Metabolic Drugs Advisory Committee on either January 11 or 12, 1996. [NOTE: In a subsequent conversation with Dr. Winn he informed me that Lilly would not have time to generate the material for the Advisory Committee (by 4 weeks prior to the meeting), and asked if we could delay the meeting. I told him that the next meeting would be February 29 and March 1, 1996. I informed him that this would be too close to Goal Date of 3/14/96, and unless the Goal Date were extended 90 days as a result of a major amendment within the last 90 days of the original Goal Date, we could not change the meeting date. I told him that if Lilly wanted to delay the advisory committee meeting, they should make a submission to the NDA explaining why they cannot make the 1/11-12/96 date, and provide a commitment that there would be an amendment to the NDA during the 90 days prior to 3/14/96 which could be classified as a Major Amendment, extending the Goal Date 90 days (to 6/14/96). He said he would take this information to his management for discussion. I also told him that one way or another we will have an advisory committee meeting to discuss this drug.]

12/20/95

John R. Short
Consumer Safety Officer

cc Original NDA 20-563
HFD-510/Div File
HFD-510/EKoller, RMisbin, AFleming, SSobel
HFD-510/JShort 10/24/95 \N20563MT.2JS

TELECON

Short

NDA 20-563

SEP 13 1995

Lilly Research Laboratories
Attention: Timothy R. Franson, M.D.
Executive Director, North American Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Franson:

Please refer to your pending March 13, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Humalog [insulin lispro (rDNA origin)] Injection, 100 units/mL.

We also refer to your amendment dated August 18, 1995, providing a confirmation of clinical questions and comments made at a CANDA session at the Agency on August 10, 1995.

We have completed our review of the agreements included in your submission and offer the following response related to comment #2. Comment #2 is stated as follows in your August 18 communication:

> 2. What was the justification for using the changed in the 1 and 2 hour postprandial glucose excursions as a primary measure of efficacy? Explain why these changes are not at variance with changes in hemoglobin A1c and fasting glucose.

The issue is not why changes in 1- and 2-hour postprandial glucose excursions may sometimes be at variance with changes in HbA_{1c} and fasting glucose. The issue is the clinical importance of changes in postprandial glucose excursion.

Lilly has previously stated the case as follows:

> By decreasing glucose excursion following a meal, the exposure of elevated glucose and its potential to cause long-term complications is reduced . . . Therefore, the 2-hour postprandial blood glucose excursion was used as the primary efficacy variable. (page 125/6, volume 1.1A)

Although this may appear reasonable on the surface, it ignores the possibility that a rapid-acting insulin might give rise to delayed postprandial hyperglycemia, 3-5 hours after eating. Also, the 2-hour postprandial glucose excursion has not previously been validated as a measure of glycemic control, nor has it been shown to correlate with the development of diabetic complications. Indeed, the only measure of glycemic control which has been clearly shown to correlate with the development of diabetic complications is HbA_{1c}. Therefore, an insulin product which improved the 2-hour postprandial glucose excursion at the expense of HbA_{1c} would actually be deleterious to the primary goal of therapy, which is to reduce the risk of complications. FDA's Endocrinologic and Metabolic Drugs Advisory Committee and the

American Diabetes Association are both on record as supporting the recommendation that it is desirable to lower HbA_{1c} by pharmacological means. It follows that overall glycemic control as reflected by HbA_{1c} outcome should be a primary consideration in the evaluation of any insulin drug product intended for chronic use.

Our risk/benefit assessment of lispro would be assisted if Lilly would provide evidence that a reduction in 2-hour glycemia excursion is desirable in itself. We also would be reassured by pharmacodynamic data that demonstrate that the effect of lispro at the 2-hour postprandial time point does not result in worsening of glycemic control at subsequent time points.

If you have any questions, please contact:

John R. Short, R.Ph.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,

9/13/95

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Original NDA 20-563
HFD-510/Div. Files
DISTRICT OFFICE
HFD-510/CSO/J.R.Short
HFD-510/EKoller, RMisbin, AFleming

drafted: JShort/9/8/95/N20563AD.JRS
r/c Initials: EKoller, RMisbin 9/8, AFleming 9/11/95
Revised as per Dr. Fleming's comments – JShort 9/13/95
final: JShort 9/13/95

ADVICE LETTER

9/13/95

J. Short

NDA 20-563

SEP - 6 1995

Lilly Research Laboratories
Attention: Timothy R. Franson, M.D.
Executive Director, North American Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Franson:

Please refer to your pending March 13, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Humalog [insulin lispro (rDNA origin)] Injection, 100 units/mL.

We also refer to your amendment dated June 5, 1995, providing additional microbiology information.

We have completed our review of the environmental assessment and microbiology sections of your submission and have identified the following deficiencies:

Environmental Assessment

The responses to deficiencies 1) and 2) may be provided in a non-confidential addendum to the EA if you prefer, rather than reformatting the current EA to incorporate the information.

1) Regarding Section 4, description of proposed action:

Information should be provided on accommodations for the disposal of waste or rejected drug substance and rejected or returned product. The name and location of current facilities used, whether the facility is a landfill or incinerator, and the licensing information (responsible regulatory agency, permit number, permit expiration date, if applicable) should be provided.

2) Regarding Section 6, introduction of substances into the environment for the sites of production:

The discussion of the disposition of solid wastes is not adequate. These wastes from all facilities are said to be sent to "appropriate waste facilities". Information should be provided about these disposal facilities, including whether they are landfills or incinerators, and licensing information (see deficiency 1).

3) Please provide an EA document suitable for public release or confirmation that pages 6-95 of the EA dated January 1995 may be released.

Microbiology

Please provide an amendment to address the following concerns:

1) For both manufacturing sites, please specify holding time limits between

2)

specified for both manufacturing sites. Actions to be taken if these limits are exceeded should also be specified.

3)

4)

5)

6)

7)

8)

9)

10)

11)

12)

13)

provided.

14)

15) Detailed information regarding the container/closure integrity testing of both

Industry for the Documentation for Sterilization Processes Validation in Applications for Human and Veterinary Drug Products. The Guidance states (in part):

"The applicant should provide scientific validation studies (and data) in support of the microbial integrity of the drug packaging and components. The following information should be included:

1.

2.

3.

4.

5.

16)

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

John R. Short, R.Ph.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,

9/1/95

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Original NDA 20-563
HFD-510/Div. Files
DISTRICT OFFICE
HFD-004/RJerussi
HFD-005/MJones
HFD-102/PVincent
HFD-160/PStinavage, PCooney
HFD-510/CSO/J.R.Short
HFD-510/SMoore, YYChiu

drafted: JShort/August 25, 1995/N20563IR.JRS
r/d Initials: Strinavage/8/25/95/Cooney/8/25/95/Moore/8/25/95/Chiu/8/25/95
final: THenry/9/1/95

INFORMATION REQUEST (IR)

JShort
9/1/95

Short

AUG 25 1995

MEMORANDUM OF A TELEPHONE CONVERSATION 8/25/95 NDA #20,563
Sponsor: Lilly Laboratories
Indianapolis, IN 46285
317-276-2000

After consultation with Dr. Fleming regarding the 8 cases of retinal disorder in the treatment group versus none in the standard therapy group, Drs. Koller and Misbin contacted Dr. Jeff Winn (Regulatory) at 2:30 P.M. 8/25/95 to ask that investigators be notified of these findings. (Refer to separate memorandum.) In response to this request, Dr. Timothy Franson (Executive Director-North American Regulatory Affairs), contacted me. It was agreed that, on 8/28/95, the sponsor would make a presentation in which they would explain their view of the findings that would, perhaps, change our position. Drs. Koller and Misbin were in attendance during the phone conversation.

Sol Sobel, M.D.
DMEDP-Division Director

cc: NDA Arch
HFD-570
HFD-570/AFleming, BKoller, RMisbin, JShort

TELEFAX

TO: Jeff Winn, Ph.D.

FAX: 317-276-1652

PHONE:

FROM: John R. Short
Food and Drug Administration
Division of Metabolism and Endocrine Drug Products
5600 Fishers Lane--HFD-510
Rockville, Maryland 20857-1706

FAX: 301/443-9282
PHONE: 301/443-3510

DATE: 4/7/95

PAGES: 3 [inclusive]

COMMENTS: Subject: NDA 20-563

1. Microbiology: See attached page. On 4/6/95 I mailed to you a copy of DA's "Guideline for Submitting Documentation for Sterilization Process Validatioin in Applications for Human and Veterinary Drug Products."
2. Biostatistics: See attached page.
3. Biopharmaceutics: Contact the Division of Biopharmaceutics to discuss possible additional data analyses as related to the evaluation of postprandial glucose excursion using alternative measurement parameter (i.e., AUC).

---

cc: NDA Arch (20-563), HFD-510
HFD-510/Fleming, Short, SMoore, YYChiu, EKoller
HFD-427/JHunt
HFD-160/DHussong HFD-713/BTaneja, ENevius

NDA 20-563

During our filing meeting held April 4, 1995, it was determined that additional information is needed from the statistical standpoint, as follows:

1. Data on demographic and primary efficacy variables in ASCII file on a diskette.

2. Computer programs to reproduce the sponsor's analyses on demographic and primary efficacy variables.

3. An investigation of the effect of dropouts on analyses (demographic and primary efficacy variables) including the following:

   (a) how many dropouts at each timepoint for each treatment
   (b) analyses comparing the cohorts of dropouts for the two treatments at each timepoint
   (c) a sequence of graphs for the analyses in (b) plotting demographic and primary efficacy variables on vertical axis and timepoints on horizontal axis.

Approved by

Solomon Sobel, M.D.
Director, DMEDP

NDA 20-563

During our filing meeting held April 4, 1995, it was determined that considerable Microbiology information was missing from the application and must be provided as soon as possible. The information missing is listed below. It is hoped that this information can be provided by Friday, May 12, 1995 (the filing date is Saturday, May 13, 1995). If not, a commitment must be made by May 12, 1995, that the data will be submitted by July 12, 1995, or the application may not be filed.

Specific process information for product registration batches was provided. Representative batch (registration batch) histories were concisely summarized,

2) were not provided. These should be briefly described including methods

3) Sterilization validation information (methods and brief data summaries) were not provided for components and equipment. Such validation experiments should include, for example,

4)

summaries) were not provided.

5)

Approved by

4/7/95

Solomon Sobel, M.D.
Director, DMEDP

NDA 20-563

MAR 30 1995

Lilly Research Laboratories
Attention: Timothy R. Franson, M.D.
Executive Director, North American Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Franson:

We have received your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Humalog [insulin lispro (rDNA origin)] Injection, 100 units/ml
Therapeutic Classification:	S
Date of Application:	March 13, 1995
Date of Receipt:	March 14, 1995
Our Reference Number:	NDA 20-563

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 13, 1995, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations and in accordance with the policy described in the Center for Drug Evaluation and Research Staff Manual Guide CDER 4820.6, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact:

Mr. John R. Short
Consumer Safety Officer
(301) 443-3510

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

3.30.95

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

cc: Orig. NDA
HFD-510
DISTRICT OFFICE
HFD-510/JShort 3/16/95 \N20563AC.JRS
Concurrence: EGalliers 3/30/95

ACKNOWLEDGEMENT - AC

3/30/95

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

May 28, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 20-563--Humalog™(insulin lispro, rDNA origin)

Eli Lilly and Company is amending NDA 20-563 to provide the FDA Division of Metabolism and Endocrine Drug Products a copy of changes (indicated by bolding and strikethrough marks) and a clean copy of the physician's package insert for Humalog (insulin lispro, rDNA origin). This is the same version that was FAX'd and provided via e-mail on May 24, 1996.

Please call Dr. Jeffrey Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

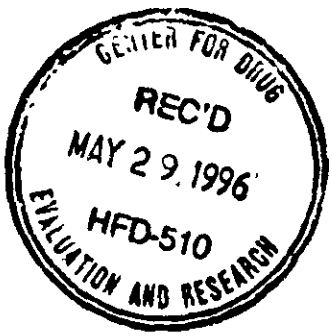
Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

attachment

cc Ms. Jena Weber (desk copy)
Mr. John Short (desk copy)



Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

May 28, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine,
Drug Products, HFD-510
Attention: Document Control Room 14B-03
5600 Fishers Lane
Rockville, Maryland 20857-1706

Re: **NDA 20-563 Humalog, insulin lispro**

The enclosed amendment contains a phase IV commitment
This commitment was requested by Dr. Steven Moore (FDA) in a telephone conversation with Dr. Gregory Davis (Lilly) on May 23, 1996.

