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Insulin Lispro Low Mixture (LM) as compared to Human Insulin 30/70 in Treatment of Types 2 Diabetes in elderly patients.

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Eli Lilly and Company (India) Pvt.Ltd.

July 2002

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Study Report for the Clinical Trial F3Z-IN-IONL (Analyses For The Data From All Sites) CONFIDENTIAL

Title:	Insulin Lispro Low Mixture (LM) as compared to Human Insulin 30/70 in Treatment of Type 2 Diabetes in elderly patients.
Development Phase:	IV
Study Drug:	Insulin Lispro Low Mixture (LM) Vs Human Insulin 30/70
Protocol Id:	F3Z-IN-IONL
Indication:	Elderly Subjects of either sex suffering from Type 2 Diabetes Mellitus.
Principal Investigators:	1. Dr. Bipinkumar Sethi 2. Dr. C.S.Yajnik 3. Dr. Sanjib Dhungel 4. Dr. (Prof) Devaka Fernando 5. Dr. V. Mohan
Date of First Visit:	17th April 2001
Date of Last Visit:	10th April 2002
Date Report approved:	30th July 2002

Clinical Study Synopsis F3Z-IN-IONL

Insulin Lispro Low Mixture (LM) as compared to Human insulin 30/70 in Treatment of Type 2 Diabetes in elderly patients.

Name of Company: Eli Lilly and Company (India) Pvt. Ltd. Name of the Finished Product: Insulin Lispro (LM) Vs Human Insulin 30/70 Name of the Active Substance: Insulin Lispro Protamine suspension	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	

CLINICAL STUDY SYNOPSIS

Study F3Z-IN-IONL

Title :

Insulin Lispro Low Mixture (LM) as compared to Human insulin 30/70 in Treatment of Type 2 Diabetes in elderly patients.

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Title of the study: F3Z-IN-IONL

Insulin Lispro Low Mixture (LM) as compared to Human insulin 30/70 in Treatment of Type 2 Diabetes in elderly patients.

Principal Investigators and study centers:

Investigators / Initials	Center No.	Investigational sites	Location
Dr. Bipin kumar Sethi (BKS)	001	Care Hospital 6-3-248/1/1A Road No. 1 Banjara Hills Hyderabad – 500 034	India
Dr. C. S. Yajnik (CSY)	003	Diabetes Unit KEM Hospital Research Center Rasta Peth Pune	India
Dr. Sanjib Dhungel	005	Department of Medicine Nepal Medical College Teaching Hospital (NMCTH) Attarkhel, Jorpati Kathmandu Nepal	Nepal
Dr. (Prof) Devaka Fernando	006	Univeristy of Sri Jayawardena Pura, No. 5, Second Lane, Ratmalana Sri Lanka	Srilanka
Dr V. Mohan	007	Madras Diabetes Research Foundation 6B Conron Smith Road, Gopalapuram Chennai – 600 086	India

Study Period: Date of First Visit: 17th April 2001 Date of Last Visit: 10th April 2002	Clinical Phase : IV

Name of Company: Eli Lilly and Company (India) Pvt. Ltd. Name of the Finished Product: Insulin Lispro (LM) Vs Human Insulin 30/70 Name of the Active Substance: Insulin Lispro Protamine suspension	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	

Objectives:

Primary Objective

The Primary objective of this study was to test the hypothesis that insulin lispro low mixture (LM) improves glycemic control in elderly patients as compared to Human Insulin 30/70 as measured by morning and evening glycemic excursion.

Secondary Objectives

The secondary objectives of the study were :

- To compare the two treatments with regard to the glycemic control as indicated by
  - Blood glucose before morning and evening meals.
  - Post prandial blood glucose (2hours after morning and evening meals)
- To compare the two treatment with respect to
  - Number and frequency of hypoglycemic episodes.
  - Hemoglobin A1c.
  - Treatment acceptance by patient

Methodology:

Study Design: Randomized, multicentric, multicountry, crossover, open-label, comparative study involving elderly patients who had received therapy with intermediate acting insulin for at least 4 weeks prior to entering the study.