Please call Dr. Jeffrey Winn, (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Very truly yours,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

TRF/rl

Lilly

Lilly Research Laboratories

May 24, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 20-563--Humalog™(insulin lispro, rDNA origin)

Eli Lilly and Company is amending NDA 20-563 to address the phase 4 plan for Humalog. The information provided in this letter is intended to answer the questions asked by the FDA Division of Metabolism and Endocrine Drug Products in a telephone conversation between Dr. Robert Misbin (FDA), Dr. Elizabeth Koller (FDA), and Dr. Jeffrey Winn (Eli Lilly and Company) on May 23, 1996 regarding NDA 20-563.

We have attached the phase 4 plan for Humalog.

Please call Dr. Jeffrey Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

for Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

attachment

cc: G. Alexander Fleming, M.D. (desk copy)
Solomen Sobel, M.D. (desk copy)
Robert Misbin, M.D. (desk copy)
Elizabeth Koller, M.D. (desk copy)

The following table includes those phase 4 studies that are to be conducted with Humalog® (insulin lispro).

Study Title	Comments

ORIGINAL

Lilly

Lilly Research Laboratories

May 14, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 20-563--Humalog™(insulin lispro, rDNA origin)

The information provided in this letter is intended to answer the questions asked by the FDA Division of Metabolism and Endocrine Drug Products in a letter dated April 30, 1996 regarding NDA 20-563. For your convenience, a copy of the letter accompanies the response.

Please call Dr. Jeffrey Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

attachments

ORIGINAL

PL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

April 22, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 20-563–Humalog® (insulin lispro, rDNA origin)

Lilly is herewith submitting labeling for Humalog pursuant to regulations cited in 21 CFR 201 Subpart B--Labeling Requirements for Prescription Drugs and/or Insulin, including the appropriate format, and 21 CFR 429 Subpart B.

The current document contains changes from that FAXed from the FDA to Eli Lilly and Company on April 15, 1996. Please see Note to Reviewer for an explanation of the changes.

Enclosed are copies of the physican's package insert, patient information for vials and cartridges, and cartons/labels for Humalog.

Please call Dr. Jeffrey L. Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

enclosure

cc: G. Alexander Fleming, MD (desk copy)
cc: Michael Fossler, PhD (desk copy)
cc: Elizabeth Koller, MD (desk copy)
cc: Robert Misbin, MD (desk copy)
cc: William Berlin, PhD (desk copy)

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis Indiana 46285
(317) 276-2000

April 3, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 20-563 Humalog™ (insulin lispro injection, rDNA origin)

Reference is made to a telephone conversation between G. Alexander Fleming (FDA) and Dr. Jeffrey Winn (Lilly) on April 2, 1996. We are herewith submitting a diskette entitled Humalog Physician Insert (Humapwp.doc) in the format WordPerfect 6.1 as requested by Dr. Fleming.

Eli Lilly had requested a meeting on April 11, 1996 to discuss the proposed physician insert, however, it was noted that by using a secure system, the internet would be a useful method by which to communicate. Dr. Winn will provide the Division with his internet address when it becomes available.

Please call Dr. Jeffrey L. Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

enclosure

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317 276-2000

April 1, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 20-563--Humalog™ (insulin lispro, rDNA origin)

We are herewith submitting labeling for Humalog pursuant to 21 CFR 201 Subpart B--Labeling Requirements for Prescription Drugs and/or Insulin and 21 CFR 429 Subpart B.

The current document contains editorial changes from that which was FAXed to the FDA on March 29, 1996. In the *Information for Patients* section, the first sentence in the second paragraph has been changed to "Patients should be advised to inform their physician if they contemplate or become pregnant". Also in that section, the first sentence of the third paragraph has been edited to "Refer patients to the Information For The Patient circular...". In the *Dosage and Administration* section under Mixing with longer-acting insulins, the fourth sentence has been changed from "isophane insulin human suspension, USP", to "Humulin N".

We have included the annotated Physician's labeling. The annotated Information For The Patient can be found in volume 1.1A, page 7, of the original submission (March 13, 1994). Additionally, we have included the reformatted cartons and labels for your review.

Please call Dr. Jeffrey L. Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Allan J Weinstein

for Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

enclosure

cc G Alexander Fleming, MD (desk copy)
cc Michael Fossler, PhD (desk copy)
cc Elizabeth Koller, MD (desk copy)
cc Robert Misbin, MD (desk copy)
cc Stephen Moore, PhD (desk copy)

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

February 14, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 20-563--Humalog™(insulin lispro, rDNA origin)

The information provided in this letter is to correct a mistake that was discovered in the amendment to NDA 20-563 submitted February 6, 1996. The mistake was noted in Table (see below). The Humalog values were inadvertently transposed with the Humulin R values. This transposition has only a small effect of the data interpretation since the means were not found to be statistically significantly different. The values in Table 1 were summarized from a larger computer generated table presented in Appendix 1 of the February 6, 1996 submission.

Mr. Rocco Brunelle (Lilly) telephoned Dr. Taneja (FDA) on February 13, 1996. Dr. Teneja indicated that he had noted the transposition while checking the numbers in the tables against the computer generated tables in the attachments.

It should also be noted that although there is no significant difference between the treatments for the mean hypoglycemia rate per 30 days using the new definition, the mean was slightly lower during Humalog therapy when compared to Humulin R therapy. This is consistent with the treatment comparisons observed for the original definition of hypoglycemia as presented in Table 1A (see below). When using all the hypoglycemic episodes, the mean hypoglycemia rate per 30 days was significantly lower during Humalog therapy when compared to Humulin R therapy ($p<.001$). This difference in the results is attributable to the difference in the definitions of hypoglycemia. The new definition (blood glucose ≤ 2.0 mmol/L, or the patient indicated that they were not able to self-treat the hypoglycemic episode) accounts for only 6.35% of the total hypoglycemic episodes, thus reducing the frequency of hypoglycemic episodes and reducing the hypoglycemic rate per 30 days

Please call Dr. Jeffrey Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

attachments

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

Noted
3/4/16

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

February 6, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 20-563–Humalog™(insulin lispro, rDNA origin)

The attached document contains information requested by the medical reviewing officer and the statisticians responsible for the review of Humalog. This document is the reply to the questions requested by Drs. Misbin, Taneja and Marticello (Food and Drug Administration) during a conference call with Mr. Rocco Brunelle (Eli Lilly and Company) on Wednesday, January 31, 1996.

Please call Dr. Jeffrey Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

December 19, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 20-563--Humalog™ (insulin lispro, rDNA origin)

Eli Lilly is herewith amending NDA 20-563 to provide a draft physician's package insert requested by Mr John Short (FDA) to Dr. Jeffrey Winn (Eli Lilly and Company). Mr Short verbally asked Dr Winn to submit draft labeling following the amendment on December 18, 1995 It is understood that the action letter will be issued on, or before, June 13, 1996

Please call Dr Jeffrey Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions Thank you for your continued cooperation and assistance

Sincerely,

ELI LILLY AND COMPANY

for Timothy R Franson, M D
Executive Director
North American Regulatory Affairs

enclosure

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

December 13, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

GENERAL CORRESPONDENCE

Re: NDA 20-563--Humalog™ (insulin lispro, rDNA origin)

Eli Lilly is herewith amending NDA 20-563 to provide responses to questions provided in a letter from the FDA to Eli Lilly and Company dated September 6, 1995. A copy of the letter has been provided for the reviewer.

Please call Dr. Jeffrey Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D
Executive Director
North American Regulatory Affairs

enclosures

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

December 8, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

GENERAL CORRESPONDENCE

Re: NDA 20-563--Humalog™ (insulin lispro, rDNA origin)

Eli Lilly and Company is herewith submitting to NDA 20-563 electrocardiograms for visits one and nine from F3Z-MC-IOAA, F3Z-MC-IOAB, and F3Z-MC-IOAC conducted in Canada. The QTc intervals were calculated by an outside cardiologist , and have been placed in an Excel spreadsheet.

We are also submitting the final quality of life report and sample questionnaire for F3Z-MC-IOAG and F3Z-MC-IOAH conducted in Belgium and The Netherlands.

Please call Dr. Jeffrey Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

enclosures

PSC

ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

November 6, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

AMENDMENT

Re: NDA 20-563--Humalog™ (insulin lispro, rDNA origin)

The attached amendment is for vials (VL-7510) and Cartridges (VL-7515) of Humalog™ (insulin lispro)

This amendment includes data on the stability of process intermediates and approximate holding times for each process intermediate. Stability data from full-scale lots of Vials and Cartridges of insulin lispro were provided in an NDA 20-563 amendment dated July 21, 1995. Since that time, _ data have become available for the three full-scale cartridge lots. A summary of those data are provided within this amendment.

Please call Dr. Gregory Davis at (317) 276-4125 or Dr. Jeffrey Winn at (317) 276-2098 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

enclosure

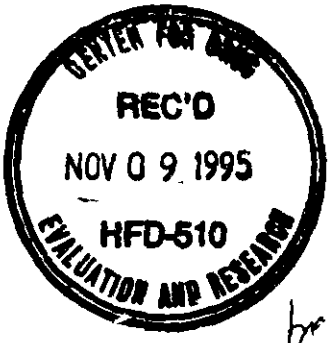
cc Y.-Y. Chiu, PhD (desk copy)
Stephen Moore, PhD (desk copy)

ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000



November 3, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 20-563 -Humalog™ (insulin lispro, rDNA origin)

This letter to NDA 20-563 is to document within the NDA that the following information has been submitted to IND insulin lispro, (rDNA origin) with Serial Number 265. The correspondence is in response to a telephone conversation between Dr Gurston Turner (FDA) and Dr Jeffrey Winn (Lilly) on October 17, 1995. During the conversation, Dr Turner stated that he would perform audits at the sites of investigator number 003 (F3Z-MC-IOAA) and investigator number 24 (F3Z-MC-IOAF)

As per Dr Turner's request, we submitted the audit printouts for the 9 patients for investigator number 24 and eleven patients requested for investigator number 003 to IND for insulin lispro,(rDNA origin) and are in sequential order by patient number.

Please call Dr Jeffrey Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D

Timothy R. Franson, M.D
Executive Director
North American Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I.

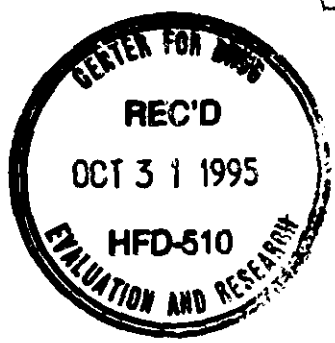
CSO INITIALS DATE

ORIGINAL NDA ORIG AMENDMENT

BM

Question regarding Lilly What diagnosed & recruit baseline

Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000



October 30, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

GENERAL CORRESPONDENCE

Re: NDA 20-563--Humalog™ (insulin lispro, rDNA origin)

This correspondence is in response to a question from Elizabeth Koller, MD of the Food and Drug Administrations Division of Metabolism and Endocrine Drug Products on September 7, 1995 to Mr Mark Richdarson (Lilly).

During a meeting with Dr Koller, Mr Richardson was asked to provide in writing wher Lilly determined the baseline during the clinical investigation of Humalog. We have attached the answer to that question.