Number of subjects:

Planned:	110
Entered	130
Enrolled	114
Analyzed for safety	114
Completed	106
Exclusions	4
Drop outs before Visit 2	12
Drop outs / Discontinuations after Visit 2	8
Number of subjects for Efficacy Analysis	106

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Diagnosis and main criteria for inclusion:

For the purpose of this study, only elderly subjects (age at least 65 years) and suffering from Type 2 Diabetes Mellitus for atleast 6 months who had received therapy with Human Insulin 30/70 or intermediate acting insulin with or without short acting insulin for at least 4 weeks prior to entering the study were included in the

Study Drug, Dose, Mode of administration:

- Patients administered either Insulin Lispro low mixture (LM) or Human Insulin 30/70 twice daily before the morning and evening meals.
- Patients administered Human Insulin 30/70 twice daily at their usual time. Patients, who received LM, administered it twice daily immediately before morning and evening meals.
- The patients were monitored carefully for changes in insulin requirements and doses adjusted in accordance with their metabolic needs in order to achieve the target goals for this study which were pre-meal blood glucose values < 7mmol/L (126 mg/dL). And 2 hour postprandial blood glucose < 10mmol/L (180 mg/dL).
- The insulin dose was adjusted to achieve the above goals unless further adjustment resulted in hypoglycemia.
- Insulin used by the patients were the ones specifically provided by the sponsor.
- The study drugs were administered by subcutaneous route.

Materials and Supplies:

The primary study material were:

Lead in period:

- Human Insulin 30/70 – 3.0 ml cartridges for subcutaneous injection.

Treatment periods

- Insulin Lispro (LM) 3.0 ml cartridges for subcutaneous injection.
- Human insulin 30/70 – 3.0 ml cartridges for subcutaneous injection

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Duration of Treatment:

Approximately 7 months per subject. Each patient was on 30/70 for 4 weeks lead-in period and then was on assigned treatment insulin lispro (LM) or Human Insulin 30/70 for 3 months and then after 3 months the assigned treatments were reversed for another 3 months.

Criteria for evaluation:

Efficacy Evaluations:

- Primary Efficacy Criteria:

  Glycemic Control: The overall glycemic control, as determined by post prandial blood glucose excursion was tested hypothetically to prove that insulin lispro low mixture (LM) improves glycemic control in elderly patients suffering from Type 2 Diabetes Mellitus as compared to Human Insulin 30/70

- Secondary Efficacy Criteria:
  - Glycemic Control : Glycosulated hemoglobin A (HbA1c)
    Glycosulated hemoglobin A (HbA1c) was compared between two groups (sequence), periods and treatments.
  - Glycemic Control : 4 – point Blood glucose profile

    4 - point Blood Glucose Profile was compared between the two groups (sequence), periods and treatments.
  - The incidence and the rate of hypoglycemia in patients between the two groups (sequence), periods and treatments was compared.
  - Treatment Satisfaction Questionnaire of patients was compared between two study insulins.

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Criteria for evaluation:

- **Safety Criteria:**

Information about any pre-existing condition was summarized.

The occurrence and nature of adverse events such as Hypertension, Hyperlipidaemia and Ischemic Heart Disease was summarized.

The no. of Hypoglycemic events were analyzed using factorial ANOVA model between groups(sequence),Periods,patients and Treatments and were summarized by finding mean, standard Deviation (S.D.), Standard Error, Sample Size and Median.

The no. Of Hypoglycemic Events were summarized within each Visit and over entire study i.e. over treatments and periods.

- **General Criteria:**

At the first visit vitals including age, height, weight, BMI were summarized.

Statistical Methods:

Efficacy Analyses:

- The efficacy variable is glycemic excursion (morning and evening), HbA1c levels, pre-breakfast Blood glucose, 2-hr post breakfast Blood glucose, pre dinner Blood glucose, 2hr post dinner Blood Glucose, 4-point blood glucose profiles, body weight, insulin dose (morning and evening) were analyzed using factorial ANOVA model between groups (sequence), Periods, patients and Treatments and were summarized by finding Mean, Standard Deviation (S.D), Standard Error (S.E.M), Sample Size, Median and Range.
- For significant ANOVA results, paired 't' Test was performed.
- The Treatment Satisfaction Questionnaire was analyzed for each question using Macnamar's paired chi-square test.

Name of Company: Eli Lilly and Company (India) Pvt. Ltd. Name of the Finished Product: Insulin Lispro (LM) Vs Human Insulin 30/70 Name of the Active Substance: Insulin Lispro Protamine suspension	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	

Safety Analyses:

- The no. of Hypoglycemic events were analyzed using factorial ANOVA model between groups(sequence),Periods,patients and Treatments and were summarized by finding mean, standard Deviation (S.D.), Standard Error, Sample Size and Median.
- The no. Of Hypoglycemic Events were summarized within each Visit and over entire study i.e. over treatments and periods.
- Listing of the Adverse Events was given patient wise.
- The percentage of patients having pre-existing conditions such as Hypertension, Hyperlipidaemia and Ischemic Heart Disease was summarized.

Subgroup Analyses:

- No Sub Group Analyses was performed.

Interim Analyses:

- No interim analyses were performed.

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Summary Conclusions:

Efficacy Results :

- Morning Blood Glucose Excursion, 2hr. Post morning blood glucose level, 2hr. post evening blood glucose level, HbA1c, Change in HbA1c, Evening Dose and Change in Evening Dose, No. of Hypoglycemic Episodes.
  - There is no significant difference in above-mentioned variables between groups, between periods and between treatments : insulin lispro low mixture(LM) and Human Insulin 30/70
- Evening Blood Glucose Excursion, pre-morning blood glucose level, pre-evening blood glucose level, 4-point blood glucose profiles, Morning Dose and Change in Morning Dose and treatment satisfaction questionnaire: Q3 and Q5.
  - There is significant difference in above-mentioned variable between treatments insulin lispro low mixture (LM) and Human Insulin 30/70 using Crossover ANOVA model.
  - Out of these significant results Evening Excursion (p-value: 0.0035) and Morning Dose (p-value: 0.0492) goes in the favor of Study drug Insulin Lispro (LM) and Pre morning blood glucose level (p-value: 0.0006), Pre evening blood glucose level (p-value: 0.0088), 4-point blood glucose profile (p-value: 0.0226). (These p-values are from Paired 't' test)
  - Treatment preference questionnaire Q3(p-value: 0.0243) and Q5 (p-value: 0.0253) goes in the favor of drug Human insulin 30/70. These p-values are from Macnamer's paired Chi square test.

Safety Results:

- Hypoglycemic Events:
  - There is no significant difference in no. of Hypoglycemic events between groups(sequence) between periods and between treatments insulin lispro (LM) and Human Insulin 30/70
  - Out of total 11 SAE's, 2 were deaths and 9 hospitalization.

Name of Company: Eli Lilly and Company (India) Pvt. Ltd. Name of the Finished Product: Insulin Lispro (LM) Vs Human Insulin 30/70 Name of the Active Substance: Insulin Lispro Protamine suspension	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER Volume: Page:	

Conclusions:

The evening glycemic excursion in elderly patients (≥65years) with type 2 diabetes was significantly lower in patients on Low Mixture as compared to Human Insulin 30/70. It is possible that morning excursion was not found to be significantly different in case of LM because the morning dose of LM was significantly lower as compared to HI 30/70. Low mix and HI 30/70 were similarly effective in controlling morning and evening post-prandial blood glucose levels. Pre-morning, pre-evening and average blood sugar levels were better in case of HI 30/70 but no difference was seen in HbA1c levels.

Though treatment satisfaction questionnaire showed patients can concentrate more after meals and they feel less sleepy after meals when on Human Insulin 30/70 there was no difference in LM and HI 30/70 as far as management of diabetes and convenience was considered.

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2. List of Abbreviations and Definitions of Terms

LM	Insulin Lispro low mixture
HI 30/70	Human Insulin 30/70
Hypo	Hypoglycemic event
AE	Adverse Event
CRF	Case Report Form
SAE	Serious Adverse Events
WHO	World Health Organization
S.D.	Standard Deviation
SEM	Standard Error Of Mean (Standard Error)
ANOVA	Analysis Of Variance

3. Introduction

Insulin Lispro low mixture (LM) consists of a 1 to 3 ratio of insulin lispro to NPL. NPL represents a new formulation in which insulin lispro is co-crystallized with protamine to produce a sustained-release preparation analogous to the human insulin / protamine complex known as human insulin isophane (NPH). This ratio of 1:3 may be useful within a twice –daily regimen in which an insulin mixture is given prior to the morning and evening meals. The short acting component addresses the insulin requirements related to the morning and evening meals, and the intermediate-acting component addresses the insulin requirements associated with the midday meal and provides "basal" insulin throughout the day and during the overnight period.

4.Study Objective

4.1 Primary Objective

The Primary objective of this study was to test the hypothesis that insulin lispro low mixture (LM) improves glycemic control in elderly patients with Type 2 diabetes mellitus as compared to Human Insulin 30/70 as measured by morning and evening glycemic excursion.

4.2 Secondary Objectives

The secondary objectives of the study were:

- To compare the two treatments with regard to the glycemic control as indicated by
  - Blood glucose before morning and evening meals.
  - Post prandial blood glucose (2hours after morning and evening meals)
- To compare the two treatment with respect to:
  - Number and frequency of hypoglycemic episodes.
  - Hemoglobin A1c
  - Treatment preference of patients between the two study insulins.