Please call Dr Jeffrey Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R Franson, M D
Executive Director
North American Regulatory Affairs

enclosure

cc Dr Elizabeth Koller (desk copy)

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

NDA ORIG AMENDMENT

Lilly ORIGINAL

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

October 27, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

GENERAL CORRESPONDENCE

Re: NDA 20-563—Humalog™ (insulin lispro, rDNA origin)

This correspondence is in response to a letter from the Food and Drug Administrations Division of Metabolism and Endocrine Drug Products dated March 6, 1995 We have attached a copy of that letter for your reference

The letter stated that additional information on subject #242-2408 Following a review of the IND and follow-up with the investigational site, we believe that the subject number of interest is #241-2408 We have attached the additional information requested for subject #241-2408 and a copy of the Clinical Study Report for F3Z-EW-E002 from Item 6, volume 1 52, pp 206-234 of the NDA for your convenience

Please call Dr Jeffrey Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions Thank you for your continued cooperation and assistance

Sincerely,

ELI LILLY AND COMPANY

Timothy R Franson, M.D
Executive Director
North American Regulatory Affairs

enclosure

cc Dr Elizabeth Koller (desk copy)

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

Lilly

ORIGINAL

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

October 26, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

Original

Re: NDA 20-563--Humalog™ (insulin lispro, rDNA origin)

We are herewith submitting the following information regarding Patient 907-9342 enrolled in study F3Z-MC-IOAH requested by Dr Elizabeth Koller Additionally, the same questions were asked verbally by Dr E Koller on September 14, 1995 regarding Patient 913-9361 enrolled in study F3Z-MC-IOAH

Patient 907-9342 was diagnosed with NIDDM in 1976 The patient was treated with various combinations of sulfonylureas and metformin. At the time the investigator initially began to see the patient, the patient was taking glipizide and metformin The patient's glycemic control was thought to be suboptimal (HbA_{1c} was 9 1%, August 7, 1991) The patient was changed to a twice a day mixed insulin regimen in October 1991, using Actaphane Pensets® and the oral therapy was stopped.

Patient 913-9361 was diagnosed with NIDDM in 1978 The patient was treated with chlorpropamide from 1978 to 1982 and with glibenclamide from 1982 to 1983 The patient began insulin therapy in 1983

This background information should answer the questions that the reviewer has asked

Please call Dr. Jeffrey Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

cc: Elizabeth Koller, MD

[redacted]

ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

October 25, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 20-563–Humalog™ (insulin lispro, rDNA origin)

This correspondence is in response to letters received from the Division of Metabolism and Endocrine Drug Products dated September 14, 1995, and on October 6, 1995. I have enclosed copies of those letters for the reviewers convenience.

Please call Dr. Jeffrey Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

cc: Elizabeth Koller, M.D. (desk copy)
Robert Misbin, M.D. (desk copy)
Alexander Fleming, M.D. (desk copy)

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I.
INITIALS
DATE

ORIGINAL

DRUG ADMINISTRATION

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

October 23, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 20-563—Humalog™ (insulin lispro, rDNA origin)

This correspondence is in response to a questions from Dr Robert Misbin (FDA) to Dr Jeffrey Winn (Lilly) on August 10, 1995 and subsequent telephone conversations between Dr Michael Fossler (FDA) and Dr. James Woodworth (Lilly). The questions involve the availability of caloric intake and composition from the pharmacokinetic study F3Z-LC-IMAD.

We are herewith submitting the data as requested to the NDA for review. Please find attached the study report "Pharmacokinetic and Analytical Report, Study F3Z-LC-IMAD (attachment 1), a printout of the caloric intake, blood glucose measurements, and insulin doses for all patients tested in study IMAD (attachment 2) and meal composition (attachment 3).

Lilly was also asked during the August 10, 1995 meeting and subsequent telephone conversations with Dr Michael Fossler if insulin antibody titers for study F3Z-MC-IOAJ patients are available. We have attached (attachment 4) those data available.

Please call Dr Jeffrey Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

enclosures

cc Dr Michael Fossler (desk copy)
Dr Elizabeth Koller (desk copy)
Dr Robert Misbin (desk copy)

22 pages
dated 11/1/95

ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

October 11, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

GENERAL CORRESPONDENCE

Re: NDA 20-563--Humalog™ (insulin lispro, rDNA origin)

This letter is in response to a telephone conversation between Dr. Gurston Turner (FDA) and Dr. Jeffrey Winn (Lilly) on October 10, 1995. During the conversation, Dr. Turner noted that he would perform site audits in Moscow (F3Z-MC-IOAJ) and in Barcelona, Spain (F3Z-MC-IOAA)

As per Dr. Turner's request, we are herewith providing the protocols for the two studies, investigator list for IOAA and patient numbers for the various sites in Spain for IOAA. Please note that the study is listed in the NDA as multicenter and multinational and only investigators 600, 601 and 602 are located in Spain and are indicated with an asterisk. Investigator 601 and 602 are located in Barcelona.

Please call Dr. Jeffrey Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

c Dr. Gurston Turner (HFD-344)

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

ORIGINAL

October 10, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 20-563--Humalog™ (insulin lispro, rDNA origin)

Lilly is herewith submitting the remaining EKG data as requested by the Division of Metabolism and Endocrine Drug Products on January 19, 1995, regarding F3Z-MC-IOAC(b)(1) and in a letter from the Agency dated October 6, 1995.

FDA Question: Provide serial EKG data on the Canadian and Australian subjects (as well as any other patients for whom it is available). Please include the QRS duration and the QTc interval.

Lilly Response: Please refer to attachment A (F3Z-MC-IOAC data), attachment B (F3Z-IOAG data), and attachment C (F3Z-MC-IOAH data). To assist the reviewers, we have provided an EXCEL spreadsheet containing the investigator, patient, and visit results for both the QRS duration and the QT_c interval, electrocardiogram report, and the EKG tracing. If data were supplied in the September 6, 1995, submission, an asterisk will be next to the visit number on the spreadsheets. All other results on the spreadsheets are new.

All new data are accompanied by an "Electrocardiogram Report" and the EKG tracing. The electrocardiogram report was completed by the external cardiologist who analyzed the tracings. Certain investigators did not have new data: (investigator 961 from F3Z-MC-IOAC, investigator 960 from F3Z-MC-IOAG, and investigator 961 from F3Z-MC-IOAH). To assist the reviewers, only the EXCEL spreadsheet is provided containing the previously reported results from these investigators. The EKG tracings can be found in the September 6, 1995, submission.

Additionally, please note that the FDA question number one was answered incorrectly in the submission from Eli Lilly and Company to the Division of Metabolism and Endocrine Drug Products dated September 6, 1995. The question, answer and corrected answer are provided below.

FDA Question 1: Which studies document the blood concentrations of insulin lispro and insulin in patients with diabetes? What are the results of those measurements? How was the validity of those measurements assessed with respect to endogenous antibodies in those patients?

Lilly Answer: Please see attachment **A**

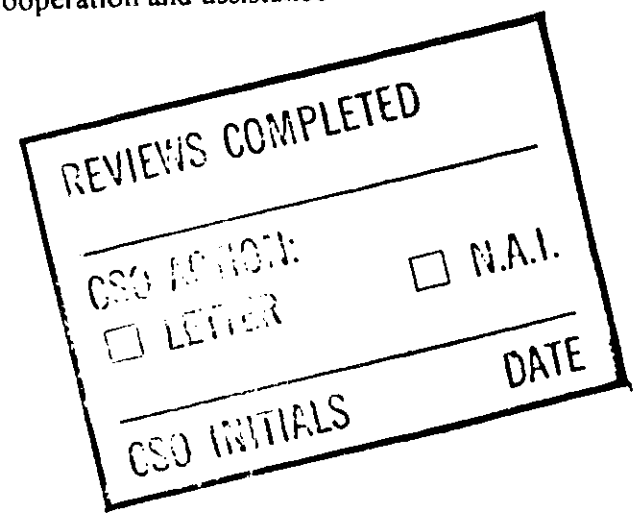
The answer should have indicated that these issues were discussed during the teleconference on August 29, 1995, between members of the FDA Division of Metabolism and Endocrine Drug products and Eli Lilly and Company. In a telephone conversation between Dr. Mike Fossler (FDA) and Dr. James Woodworth on October 4, 1995, Dr. Woodworth indicated that Lilly was in the process of collating the requested information for the study F3Z-LC-IMAD. This information will be submitted to NDA 20-563 when available. We apologize for any inconvenience this incorrect answer may have caused the reviewers.

Please call Dr. Jeffrey Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs



Attachment

cc Elizabeth Koller, MD (desk copy)

Lilly

BC

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

ORIGINAL

October 5, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 20-563--Humalog™ (insulin lispro, rDNA origin)

The following information is in reply to three verbal questions that were asked by Dr Baldeo Tenaja (FDA) to Mr Rocco Brunelle (Lilly) during a meeting on Thursday, September 21, 1995 at the FDA. To assist the reviewer we have provided the questions in written format followed by our response

Please call Dr Jeffrey Winn at (317) 276-2098 or me at (317) 276-2574 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D
Executive Director
North American Regulatory Affairs

enclosure
cc Baldeo Teneja, Ph D (HFD 713)

2

10/2/95

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

Dist. copies to
SS, AF, EB, RM
9/25/95
9:15 pm

September 22, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

Faxed letter about meeting to our consultants Dr. Chambers and Dr. Kinzler
9/25/95

Re: **NDA 20-563—Humalog™ (insulin lispro, rDNA origin)**

This letter and attachments are in response to the commitment by Eli Lilly to supply the enclosed protocol proposal to the Division of Metabolism and Endocrine Drug Products.

Although it was suggested by Dr. Sobel that two weeks would be appropriate to perform a feasibility analysis and development of the proposal, a conversation between Dr. Solomon Sobel (FDA) and Dr. Philip Reid (Lilly) on September 18, 1995, indicated that the proposal would be submitted at this time rather than on September 19, 1995. The proposal was developed in concert with both Lawrence Rand, MD and Ronald Klein, MD, MPH. We feel that the enclosed proposal will provide the best information that can be obtained from the limited number of patients available from the parallel studies.

It is Eli Lilly and Company's understanding that the submission of the enclosed protocol proposal does not obligate us to perform the study.

Also enclosed is a faxed letter from Dr. Ronald Klein regarding the retinal disorders. Additionally, I am sending a desk copy of the September 15, 1995, submission regarding the laser therapy/photocoagulation information to Dr. Wiley Chambers.

Please call Dr. Jeffrey Winn at (317) 276-2098 or me at (317) 276-2574 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson MD

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

[redacted] Calorie data ns

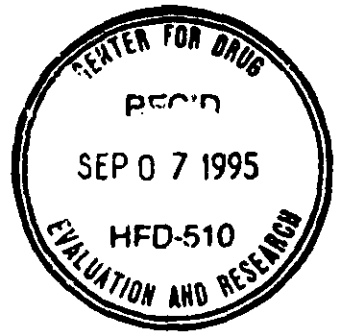
ORIGINAL

Lilly

B2 [redacted]

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000



September 6, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

GENERAL CORRESPONDENCE

Re: NDA 20-563—Humalog™ (insulin lispro, rDNA origin)

This letter is in response prior commitments and current commitments by Eli Lilly, as well as to a telephone conversation between Solomon Sobel, MD, of the Division of Metabolism and Endocrine Drug Products and Jeffrey Winn, DDS (Lilly) on September 1, 1995. As agreed to by Dr Winn and Dr Xan Fleming on August 29 1995, the following answers would be provided by Eli Lilly and Company on 5 September 1995 to the FDA Additionally, a call was initiated by Dr Winn to clarify the time-frame for the feasibility analysis and protocol proposal regarding retinal disorders as suggested by Dr Sobel on Monday, August 28, 1995, and as discussed by Dr Winn and Dr Sobel on August 31, 1995.

It was suggested by Dr Sobel that 2 weeks would be appropriate to perform a feasibility analysis and development of the proposal Lilly will perform the feasibility analysis immediately and the proposal will be drafted and sent to the FDA on September 19, 1995 due to the late afternoon discussion between Dr Sobel and Dr Winn, the time requirements for the feasibility analysis (to determine scientific validity), and the development of the proposal

The following questions are provided pursuant to the questions delineated in a letter from Eli Lilly and Company to the FDA on 18 August 1995, as well as those questions requiring follow-up and Faxed questions Lilly will continue to provide the medical reviewers information regarding the additional information requested for the adverse drug experience reports as they become available to us

[redacted]

Please call Dr. Jeffrey Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

cc: Alexander Fleming, MD (desk copy)
Michael Fossler, PhD (desk copy)
Elizabeth Kolier, MD (desk copy)
Robert Misbin, MD (desk copy)
Solomon Sobel, MD (desk copy)

ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

August 18, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 20-563--Humalog™ (insulin lispro, rDNA origin)

This letter is in response to questions received (both verbally and written) during our meeting with members of the Division of Metabolism and Endocrine Drug Products on July 27, and on August 10, 1995.

The meeting on 10 August 1995, was intended to be a training session for the CANDA and only non-clinicians were present. We would like to avoid any misunderstandings of the information requested and eliminate delay by restating your clinical questions and comments as we understand them. Similar information has been provided previously in replies to questions from the Division, but we would like provide a complete response to assist a timely and productive review. We would ask for your confirmation that this is the complete list and that we have not omitted any of your questions.