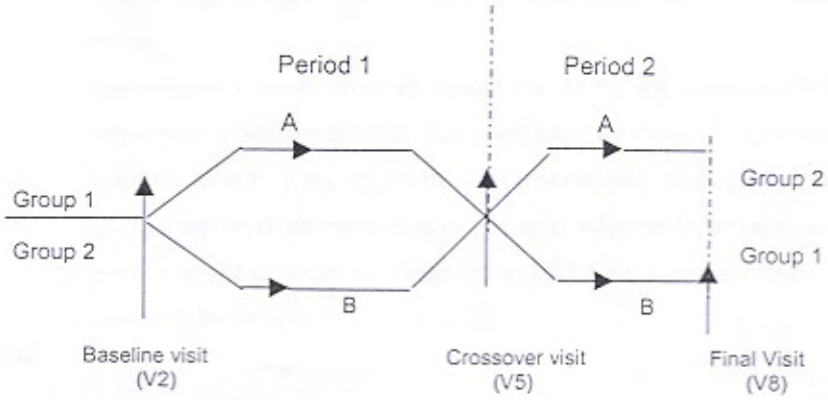
5. Methodology

5.1Study Design

- Experimental design: open label, randomized, multi-centric, multi-country, crossover, comparative study of elderly patients with Type 2 diabetes who have received therapy with Human Insulin 30/70 or intermediate acting insulin with or without metformin for at least 4 weeks prior to entering the study.
- Patients were randomized to one of the two treatment sequences:
  - Insulin lispro (LM) for 12 weeks followed by therapy with Human Insulin 30/70 for an additional 12 weeks.[Group 1 or Sequence AB]
  - Human Insulin 30/70 for 12 weeks followed by therapy Insulin lispro (LM) for an additional 12 weeks.[Group 2 or Sequence BA]
- Indication: Elderly Patients suffering from Type 2 Diabetes Mellitus.
- Total duration of study per subject was approximately 6 months.
- Data collection: hard copy of CRF.

Summary of Study Design

The study design is illustrated in the figure given below:



A: Insulin Lispro (LM)
B: Human Insulin 30/70

Group 1(Sequence AB): First treatment therapy given is A (Insulin Lispro (LM) and crossover treatment therapy given is B (Human Insulin 30/70).

Group 2 (Sequence BA): First treatment therapy given is B (Human Insulin 30/70) and crossover treatment therapy given is A (Insulin Lispro (LM).

Duration Between Visits

5.2 Principal Investigators and study centers:

Investigators / Initials	Center No.	Investigational sites	Location
Dr. Bipin kumar Sethi (BKS)	001	Care Hospital 6-3-248/1/1A Road No. 1 Banjara Hills Hyderabad – 500 034	India
Dr. C. S. Yajnik (CSY)	003	Diabetes Unit KEM Hospital Research Center Rasta Peth Pune	India
Dr. Sanjib Dhungel	005	Department of Medicine Nepal Medical College Teaching Hospital (NMCTH) Attarkhel, Jorpati Kathmandu Nepal	Nepal
Dr. (Prof) Devaka Fernando	006	Univeristy of Sri Jayawardena Pura, No. 5, Second Lane, Ratmalana Sri Lanka	Srilanka
Dr V. Mohan	007	Madras Diabetes Research Foundation 6B Conron Smith Road, Gopalapuram Chennai – 600 086	India

5.3 Ethics

The study was conducted according to the ethical principles stated in most recent version of the Declaration of Helsinki or the applicable guidelines on good clinical practice.

The ethical review board approval was taken by investigator before starting study.

The subjects were informed about the aims, expected benefits, possible risks (including a statement that the particular treatment might involve risks to the subject, which were currently unforeseeable) and procedures of the study using Informed consent document and informed consent was obtained from each subject or legal representative by taking signature and date on informed consent document.

Investigators Name	Center No.	ERB address	ERB Approval Date
Dr Bipin Sethi	001	Institutional Ethics Commmitee Care Hospital & Care Foundation Exhibition Raod, Nampally	25-01-2001
Dr C. S.Yajnik	003	KEM Research Centre Rastapeth, Pune – 411 011	19-04-2001
Dr Sanjib Dhungel	005	Ethical and Technical Committee Nepal Medical College and Teaching Hospital Atterkhel, Jorpati, Kathmandu (Nepal) P.O. Box 13344	13-02-2001
Prof Devaka Fernando	006	Faculty of Medical Sciences University of SriJayawardenapura Srilanka	29-05-2001
Dr V Mohan	007	Madras Diabetes Research Foundation 6B, Conran Smith Road Gopalapuram Chennai – 600 086	26-07-2001

5.4 Selection of Study Population

The study population was comprised of elderly patients suffering from Type 2 Diabetes Mellitus.