1 Which studies document the blood concentrations of insulin lispro and insulin in patients with diabetes ? What are the results of those measurements ? How was the validity of those measurements assessed with respect to endogenous antibodies in those patients ?

2 What was the justification for using the changes in the 1 and 2 hour postprandial glucose excursions as a primary measure of efficacy ? Explain why these changes are not at variance with changes in hemoglobin A1c and fasting glucoses

3 Since the reviewers state the meals were not standardized, can we provide information on the equivalence of the meals between the lispro and Humulin R groups ? Can Lilly provide calorie counts and carbohydrate (simple and complex) content ?

4 Please provide more details about the patients who developed retinal disorder, rash

5. "Differences in subjective reporting of hypoglycemia is not a valid safety measure in a study which is unblinded." Please provide data analysis using documented hypoglycemia (defined as only those hypoglycemia episodes documented by a blood glucose value).

6. Please provide the progression of creatinine values for each patient in the registration trials who had a creatinine equal or greater than 1.5 mg/dL (133 µmol/L).

7. Provide information on the rapid absorption and onset of activity in patients with diabetes.

In addition, the following biopharmaceutics issues will be addressed:

1. Precision and accuracy data (both intra and inter-day) justifying the proposed quantitation limit of 0.12 ng/mL has not been provided in the submission.

2. In studies which measured serum insulin, the results are suspect since samples were not "cleaned up."

3. Use of C-peptide measurements to correct for endogenous insulin secretion is not valid. Calculation of AUCs are suspect since "return to baseline" is somewhat subjective.

4. Study D (assumed to be study IMAD, not IOAL) had too many differences with respect to treatment days, meals, sample times and insulin/lispro doses. Method of adjusting for basal insulin invokes numerous assumptions.

5 Population PK study not designed properly to answer question - is lispro absorbed faster than insulin in patients with diabetes.

We plan to have a conference call with Dr. Fossler from the FDA and pharmacokinetic, medical and regulatory representatives from Lilly.

Written resp nses to the above questions will be provided by 1 September 1995

[redacted]

e3
Letter
JA 20-563
August 18, 1995

Please call Dr. Jeffrey Winn at (317) 276-2098 or me at (317) 276-2574 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

cc: Elizabeth Koller, MD (desk copy)
Robert Misbin, MD (desk copy)
Alexander Fleming, MD (desk copy)
Mike Fossler, PhD (desk copy)

[redacted] ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

July 21, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

AMENDMENT

Re: NDA 20-563, Humalog™, (insulin lispro, rDNA origin)

Pursuant to the agreement arranged at the pre-NDA meeting between representatives of the Division of Metabolism and Endocrine Drug Products, FDA, and Lilly, as well as a telephone conversation between Dr. Greg Davis (Lilly) and Dr. Chiu (FDA) on July 10, 1995, we are herewith submitting a Chemistry, Manufacturing, and Control (CM&C) amendment to the NDA.

Please see the note to the reviewer for detailed information regarding the amendment.

Please call Dr. Jeffrey L. Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

enclosure

cc: Dr. Y.-Y. Chiu (desk copy)

50 ORIGINAL

Orig Amend

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

July 13, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 20-563–Humalog™ (insulin lispro, rDNA origin)

We are herewith submitting the 4-month safety update pursuant to 21 CFR 314.50(d)(5)(vi)(b) and as otherwise noted in the Guideline for The Format and Content of the clinical and Statistical Sections of NEW DRUG APPLICATIONS.

This document summarizes all of the new safety information for Humalog™ from patients treated in completed and ongoing clinical studies conducted by the sponsor through 1 April 1995. There have been 800 patient-years additional exposure in 1901 patients which represents 38% new exposure since the NDA. According to the Guideline for The Format and Content of the Clinical and Statistical Sections of NEW DRUG APPLICATIONS (July 1988), "if the total exposure has substantially changed (rule of thumb, increased by 25% or more)" then a reanalysis of appropriate safety data should be performed. Therefore, the new safety information from completed studies or interim analyses of ongoing studies including exposure, adverse events, hypoglycemia, antibodies, and vital signs was reanalyzed with the previous safety information. All serious events from all completed and ongoing studies that occurred between 2 April 1994 and 1 April 1995 are also included.

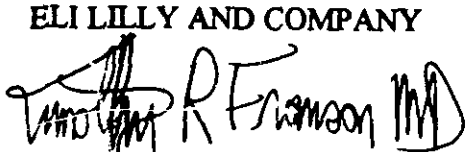
The following paragraph documents an agreement reached with the Food and Drug Administration's Division of Metabolism and Endocrine Drug Products and Eli Lilly and Company since filing the IND for this drug (IND , on June 1, 1990, and as previously noted in the cover letter for the NDA 20-563 (dated March 13, 1995).

> A July 11, 1994, letter from Dr. Solomon Sobel, FDA, to Dr. Max Talbott, Lilly. This letter approved a written request (February 28, 1994) to waive the requirement [21 CFR 314.50(f)(2)] that paper copies of the case report forms be submitted in an NDA for "...each patient who died during a clinical study or who did not complete the study because of an adverse event...". This waiver was requested because Lilly utilized an electronic format for capturing the data from the large-scale clinical trials, and subsequent extension trials for this drug, resulting in an absence of paper case report forms.

Please call Dr. Jeffrey Winn at (317) 276-2098 or me at (317) 276-2574 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY



Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

cc: Elizabeth Koller, MD (desk copy)

ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

June 12, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

GENERAL CORRESPONDENCE

Re: NDA 20-563--Humalog™ (insulin lispro, rDNA origin)

Reference is made to the letter from the FDA regarding the final report for protocol F3Z-MC-IOAF , and dated March 6, 1995. The letter contained 38 questions from the Division of Metabolism and Endocrine Drug Products regarding the New Drug Application (NDA 20-563) for Humalog™ (insulin lispro, rDNA origin). At this time we are submitting detailed responses to each of the 38 questions. To aid the reviewer, we have listed each FDA question/issue with the corresponding response from Lilly. Additionally, we are including a copy of the FDA letter dated dated March 6, 1995.

Please call Dr. Jeffrey L. Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

enclosure
cc: Elizabeth Koller, MD (desk copy)

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N/A

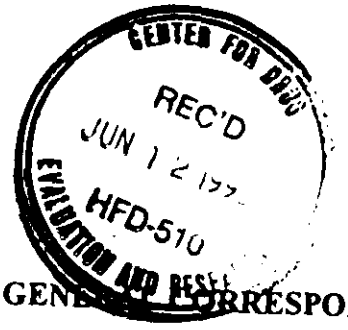
CSO INITIALS DATE

ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000



June 9, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

GENERAL CORRESPONDENCE

Re: NDA 20-563--Humalog™ (insulin lispro, rDNA origin)

Reference is made to the letter from the FDA regarding the final report for protocol F3Z-MC-IOAE, and dated March 6, 1995. The letter contained 24 questions from the Division of Metabolism and Endocrine Drug Products regarding the New Drug Application (NDA 20-563) for Humalog™ (insulin lispro, rDNA origin). At this time we are submitting detailed responses to each of the 24 questions. To aid the reviewer, we have listed each FDA question/issue with the corresponding response from Lilly. Additionally, we are including a copy of the FDA letter dated dated March 6, 1995.

Please call Dr. Jeffrey L. Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

enclosure
cc: Elizabeth Koller, MD (desk copy)

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☒ N.A.I.

CSO INITIALS DATE

ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
(317) 276-2000

June 8, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

GENERAL CORRESPONDENCE

IND

Re: NDA 20-563--Humalog™ (insulin lispro, rDNA origin)

Reference is made to the letter from the FDA regarding the final report for protocol F3Z-MC-IOAD(b)(1), and dated March 6, 1995. The letter contained 16 questions from the Division of Metabolism and Endocrine Drug Products regarding the New Drug Application (NDA 20-563) for Humalog™ (insulin lispro, rDNA origin). At this time we are submitting detailed responses to each of the 16 questions. To aid the reviewer, we have listed each FDA question/issue with the corresponding response from Lilly. Additionally, we are including a copy of the FDA letter dated dated March 6, 1995

Please call Dr Jeffrey L Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R Franson, MD

Timothy R. Franson, M D
Executive Director
North American Regulatory Affairs

enclosure
cc: Elizabeth Koller, MD (desk copy)

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

[redacted]

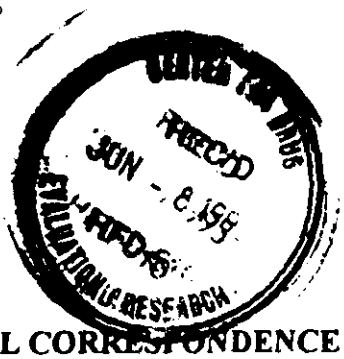
ORIGINAL

Lilly

[redacted]

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000



June 7, 1995

GENERAL CORRESPONDENCE

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 20-563--Humalog™ (insulin lispro, rDNA origin)

Reference is made to the letter from the FDA regarding the final report for protocol F3Z-MC-IOAC(b)(1), and dated January 19, 1995. The letter contained 19 questions from the Division of Metabolism and Endocrine Drug Products regarding the New Drug Application (NDA 20-563) for Humalog™ (insulin lispro, rDNA origin). At this time we are submitting detailed responses to each of the 19 questions. To aid the reviewer, we have listed each FDA question/issue with the corresponding response from Lilly Additionally, we are providing a copy of the FDA letter dated January 19, 1995.

Please call Dr Jeffrey L. Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R Franson MD

Timothy R Franson, M D
Executive Director
North American Regulatory Affairs

enclosure

cc: Elizabeth Koller, MD (desk copy)

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

IOAC.X

ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

June 6, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

GENERAL CORRESPONDENCE

Re: NDA 20-563--Humalog™ (insulin lispro, rDNA origin)

Reference is made to the letter from the FDA regarding the final report for protocol F3Z-MC-IOAA(b), and dated March 6, 1995. The letter contained 13 questions from the Division of Metabolism and Endocrine Drug Products regarding the New Drug Application (NDA 20-563) for Humalog™ (insulin lispro, rDNA origin). At this time we are submitting detailed responses to each of the 13 questions. To aid the reviewer, we have listed each FDA question/issue with the corresponding response from Lilly. We have also included a copy of the letter from the FDA dated March 6, 1995.

Please call Dr. Jeffrey L. Winn at (317) 276-2098 or me at (317) 27[illegible] there are any questions. Thank you for your continued cooperation and assist[illegible]ce.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN - 7 1995
HFD-510

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

enclosure

cc Elizabeth Koller, M.D (desk copy)

FDA Letter

Appendix IOAA.AR

Lilly

Lilly Research Laboratories

June 5, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857-1706

GENERAL CORRESPONDENCE

ATTN: Mr. John Short

Re: NDA 20-563–Humalog™ (insulin lispro, rDNA origin)

This duplicate copy of the following document is being sent by the request of Mr. John Short. The original amendment was submitted on June 5, 1995.

Reference is made to the FAX communication (dated April 7, 1995) from Mr. John Short (FDA to Dr. Jeff Winn (Lilly) detailing the comments made by the Division of Metabolism and Endocrine Drug Products at the April 4, 1995 filing meeting regarding the New Drug Application (NDA 20-563) for Humalog™ (insulin lispro, rDNA origin). Specifically, this amendment satisfies the commitment for Eli Lilly and Company to provide the requested microbiology information.

Please call Dr. Jeffrey L. Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

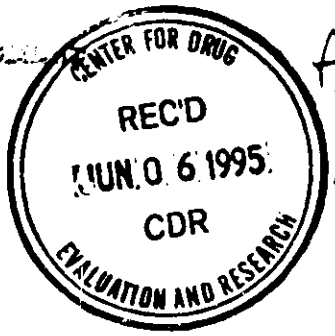
Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

enclosure

Lilly DRUG AMENDMENT

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000



AC
orig
Amend

ORIGINAL

June 5, 1995

Noted. This Submission is covered under Chem. Rev. #1 dated 4/16/96 (Under Microbiology section)
S. K. Moore
4-16-96

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12420 Parklawn Drive
Room 2-14
Rockville, MD 20857-1706

AMENDMENT

NDA 20-563--Humalog™ (insulin lispro, rDNA origin)

Reference is made to the FAX communication (dated April 7, 1995) from Mr. John Short (FDA to Dr. Jeff Winn (Lilly) detailing the comments made by the Division of Metabolism and Endocrine Drug Products at the April 4, 1995 filing meeting regarding the New Drug Application (NDA 20-563) for Humalog™ (insulin lispro, rDNA origin). Specifically, this amendment satisfies the commitment for Eli Lilly and Company to provide the requested microbiology information.

Please call Dr. Jeffrey L. Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

sure

Lilly Research Laboratories

May 9, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

GENERAL CORRESPONDENCE

Re: NDA 20-563--Humalog™ (insulin lispro, recombinant DNA origin)

Reference is made to the Fax communication (dated April 7, 1995) from Mr. John Short (FDA) to Dr. Jeff Winn (Lilly) detailing the comments made by the Division of Metabolism and Endocrine Drug Products at the April 4, 1995, filing meeting regarding the New Drug Application (NDA 20-563) for Humalog™ (insulin lispro). Specifically, this letter requested that a commitment be made by May 12, 1995, to submit missing Microbiology information no later than July 13, 1995.

Eli Lilly and Company hereby commits to provide the requested microbiology information as an amendment to the referenced NDA no later than May 29, 1995.

The additional comments in the April 7, 1995, Fax communication on the Biostatistics and Biopharmaceutics sections of the NDA application will be addressed in a future letter.

Please call Dr. Jeff Winn at 317-276-2098 or me at 317-277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

cc: Mr. John Short

ORIGINAL

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

March 21, 1995

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☒ N.A.I.

CSO INITIALS [redacted] DATE

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12420 Parklawn Drive
Room 2-14
Rockville, MD 20852

Re: NDA 20-563; Humalog™ (insulin lispro, rDNA origin)

In response to a facsimile inquiry by Elizabeth Koller, M D. on January 4, 1995, requesting further details on the adverse event described in the Drug Experience Report with manufacturer's control number ZA94123094A, with patient number F3ZMCIOAO9059105 and with prior submissions on December 19, 1994, and December 23, 1994, we are herewith enclosing the official submission of the follow-up report by the treating physician. All information obtainable at this time is included in this report.

Please call Dr. Jeffrey L. Winn at (317) 276-2098 or me at (317) 277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M D
Executive Director
North American Regulatory Affairs

Attachment

cc: Beth Koller, M D (desk copy)

Lilly Research Laboratories

March 15, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine
Drug Products, HFD-510
Attn Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

GENERAL CORRESPONDENCE

Re: NDA 20-563--Humalog™ (insulin lispro, recombinant DNA origin)

Reference is made to the submission (dated March 13, 1995) of an original New Drug Application (NDA 20-563) for Humalog™ (insulin lispro). Reference is also made to a meeting (Tuesday, March 14, 1995, room 13-B28 of the Parklawn Building) in which Lilly representatives met with FDA representatives from the Division of Information Systems Design to deliver the CANDA (in the format of six [6] compact disks) in support of biopharmaceutics, biometrics and the medical reviewers for the Humalog NDA. At that meeting, it was agreed that the delivery of the CANDA would be documented by submission of this letter to the NDA file. We are enclosing a copy of the letter that was delivered to Mr. Dave Moss (FDA) at the referenced CANDA submission meeting.

Please call Dr. Jeff Winn at 317-276-2098 or me at 317-277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

enclosure

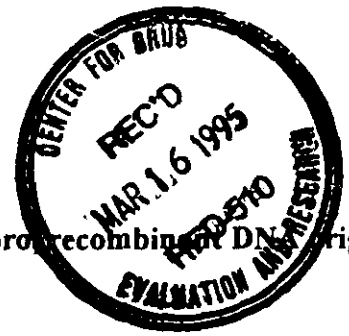
cc Dr. G. Alexander Fleming (cover letter only) HFD-510
Mr. John Hunt (cover letter only) HFD-426
Dr. Elizabeth Koller, (cover letter only) HFD-510
Mr. David Moss (cover letter only) HFD-070
Dr. Ed Nevius (cover letter only) HFD-713
Mr. John Short (cover letter only) HFD-511

Lilly ORIGINAL

Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

March 13, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room 2-14
12420 Parklawn Drive
Rockville, Maryland 20852



Re: NDA 20-563–Humalog™ (insulin lispro recombinant DNA origin)

This letter accompanies submission by Eli Lilly and Company (Lilly) of an original New Drug Application (NDA) for Humalog™ (insulin lispro). The CANDA (compact disk media) in support of biopharmaceutics, biometrics and the medical reviewers, will be submitted separately to the Division of Information Systems Design on March 14, 1995. Humalog is a new molecular entity and is an injectable human insulin analog which is designed for the treatment of diabetes mellitus. Humalog has a quick onset of action and a short duration of activity. Humalog should be injected within 15 minutes of a meal.

Please note that although there are pharmacokinetic studies referenced within this NDA using U-40 Humalog (40 units/mL, insulin lispro), Eli Lilly and Company does not intend to register this concentration for the United States.

This application is formatted and organized according to 21 CFR §314.50 and follows the "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications" and the ""Guideline on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications". The initial User Fee due for this submission has already been paid (Form 3397 is provided). A Pentium Certification and a Debarment Certification have been provided.

The following summarizes the interactions and agreements reached with the Food and Drug Administration's (FDA) Division of Metabolism and Endocrine Drug Products, the Division of Biometrics, the Division of Biopharmaceutics, and Eli Lilly and Company since filing the IND for this drug (IND on June 1, 1990.

1. The February 8, 1994, meeting between representatives of the FDA and Lilly, and confirmed in a letter of April 21, 1994, from Dr. Max Talbott. At this meeting FDA and Lilly representatives agreed that:

   a. The statistical section should be modified to include Mean on Therapy and a repeated measures analysis. Additionally, Lilly agreed to include more graphical representations of the data such as investigator-by-treatment plots for each of the efficacy variables and plots showing the demographic subgroup-by-treatment interactions.

   b. The pharmacokinetic data will be analyzed using population pharmacokinetic modeling and the effects of age and gender upon Humalog pharmacokinetics will be assessed.

2. A July 11, 1994, letter from Dr. Solomon Sobel, FDA, to Dr. Max Talbott, Lilly. This letter approved a written request (February 28, 1994) to waive the requirement [21 CFR §314.50(f)(2)] that paper copies of the case report forms be submitted in an NDA for "...each patient who died during a clinical study or who did not complete the study because of an adverse event...". This waiver was requested because Lilly utilized an electronic format for capturing the data from the large-scale clinical trials for this drug, resulting in an absence of paper case report forms. However, all data from all patients is provided in the accompanying CANDA review tool.

3 The August 16, 1994, pre-NDA meeting between representatives of the Division of Metabolism and Endocrine Drug Products, FDA, and Lilly. At this meeting it was agreed that:

   a A Chemistry, Manufacturing, and Control (CM&C) amendment to the NDA will occur approximately four months following the March 1995 NDA submission. This CM&C amendment would have, as key content, the manufacturing and analytical data for three bulk drug substance and drug product (U-100 vials and U-100 cartridges) validation lots.

   b. Lilly would submit black and white cartons and labels despite the impending change in the regulations which govern color coding for insulin products. If the regulations were revised during the review period then Lilly could submit an amendment with color-coded cartons and labels. Lilly also expressed an interest in color coding the aluminum seals and the crimp seals as an aid in product differentiation and the FDA indicated that they supported this concept.

c. Lilly would continue to submit the final reports for the eight (8) major clinical studies to the IND file as soon as they were completed and the FDA would pre-review these reports as time permitted. Note that final reports for these 8 studies were submitted to the IND file as follows:

Protocol Number	Date	Serial Number
F3Z-MC-IOAA	June 29, 1994	124
F3Z-MC-IOAB	August 2, 1994	131
F3Z-MC-IOAC	August 15, 1994	135
F3Z-MC-IOAD	September 2, 1994	139
F3Z-MC-IOAE	December 22, 1994	168
F3Z-MC-IOAF	December 22, 1994	169
F3Z-MC-IOAG	December 22, 1994	170
F3Z-MC-IOAH	December 22, 1994	171

4. August 30, September 2, 6, and 7, 1994, phone conversations between Dr. Y.-Y. Chiu, Dr. Steve Moore, and Mr. John Short (FDA) and Dr. Paul Gesellchen (Lilly). The FDA agreed to allow Lilly to use the color garnet on the aluminum crimp seals of the Humalog vials and cartridges and on the plastic flip seals of the Humalog vials. A more detailed discussion of the use of this color on the closures for Humalog cartridges and vials may be found in the Reference section of the labeling sections of Item 2 and Item 4 of the NDA.

5. A October 19, 1994, telephone call from Dr. Steven Moore, FDA to Dr. Paul Gesellchen. Dr. Moore informed Dr. Gesellchen that the Lilly request for the FDA's Labeling and Nomenclature Committee to review the Tradename of Humalog™ had been completed and no objections had been raised.

6. A Fax communication of September 19, 1994, from Dr. Baldeo Taneja, FDA, to Dr. Sharon Symanowski, Lilly, and a November 24, 1994, telephone conversation between Dr. Ed Nevius, FDA, and Mr. Rocco Brunelle, Lilly. In the Fax communication Dr. Taneja indicated particular appendices that the Biometrics Division would like to have included in the statistical section of the NDA. In the phone conversation, Dr. Nevius stated his desire to minimize paper submissions to the Division of Biometrics and therefore requested that sections of the appendices which had been indicated by the Division as being particularly useful should be submitted only in Item 11 of the NDA. However, Dr. Nevius requested that the location of these critical appendices should be clearly referenced. A detailed listing (index) of these critical appendices can be found in Item 10 (Statistical Section), Section 10.1 (Statistical Summary) beginning at page 36 of Volume 1.133 in the enclosed NDA submission.

7. A January 6, 1995, telephone conversation between Mr. John Short, FDA, and Dr. Paul Gesellchen, Lilly. At this time Mr. Short informed Dr. Gesellchen that the Lilly request of July 11, 1994, to waive the requirements for inclusion of the curriculum vitae (and the attendant English translations) for Japanese subinvestigators had been approved and a letter would be forthcoming. This request had been discussed during the Pre-NDA meeting of August 16, 1994, and in several phone conversations between Dr. Gesellchen and both Mr. Short and Dr. Beth Koller prior to the January 6, phone call. As a result of those conversations, an example of the Japanese investigator listing, which was to be provided in the NDA submission, and which was to be signed by the Japanese Chief Investigators, was submitted to the IND file on December 9, 1994 (Serial No. 161). It should be emphasized that none of the Japanese studies are part of the pivotal studies that serve as the basis for approval of this drug product in the United States. Rather these studies are Phase I and II studies that are required for Japanese approval of this drug product.

8. A February 9, 1995, meeting between representatives from the FDA and Lilly. The purpose of this meeting was to discuss shelf-life potency specifications. It was agreed that Lilly would provide a statistical justification package for potency specifications at expiry of of label claim. Due to the timing of this discussion, it was agreed that this information could be provided in an amendment to the planned NDA.

9. A March 9, 1995, telephone conversation between Dr. Y.-Y. Chiu, FDA, and Ms. Yvette Lloyd, Lilly. It was agreed that the Microbiology Section (Item 7) of the NDA would be comprised of the complete drug product volume and will include an outline of the relevant sections that are pertinent to the microbiological review.

The cut off date for the data included in the clinical sections of this submission was April 1, 1994.

To co-ordinate our activities with yours, we suggest that any facsimile (Fax) or other written communications, concerning this file, regardless of subject, be directed to:

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

FAX number: (317) 277-0594

Telephone calls should be made between the hours of 7:30 a.m. and 4:15. p.m. (EST). Any calls dealing with general issues, clinical reports, labels and literature should be made to:

Jeffrey L. Winn, D.D.S.
(317) 276-2098

or in his absence to:

Timothy R. Franson, M.D.
(317) 277-1324

Any telephone calls related to manufacturing and control issues should be made to:

Gregory Davis, Ph.D.
(317) 276-4125

or in his absence to:

Yvette Lloyd, R.Ph.
(317) 276-4122

Any calls relating to toxicology or pharmacology issues should be made to:

Douglas Morton, Ph.D.
(317) 277-4301

or in his absence to:

Gregory S. Probst, Ph.D.
(317) 277-4886

On holidays, Saturdays, or Sundays, call Dr. Winn or Dr. Franson at home using the telephone numbers indicated.

Close liaison between the Lilly personnel listed above will result in any messages, no matter how received, being brought to the attention of all concerned.

Please call Dr. Jeff Winn at 317-276-2098 or me at 317-277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

enclosures

cc: Dr. Y.-Y. Chiu (cover letter only) HFD-510
Dr. G. Alexander Fleming (cover letter only) HFD-510
Mr. John Hu. (cover letter only) HFD-426
Dr. Elizabeth Koller (cover letter only) HFD-510
Dr. Ed Nevius (cover letter only) HFD-713
Mr John Short (cover letter only) HFD-511
Dr Gurston Turner (cover letter only) HFD-344

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NDA 20-563

Humalog™

(insulin lispro)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF METABOLISM AND ENDOCRINE
DRUG PRODUCTS (HFD-510)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-563

Humalog™

(insulin lispro)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **Humalog™**, **Eli Lilly and Company** has prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product

Humalog™ (insulin lispro) is a human insulin analog synthesized by recombinant DNA technology using a special non-disease producing strain of *Escherichia coli* bacteria. The product will be injected subcutaneously by individuals with diabetes in order to achieve appropriate levels of glucose in the blood. Drug substance manufacturing operations will occur at Dista Products Limited, Liverpool, England and Eli Lilly and Company, Indianapolis, Indiana. The drug product will be manufactured at Lilly France S.A., Fegersheim, France and Eli Lilly and Company, Indianapolis, Indiana. The finished drug product will be used primarily in homes.

Insulin lispro is not expected to be introduced into the environment from use because it is destroyed in the liver and kidney. If released into the environment it is expected to be used as a source of amino acids for protein decomposers (e.g., microorganisms).

Disposal may result from production waste such as out of specification lots, returned goods and user disposal of empty or partly used product and packaging. Pharmaceutical waste will be disposed of by the manufacturer at a licensed incineration facility. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling.

Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. The manufacturing site where occurs maintains a level of containment greater than what is required by Good Industrial Large Scale Practice. which contains *E. coli* is

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

2/19/96 Nancy B Sager
DATE PREPARED BY
Nancy B. Sager
Acting Supervisor
Environmental Assessment Team
Center for Drug Evaluation and Research

2/19/96
DATE CONCURRED
Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

c.c. original NDA 20-563/JShort copy to NDA/HFD-510
HFD-357/EA File NDA #20-563
HFD-357/Docket File
HFD-019/FOI COPY

ENVIRONMENTAL ASSESSMENT FOR THE USE OF HUMATROPE® IN THE TREATMENT OF GROWTH HORMONE DEFICIENCY IN ADULTS

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

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ENVIRONMENTAL ASSESSMENT FOR THE USE OF HUMATROPE® IN THE TREATMENT OF GROWTH HORMONE DEFICIENCY IN ADULTS

1. **DATE** April 1996

2. **APPLICANT** Eli Lilly and Company

3. **ADDRESS** Lilly Corporate Center
Indianapolis, Indiana 46285

4. DESCRIPTION OF THE PROPOSED ACTION

An application has been made to extend the current approved use of Humatrope® (NDA 19-640) to use in adults with growth hormone deficiency. The active ingredient in Humatrope is somatropin, a polypeptide hormone with an amino acid sequence identical to that of human growth hormone of pituitary origin. This human growth hormone is synthesized by recombinant DNA technology using a special non-disease-producing laboratory strain of *Escherichia coli* bacteria. For adults, Humatrope will be injected subcutaneously on a long-term basis at doses that may vary based on individual patient requirements. The recommended dosage for adults at the start of therapy is not more than 0.006 mg/kg/day (0.018 IU/kg/day). The dose may be increased according to individual patient requirements to a maximum of 0.0125 mg/kg/day (0.0375 IU/kg/day). This product may be used by adults with deficiency of growth hormone throughout the United States.

Humatrope was originally approved for treatment of children under provisions of Orphan Drug status within the United States. Approval of this new application would extend use of Humatrope to adults, but would continue to be used in a very small total patient population (Vance, 1994). The current production, formulation, and packaging facilities (Eli Lilly and Company, Lilly Technology Center, 1200-1555 Kentucky Avenue, Indianapolis, IN 46285) will make the same product for use in adults.

Rejected, expired, returned, or waste drug product and drug substance will be disposed of by incineration at Clinton Laboratories (Eli Lilly and Company, State Road 63, Clinton, IN 47842) according to a Resource Conservation and Recovery Act permit issued by the U.S. EPA under facility identification number IND072040348. These materials may also be disposed of by witnessed incineration at the Indianapolis Resource Recovery Facility

This facility is operated in compliance with a solid waste permit (FPP No. 49-13) issued by the Indiana Department of Environmental Management (IDEM), air permit certificates of operation (Nos. 0123-01, 0123-02, and 0123-3) and an air permit (no. [49]1602) issued by IDEM, and a waste water discharge permit (permit 495301) issued by the City of Indianapolis.

Very small quantities of Humatrope will be used in the United States. Even with addition of adults to the patient population, less than a total of material per year would be used in the United States five years after approval of the extension. This environmental assessment will provide environmental information on the manufacturing site (temperate urban industrial environment in Indianapolis) and will address the potential for any effects from release of the product into the environment. Because of the small quantities of Humatrope used in the United States and because it is used for a rare disease with a small patient population, the environmental assessment for adults will follow an abbreviated format (pursuant to 21CFR Sect. 25(31)a(b)(3) or 21CFR Sect. 25 (31)a(a) Tier 0).

5. IDENTIFICATION OF SUBSTANCES

A. HUMATROPE

Humatrope will continue to be available as somatropin supplied in 5-mg vials, along with 5-mL vials of Diluent for Humatrope. Humatrope for injection will be dissolved in the Diluent for Humatrope. Lists of the materials supplied in these vials are in the confidential attachments to this assessment.

A material safety data sheet for somatropin is provided in Appendix A.

B. SOMATROPIN

Somatropin is a white lyophilized plug containing about 5 mg of somatropin, or about 15 IU. Somatropin is comprised of 191 amino acids in a single polypeptide chain with two intra-molecular disulfide bonds. Somatropin contains no single impurity greater than 1 percent in the finished drug product.

Chemical Name: Biosynthetic human growth hormone

CAS Number: 12629-01-5

Molecular Formula: $C_{990}H_{1528}N_{262}O_{300}S_7$

Molecular Weight: 22,125

Isoelectric Point: Approximately 5.2

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

A. PROLUCTION HOST CELL

The organism used to produce somatropin is *Escherichia coli* K12, strain (ATCC31608). This host strain contains a which is a derivative of and codes for the somatropin molecule as well as tetracycline resistance. A glossary of biotechnology terms is provided in Appendix B.

The original strain of *E. coli* K12 was isolated over 70 years ago from the feces of a hospital patient at Stanford Medical School (Bachman, 1987), and is considered to be highly debilitated with respect to the colonization potential of its original niche (Levy *et al.*, 1980; Smith, 1975). The strain has been cultured more or less continuously since then and has become a microbial genetics workhorse since Tatum and Lederberg (1947) began using the strain over 45 years ago. The original strain has been used in many laboratories, and has been repeatedly mutated to a large number of novel genotypes. Some attempt was made by Bachman (1972) to identify and trace the lineage of this organism.

The strain of *E. coli* K12 in use for somatropin production, , was first identified as such by Maurer *et al.* (1980) and is genetically distinct from its predecessors. The strain is now in common use in many laboratories around the world. A comparison of many of the characteristics which might differentiate an enteropathogenic strain of *E. coli* from either *E. coli* K12 or, more specifically, *E. coli* K12 are listed below. A description of the its sequence, and characteristics that code for somatropin is included in confidential attachments to this assessment.

Trait	Pathogenic Strain	Nominal K12	RV308
1.	-	+	+
2	+/-	+/-	-
3.	+	+/-	-
4.	-	-/+	+
5.	+/-	+/-	-
6.	+/-	+/-	-
7.	+	-	-
8	+	-	-
9	+	-	-
10.	+/-	-	-

The first three traits shown have no bearing on pathogenicity, but clearly help differentiate RV308 from most other *E. coli*.

has been shown by Smith (1975) to reduce the *in vivo* survival of a strain containing the trait.

were present, somatropin would not be produced by the production strain.

While nominally pathogenic *E. coli* may well have either a

This complex process has been thoroughly validated to insure satisfactory operation. In addition, during the course of normal operations, periodic samples are withdrawn and tested to insure a properly functioning process. The conditions used are calculated to yield less than a 10^{-6} probability that a single cell in the

for production of somatropin granules are sufficient to prevent the release of significant amounts of *E. coli* K12 (RV308/ cells even in extreme circumstances. Floor drains are closed and sealed to prevent any organisms from being released. Disinfectant and absorbent materials are used to inactivate and remove any small spill of liquid containing the host cell. Absorbent materials are autoclaved and incinerated. Any contaminated uniform are autoclaved.

Regulations for use of Recombinant Organisms in Production Processes

The Good Large-Scale Production (GLSP) category has been adopted by the National Insitutes of Health in the United States (Federal Register, 1994). This category provides principles of occupational safety and hygiene for large-scale applications with recombinant organisms of intrinsically low risk and that warrant only minimal containment. This category involves no containment measures beyond those required for process needs of the non-recombinant host cell. Other categories provide for increased containment of recombinant organisms based on the possibility of increased risk

associated with exposure to the organisms. Containment characteristics for these categories have been reviewed by Frommer *et al.* (1989).

Even though somatropin can be manufactured under the GLSP category, Eli Lilly and Company has chosen to maintain a level of containment that is generally consistent with the next higher containment category. This choice was made to help ensure containment of the production organism due to its proprietary value, not due to any perception of increased risk. This level of containment also helps to ensure the purity of

procedures for working in a recombinant production facility.

To ensure that all containment hardware continues to function properly. procedures is periodically be carried out on all vessels. Periodic environmental air sampling are carried out to determine whether or not any equipment is malfunctioning. The samples thus obtained are processed and analyzed in the laboratory for the presence of *E. coli* K12 (RV308'

The physical and operational containment steps outlined here meet or exceed the guidelines set out by NIH (Federal Register, 1994).

Survival of *E. coli* K12 (RV308' in the environment

As indicated above, it is very unlikely that viable cells of *E. coli* K12 (RV308/ , are released into the environment. Even if released into the environment, this strain could not persist.

Strains of *E. coli* K12 do not persist in soil, sewage, river water, or the normal mammalian intestinal tract. Bogosian and Kane (1991) summarized information from a

number of studies that were used to assess the environmental fate of *E. coli* K12 and the . Even under optimal conditions, the maximum survival times in natural water, soil, and sewage were 15, 20, and 10 days, respectively. The presence of competitors and predators in all of these media appeared to reduce the survival rate of the *E. coli* K12. In water, very cold temperatures (4 °C) extended the viability of the test organisms to 15 days. A recent study on the fate of an *E. coli* K12 , in sewage demonstrated that the organism was preferentially associated with the settling solids and was unable to maintain its viability even though it was initially present at concentrations higher than indigenous microorganisms (Heitkamp *et al.*, 1993). The *E. coli* K12 (RV308/ used to produce somatropin is resistant to tetracycline, but is thiamine dependent. The survival time of this strain should, therefore, be very short.

E. coli K12 would not even persist in the normal intestinal tract of a mammal. Colonization involves binding between bacterial adhesions and intestinal receptors (Bogosian and Kane, 1991). While this organism was originally isolated from the feces of a human, it no longer has the ability to colonize the conventional human intestinal tract, or that of rodents. Levy *et al.* (1980) inoculated the GI tracts of both mice and human volunteers with *E. coli* K12, either alone or containing and failed to recover any of the test organisms from the feces. Presence of an antibiotic resistance marker (Tc) on the does not seem to help the *E. coli* colonize, even when the antibiotic is fed to the test animal throughout the experiment (Ma shall *et al.* 1981, Muth, *et al.*, 1993, Yancy *et al.*, 1993). There is some evidence that *E. coli* K12 under specialized circumstances can at least transiently colonize the mammalian gut. Smith *et al.* (1985) orally administered about 1 x 10^9 *E. coli* K12 to normal (control), germ-free, and antibiotic treated mice. The strain did not colonize the control mice, but persisted in the GI tracts of both the germ-free and antibiotic treated mice to the end of the study. While most K12 strains do not colonize the GI tracts of mammals, it is likely

that some strains may under some specialized conditions persist for some period of time. , which codes for somatropin to some recipient strain in is extremely unlikely. Bogosian *et al.* (1993) demonstrated that a indigenous to water in the Missouri River. Gealt *et al.* (1985) and McPherson and Gealt (1986) demonstrated that transmission of a does not occur in

Special conditions must be present for the triparental matings to occur and certain conditions can inhibit them. The concentrations of the host strain, the mobilizer strain, and the recipient strain apparently need to be at least around 10^7 cells/mL for detectable triparental transconjugation (Mancini *et al.*, 1987). Stationary culture conditions are also needed for matings to occur (McPherson and Gealt, 1986; Khalil and Gealt, 1987). Ferric chloride severely inhibits transconjugation (Khalil and Gealt, 1987). Sodium chloride and low temperature also inhibit transconjugation (Khalil and Gealt, 1987).

Given the conditions required and the dilution, triparental matings involving *E. coli* K12 (RV308 , are not expected. *E. coli* K12 (RV308/ is grown in a solution that contains sufficient levels of Fe^{+3} to inhibit triparental transconjugation in the environment. It is also very unlikely that the host strain, the mobilizer strain, and the recipient strain would all occur at high enough concentrations to facilitate triparental matings in the environment.

Exposure of Humans to *E. coli* K12 (RV308

Based on containment processes, exposure of humans to *E. coli* K12 (RV308/ is highly improbable. Exposure to *E. coli* K12 (RV308/ would not, however, adversely affect human health.

Gorbach (1978) has cited six criteria for pathogenicity in a microorganism: 1)

survival outside the host so it can spread from host to host; 2) a mechanism for, in this case, penetrating the mucosal surface of the intestine; 3) multiplication within the host; 4) systemic spread within the host; 5) resistance to host defense mechanisms; and 6) production of toxin(s). He pointed out that *E. coli* K12 is more or less deficient in all six areas. Freter (1978) indicated that deficiency in any one of these six areas is probably sufficient to render the microbe avirulent. *E coli* K12 and *E. coli* K12 (RV308) do not

/ that have been

associated with pathogenicity.

Exposure studies done with *E. coli* K12 and with *E. coli* K12 (RV308) indicate that these organisms are safe and cannot colonize the human gut. Levy *et al.* (1980) fed *E. coli* K12 (both with and without to mice and human volunteers and was unable to recover the test organisms from feces and concluded that no colonization had taken place. Smith (1975) showed that thiamine dependent mutants are significantly less hardy than their non-dependent parents. Thus, they disappear sooner from the recoverable fecal spectrum of microorganisms, making colonization even less likely. *E. coli* K12 , is thiamine dependent. Marshall *et al.* (1981) reported that when a K12 strain was used in intestinal survival studies and it contained a with a tetracycline resistance marker, the number of recoverable cells did not increase when oral tetracycline was administered. They concluded that the K12 strain is indeed under a strong selective disadvantage, which is not mitigated by tetracycline resistance. The *E. coli* K12 strain has a tetracycline resistance marker. A colonization study with *E. coli* K12 (RV308) demonstrated that it fails to colonize the gastrointestinal tract of the rat and is eliminated from the rat within 72 hours (Muth *et al.*, 1993). Furthermore, the rats in this study displayed no abnormal clinical signs, nor any treatment-related effects on body weight, food consumption, or efficiency of food utilization.

Transmission of genetic material from a strain of *E. coli* K12 to resident cells in the gastrointestinal tract is extremely improbable (Curtiss, 1978; Levine *et al.*, 1983; Levy *et al.*, 1980). While transfer of genetic traits may occur in laboratory cultures, depending on the specific circumstances, Levine *et al.* (1983) estimated that with or derivatives which lack a mobilization trait (mob$^-$), *in vivo* mobilization of markers to a new recipient occurs at a frequency of 10^{-12} or less. The *E. coli* K12 (RV308/ used to produce somatropin lacks the mobilization trait (mob$^-$). Curtiss (1978) estimated an even lower frequency and reviewed the factors that would diminish the potential for transmission of n the gastrointestinal tract. Levine *et al.* (1983) confirmed that the likelihood is remote by reporting failure of triparental mating by *E. coli* K12 with a poorly mobilizable in 12 human volunteers, even when antibiotic selection was added. Levy *et al.* (1980) also found no evidence of transmission of from *E. coli* K12 host strains in the gastrointestinal tract of human volunteers. Finally, Yancy *et al.* (1993) concluded that transfer of does not occur in the intestinal tract.

Even if the was transferred from *E. coli* K12 (RV30 , the recipient cell would probably not survive. The presence of the would result in energy being diverted to production and storage of inactive and insoluble somatropin in the new host. The new host cell would be at a severe competitive disadvantage because of the energy diversion and would most likely die very quickly.

Based on this information, it can be concluded that *E. coli* K12 (RV308 non-pathogenic, could not colonize the human or mammalian gut, and is extremely unlikely to transfer selected or unselected genes to indigenous bacteria in the gastrointestinal tract. The proposed action is not expected to adversely affect human health.

B. INTRODUCTION OF SUBSTANCES FROM THE MANUFACTURING SITES

1. Location of Facilities Used for Manufacturing, Formulating, and Packaging

The processes for manufacturing somatropin, the operations for formulating and packaging Humatrope, and the pollution control practices at the corresponding plant site are designed to result in minimal environmental impact. These processes will not change for extension of the use of Humatrope to adults. . of somatropin granules is already carried out at facilities of Eli Lilly and Company (Lilly Technology Center, 1200 - 1555 Kentucky Avenue) in Indianapolis, Indiana. The purified drug substance is formulated and packaged at the same facilities of Eli Lilly and Company (Lilly Technology Center, 1200 - 1555 Kentucky Avenue) in Indianapolis. This product is produced under current Good Manufacturing Practices.

2. Environmental Regulatory Requirements

Facilities which produce, formulate, and package Humatrope will comply with all appropriate environmental statutes, regulations, and permits concerning emission control and waste reatment. Somatropin is produced by

. Materials used in these production processes will not change for extension of the use of Humatrope to adults. The amounts of materials used to produce somatropin are small because the amount of somatropin produced is small. Approval of the extended use of Humatrope for adults will not change compliance with emissions regulations. Since the amount of materials used in the production process are small and containment is high, the materials emitted are not expected to have a significant impact on the environment and are, therefore, not listed in this assessment as specified by the FDA CDER Guidance for Industry document.

Treatment, storage, and disposal practices for solid, liquid, and gaseous wastes from the Indiana plant site are defined by the regulations administered, in certain instances, by the Indiana Department of Environmental Management (IDEM), and in other instances

by the Indianapolis Department of Public Works (DPW). A permit associated with liquid waste discharge (DPW Permit Number 283001, expires 12/31/00) was issued by the Indianapolis Department of Public Works. Permits associated with control of emissions to the atmosphere, if required, are administered by the City of Indianapolis.

The waste water discharge from the site is received by the Indianapolis Department of Public Works Belmont Advanced Wastewater Treatment facility. This facility is designed to treat an average of 120 million gallons of waste water per day. The facility removes at least 97% of the BOD and TSS that it receives. The facility treats more than 90% of the ammonia that it receives. This public waste water treatment facility discharges into the White River.

Pretreatment of the waste water from the production, formulation, and packaging operations in Indianapolis is not required to meet the discharge limits for these facilities. The volume of water from this process represents less than 1% of the waste water discharged from these facilities. These waste waters are discharged into the Belmont Advanced Wastewater Treatment facility. Liquid process waste directly associated with the formulation, especially any with solvent levels $\geq 0.1\%$, is collected and drummed for disposal by thermal oxidation at Clinton Laboratories.

Any solid wastes from the production, formulation, and packaging operations will be collected and sent to appropriate solid waste facilities. All packaging and labeling components are collected in restricted areas at facilities in Indianapolis. Wastes from the formulation and packaging facilities will generally be cartons, paper, and plastic. Any rejected material, plastic liners, gloves, hair covers, or vials will also be collected and sent to an appropriate waste facility.

Solid wastes and rejected or returned drug substance will be disposed of by incineration at Clinton Laboratories (Eli Lilly and Company, State Road 63, Clinton, IN 47842) according to a Resource Conservation and Recovery Act permit issued by the U.S. EPA under facility identification number IND072040348. Rejected or returned drug

substance may also be disposed of by witnessed incineration at the Indianapolis Resource Recovery Facility

Regular solid wastes may also be disposed of at this facility. This facility is operated in compliance with a solid waste permit (FPP No. 49-13) issued by the Indiana Department of Environmental Management (IDEM). While this permit has an expiration date of 6/1/94, regulations indicate that the permit remains in force while the application for the new permit is being evaluated. Air permit certificates of operation (Nos. 0123-01, 0123-02, and 0123-3) and an air permit (no. [49]1602) issued by IDEM carry an expiration date of 5/31/91, but remain in force while IDEM reviews the renewal applications. A waste water discharge permit (permit 495301; expires 4/30/97) for the Indianapolis Resource Recovery Facility was issued by the City of Indianapolis.

No special environmental air emission control equipment is required for production, formulation, and packaging of Humatrope. All room air at these facilities will pass through filters and dust collectors. These collectors and filters will be packaged with solids, particulates, and dust for disposal at one of the solid waste facilities mentioned above.

C. INTRODUCTION OF SUBSTANCES FROM THE USE SITES

Humatrope will be used in the United States for long-term treatment of children and adults with growth hormone deficiency. Five years after approval for use in adults, total use of somatropin will be less than Growth hormone in mammals is extensively filtered and absorbed into renal cells in the kidney tubules. Within the renal cells, growth hormone is catabolized with at least a portion of the breakdown products being returned to the circulation (Johnson and Maack, 1977). Thus, significant elimination of somatropin from humans is unlikely. If a portion of the compound was eliminated, it would be discharged to either a sewage treatment facility or a septic tank

where microbial degradation of peptides is common. Even if all somatropin produced in a year could be eliminated as the active protein, concentrations less than 0.3 nanograms/L (< 10 kg/yr X (1/1.115 x 10^{11} L/day from POTW's in the United States) X yr/365 days X 10^{12} nanograms/kg) would be discharged from publicly owned sewage treatment works. This level is well below that which requires review of the fate and effects of the material in the aqueous environment.

Humatrope will be packaged in glass vials with a rubber stopper, sealed with an aluminum seal combined with a plastic cap. These glass containers are packaged in paper cartons. Cartons are placed in packs, overwrapped with plastic, and placed in cardboard containers for shipment. The cartons and boxes are made with recyclable material where possible. This packaging is necessary to protect products and customers by reducing the damage to the product during shipping, enhancing product stability, discouraging tampering, and providing a surface for an approved label.

7. FATE OF SUBSTANCES IN THE ENVIRONMENT

This section of the environmental assessment is not applicable because of the small amounts of somatropin used in a year and the small patient population. As noted in Section 6, above, there is little chance that any somatropin will be released into the environment.

There is little potential for absorption of somatropin as an intact molecule or for accidental systemic exposure in man. Large polar molecules, such as proteins, are not significantly absorbed across dermal layers (Malkinson and Gehlmann, 1977; Wester and Maibach, 1985). Somatropin is a polar protein with a molecular weight of 22,125. Absorption of the intact molecule after ingestion is also very unlikely. Proteins undergo acid hydrolysis in the presence of pepsin in the stomach and in the presence of trypsin, chymotrypsin, and carboxypolypeptidase secreted from the pancreas (Guyton, 1976). Amino acids and small peptides are the only components remaining after this process. Somatropin is a protein that would undergo these same digestive processes and would

lose its activity as an intact molecule.

Proteinaceous materials like somatropin are degraded in soil (Loll and Bollag, 1983). Protein decomposition is carried out by soil microorganisms, which can use the resulting amino acids as carbon and nitrogen sources. Protein decomposers, such as bacteria, actinomycetes, and fungi, are found in a wide range of environments and may comprise from 22% to 89% of the total soil population. Proteases released from these microorganisms fragment proteins by hydrolysis into peptides and amino acids which microbes can absorb and further metabolize. Any somatropin inadvertently released into the environment would quickly be inactivated and degraded by microbes.

8. EFFECTS ON THE ENVIRONMENT

This section of the environmental assessment is not applicable because of the small amounts of somatropin used in a year and the small patient population. As noted in Sections 6 and 7, above, it is extremely unlikely that any somatropin will be released into the environment or that systemic exposure to the material could occur. Somatropin is produced at one plant site. Engineering controls and personal protective equipment are used to eliminate exposure or reduce it to a safe level. Eye and face protection and protective clothing is generally required in the production areas. A Material Safety Data Sheet (Appendix A) has been created to provide information about somatropin. Employees are directed to change uniforms and thoroughly wash with soap and water in case of an accidental exposure to somatropin. The proposed action is not expected to result in adverse effects on human health.

9. UTILIZATION OF NATURAL RESOURCES AND ENERGY

This section of the environmental assessment is not applicable because of the small amounts of somatropin used in a year and the small patient population.

Production, formulation, and packaging of somatropin for use in adults will occur at

facilities already approved for production of this material for use in children. In general, production processes for Humatrope use a very small proportion of the waste treatment or recovery facilities already installed for these and other process wastes. Properties listed in the National Register of Historic Places will not be affected by the additional production of Humatrope. Endangered and threatened species are not affected by the production of Humatrope. Somatropin is not expected to reach the environment at any measureable level. All of the facilities that are part of the process to produce Humatrope are operated according to current Good Manufacturing Practices.

10. MITIGATION MEASURES

This section of the environmental assessment is not applicable because of the small amounts of somatropin used in a year and the small patient population.

As noted in Sections 6 and 7, above, it is extremely unlikely that any somatropin will be released into the environment or that systemic exposure to the material could occur. Engineering controls and waste treatment practices described in Section 6 are in place to minimize release of process materials at the production, formulation, and packaging facilities. Personal protective gear, such as eye protection and protective clothing, is worn, when necessary, to reduce the potential for exposure to all chemicals at production sites, including those involved in production of Humatrope. Humatrope is produced under current Good Manufacturing Practices. A material safety data sheet describing somatropin, its physical properties, general handling precautions, and other information is available (Appendix A).

11. ALTERNATIVES TO THE PROPOSED ACTION

This section of the environmental assessment is not applicable because of the small amounts of somatropin used in a year and the small patient population.

The proposed action would not be expected to have any significant adverse effects

on human health or the environment. While there are no known environmental benefits from the production and use of Humatrope, there are, likewise, no known significant risks to the environment. The alternative of not approving Humatrope for use in adults with growth hormone deficiency would only serve to restrict treatment options available to patients and physicians with no environmental benefits. It is, therefore, not necessary to consider this alternative to the proposed action.

12. LIST OF PREPARERS

The following personnel of Eli Lilly and Company are responsible for the preparation of this Environmental Assessment:

Roger D. Meyerhoff, Ph.D.
Head,
Environmental Science and Hazard Communications

April 12, 1996
Date

William L. Muth, Ph.D.
Research Advisor
Natural Products Research and Development

4/15/96
Date

Neil J. Parke, M.A.
Senior Environmental Affairs Representative

4/15/96
Date

Lawrence F. Fisher, D.V.M., Ph.D.
Toxicology Project Leader

April 12, 1996
Date

13. CERTIFICATION

The undersigned official certifies that the information presented in the Environmental Assessment is true, accurate, and complete to the best of his knowledge.

Gregory S. Probst, Ph.D.
Executive Director, Toxicology and Drug Disposition

Date

14. REFERENCES

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MSDS

MATERIAL SAFETY DATA SHEET

Lilly

COMMON NAME: Somatropin (rDNA Origin) for Injection
(Lilly Nos.: VL7330, VL7332, VL7335, VL7346, VL7348, VL7351, VL7360, VL7365, VL7372, VL7520, VL7522, VL7524, VL7525)

DATE: April 15, 1993

U.S. TELEPHONE NUMBERS: EMERGENCY 317-276-2000 CHEMTREC 800-424-9300

As of the date of issuance, we are providing available information relevant to the handling of this material in the workplace. All information contained herein is offered with the good faith belief that it is accurate. THIS MATERIAL SAFETY DATA SHEET SHALL NOT BE DEEMED TO CREATE ANY WARRANTY OF ANY KIND (INCLUDING WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE). In the event of an adverse incident associated with this material, this safety data sheet is not intended to be a substitute for consultation with appropriately trained personnel. Nor is this safety data sheet intended to be a substitute for product literature which may accompany the finished product.

See attached glossary for abbreviations.

SECTION 1 - MATERIAL IDENTIFICATION

Common Name: Somatropin (rDNA Origin) for Injection

Synonyms/Trade Names: Humatrope*; Biosynthetic 2 Cistron Human Growth Hormone Cystine; hGH; Humatrope Recombinant DNA Origin for Injection*; Somatropin; Somatotropin; Human Growth Hormone, Biosynthetic; Growth Hormone, Human

Mixture Ingredients Listed Below:

Common or Chemical Name	Synonyms/Trade Names	CAS Number	Percent in Mixture
Somatropin	Humatrope*	12629-01-5	13.8
Mannitol	D-Mannitol	69-65-8	69.2
Glycine	Amino acetic acid	56-40-6	13.2
Dibasic sodium phosphate	DSP	7782-85-6	3

Contains no hazardous components (one percent or greater) or carcinogens (one-tenth percent or greater) not listed above.

* Trademark of Eli Lilly and Company

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---------- SECTION 2 - PHYSICAL DATA ----------

Appearance: White lyophilized plug or powder

Odor: Odorless

Boiling Point: NA

Melting Point: NAIF

Specific Gravity: NA

pH: 6.5-8.5 (reconstituted)

Evaporation Rate: NAIF

Solubility in Water: Soluble

Vapor Density: NAIF

Vapor Pressure: NAIF

---------- SECTION 3 - FIRE AND EXPLOSION INFORMATION ----------

Extinguishing Media: Use water, carbon dioxide, dry chemical, foam, or Halon.

Unusual Fire and Explosion Hazards: As a finely divided material, may form dust mixtures in air which could explode if subjected to an ignition source.

Flash Point: NAIF

Method: NA

UEL: NAIF

LEL: NAIF

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SECTION 4 - REACTIVITY INFORMATION

Stability: Stable at normal temperatures and pressures.

Incompatibility: None known.

Hazardous Decomposition: May emit toxic fumes when heated to decomposition.

Hazardous Polymerization: Will not occur.

SECTION 5 - HEALTH HAZARD INFORMATION

Human - Occupational

Effects, Including Signs and Symptoms, of Exposure: None reported. Biosynthetic Somatropin is identical to human growth hormone of pituitary origin. It is not considered to be hazardous.

Medical Conditions Aggravated By Exposure: None known.

Primary Route(s) of Entry: Inhalation and skin contact.

Exposure Guidelines: PEL and TLV not established.

Animal Toxicity Data Single Exposure

Toxicity data for the active ingredient, Somatropin, are presented.

Oral: Somatropin - Rat, 150 mg/kg, no deaths or toxicity.

Skin: Somatropin - NAIF

Inhalation: Somatropin - NAIF

Intravenous: Somatropin - Rat, 12.5 mg/kg, no deaths or toxicity.
Dog, 3.125 mg/kg, no deaths or toxicity.

Skin Contact: Somatropin - NAIF

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DATE: April 15, 1993

---------- SECTION 5 - HEALTH HAZARD INFORMATION (continued) ----------

Animal Toxicity Data Single Exposure

Eye Contact: Somatropin - Rabbit, slight irritant

Animal Toxicity Data Repeat Exposure

Toxicity data for the active ingredient, Somatropin, are presented.

Target Organ Effects: Somatropin - Metabolic effects (skeletal growth, increased number of bone marrow osteoblasts, increased body weight, increased food consumption, increase in serum alkaline phosphatase, changes in protein, carbohydrate and fat metabolism, and increased number and size of muscle cells).

Reproduction: Somatropin - NAIF

Sensitization: Somatropin - NAIF

Mutagenicity: Somatropin - Not mutagenic in bacterial cells.

Carcinogenicity: Somatropin - Since the amino acid sequence of the compound is identical to human growth hormone of pituitary origin, carcinogenicity studies are not considered necessary to support the safety of somatropin. Not listed as carcinogenic by IARC, NCI/NTP, ACGIH, or OSHA.

---------- SECTION 6 - EMERGENCY AND FIRST AID PROCEDURES ----------

Eyes: Flush eyes with plenty of water. Get medical attention.

Skin: Remove contaminated clothing and clean before reuse. Wash all exposed areas of skin with plenty of soap and water. Get medical attention if irritation develops.

Inhalation: Move individual to fresh air. Get medical attention if breathing difficulty occurs. If not breathing, provide artificial respiration assistance (mouth-to-mouth) and call a physician immediately.

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DATE: April 15, 1993

SECTION 6 - EMERGENCY AND FIRST AID PROCEDURES (continued)

Ingestion: Do not induce vomiting. Call a physician or poison control center. If available, administer activated charcoal (6-8 heaping teaspoons) with two to three glasses of water. Do not give anything by mouth to an unconscious person. Immediately transport to a medical care facility and see a physician.

SECTION 7 - HANDLING PRECAUTIONS

Under normal use and handling conditions, no protective equipment is required. The following is recommended for a production setting:

Respiratory Protection: NIOSH approved respirator or laboratory fume hood.

Eye Protection: Safety glasses.

Ventilation: Laboratory fume hood or local exhaust ventilation.

Other Protective Equipment: Impervious gloves and body covering to prevent skin contact.

SECTION 8 - SPILL, LEAK AND DISPOSAL PROCEDURES

Spills: Contain dry material by sweeping up or vacuuming. Vacuuming may disperse dust if appropriate dust collection filter is not part of the vacuum. Be aware of potential for dust explosion when using electrical equipment. Wear protective equipment, including eye protection, to avoid exposure (see Section 7 for specific handling precautions).

Waste Disposal: Dispose of any cleanup materials and waste residue according to applicable federal, state, and local regulations. Material is not a RCRA hazardous waste for disposal.

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DATE: April 15, 1993

SECTION 9 - SHIPPING INFORMATION

(Proper Shipping Name / Hazard Class / UN Number)

DOT: Not regulated for surface transport.

ICAO: Not regulated for air transport.

IMO: Not regulated for water transport.

For additional information call: Occupational Health and Safety
Eli Lilly and Company 317-276-3494

For additional copies call: Customer Services
Eli Lilly and Company 1-800-LILLY-Rx
(1-800-545-5979)

MSDS
MATERIAL SAFETY DATA SHEET

Lilly

GLOSSARY
Abbreviations Used in Material Safety Data Sheets

ACGIH = American Conference of Governmental Industrial Hygienists
BEI = Biological Exposure Index
CAS Number = Chemical Abstract Service Registry Number
CERCLA = Comprehensive Environmental Response Compensation and Liability Act (of 1980)
CHEMTREC = Chemical Transportation Emergency Center
CWA = Clean Water Act
DOT = Department of Transportation
EP = Extraction Procedure as defined under RCRA Regulations
EPA = Environmental Protection Agency
HEPA = High Efficiency Particulate Air (Filter)
HSDB = Hazardous Substance Data Base
IARC = International Agency for Research on Cancer
ICAO = International Civil Aviation Organization
IMO = International Maritime Organization
LEG = Lilly Exposure Guideline
LEL = Lower Explosive Limit
MSDS = Material Safety Data Sheet
NA = Not Applicable, except in Section 9 where NA = North America
NAIF = No Applicable Information Found
NCI/NTP = National Cancer Institute/National Toxicology Program
NIOSH = National Institute for Occupational Safety and Health
NOS = Not Otherwise Specified
OHS = Occupational Health Services
OSHA = Occupational Safety and Health Administration
PEL = Permissible Exposure Limit
PSN = Proper Shipping Name
RCRA = Resource Conservation and Recovery Act
RTECS = Registry of Toxic Effects of Chemical Substances
SARA = Superfund Ammendments and Reauthorization Act
STEL = Short Term Exposure Limit
TLV = Threshold Limit Value
TSCA = Toxic Substances Control Act
TWA = Time Weighted Average/8 Hours Unless Otherwise Noted
UEL = Upper Explosive Limit
UN = United Nations

END

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J.H.M. Research & Development, Inc., 5776 Second Street, N.E., Washington, D.C. 20011