5.4.1 Inclusion Criteria

Subjects who met all the following criteria were enrolled in the study.

- Suffering from Type 2 Diabetes for at least 6 months [WHO classification].
- Age atleast 65 years.
- Had received intermediate acting insulin with or without short acting insulin or HI 30/70 twice daily with or without metformin as their diabetes therapy for at least 30days prior to entering the study.
- Had achieved compliance with their prescribed diet and insulin therapy as determined by the investigator and were capable and willing to: Perform self blood glucose monitoring, learn how to use the insulin injection pen, used the patient diary as required for this protocol.
- Had given written informed consent to participate in the study in accordance with local regulations.

5.4.2 Exclusion Criteria

Subjects were excluded from the study for any of the following reasons:

- Therapy for malignancy, other than basal cell or squamous cell skin cancer.
- Cardiac disease that is Class III or IV
- History of renal transplantation or receiving renal dialysis.

- Clinical signs or symptoms of liver disease, acute or chronic hepatitis, or alanine transaminase (ALT or SGPT) greater than three times the upper limit of the reference range of laboratory.
- Serum creatinine greater than 1.5mg/dl for patients using metformin and greater than 2mg/dl for patients not using metformin.
- Hemoglobinopathy or anemia (Hb<10gm/dl).
- History of drug or alcohol abuse.
- Allergy to insulin or excipients contained in insulin products.
- Used any oral antidiabetic agents, except metformin (for example, sulphonylureas, glucosidase inhibitors, and thiazolidinediones) for the treatment of diabetes within 14 days prior to entry into the study.
- Received chronic (lasting longer than 2 weeks) systemic glucocorticoid therapy or have received such therapy within 2 weeks of entry.

- Received a total daily dose of insulin greater than 2.0 units per kg

- Had more than one episode of serious hypoglycemia within 6 months prior to entry into the study.
- History of hypoglycemia episodes unawareness
- Body mass index greater than 35kg/m^2
- Participation in an interventional medical, surgical or pharmaceutical study within 30 days prior to entry into the study.
- Had any other condition that precludes the patient from following and completing the protocol.
- Investigators and their immediate families.
- Treatment with a drug within the last 30 days that had not received regulatory approval at the time of study entry.
- Had active proliferative diabetic retinopathy.

5.5 Study Drug and administration

5.5.1 Study Drug composition

- The study materials were:

  Insulin Lispro LM (Lilly) supplied in cartridges (3.0ml)

  Human Insulin 30/70 (Lilly) supplied in. cartridges (3.0ml)

5.5.2 Dosage and Administration

- Patients administered either insulin lispro LM or Human Insulin 30/70 twice daily before morning and evening meals.

Human Insulin 30/70 was administered before meals at their usual time and Insulin lispro LM was given immediately before meals.

- The patients were monitored carefully for changes in insulin requirements and doses adjusted in accordance with their metabolic needs in order to achieve the target goals for this study which were pre-meal blood glucose values < 7mmol/L (126 mg/dL). and 2 hour postprandial blood glucose < 10mmol/L (180 mg/dL)
- The insulin dose was adjusted to achieve the above goals unless further adjustment resulted in hypoglycemia.
- Insulins used by the patients were the ones specifically provided by the sponsor.
- The study drugs were administered by subcutaneous route.

5.6 Treatment allocation and randomization

- Patients were randomized to one of the two treatment sequences:
  - Insulin lispro LM for 12 weeks followed by therapy with Human Insulin 30/70 for an additional 12 weeks.[Group 1 or Sequence AB]
  - Human Insulin 30/70 for 12 weeks followed by therapy Insulin lispro LM for an additional 12 weeks.[Group 2 or Sequence BA]

Thus out of **130** patients entered in the study **4** patients did not meet entry criteria i.e. Exclusions and other **12** patients were drop outs before enrollment and only **114** patients were enrolled out of that **53** were randomized to treatment A : Insulin Lispro {Group 1[Sequence AB] } and rest **61** patients were randomized to treatment B : Human Insulin 30/70 {Group 2 [Sequence BA] }

5.7 Blinding

- Not applicable

5.8 Study Procedure

The following table outlines the study procedures for Study Drugs for subjects as per Scheduled events given in the protocol.

Outline of Study Procedures for subjects as per scheduled events

Visit Number	1	2	3	4	5	6	7	8	ET[a]
Week Number	-4 (+/-) 1 week	0	4 (+/-) 1 week	8 (+/-) 1 week	12 (+/-) 1 week	16 (+/-) 1 week	20 (+/-) 1 week	24 (+/-) 1 week	
Informed Consent	X								
Patient number assigned	X								
Randomization		X							
Concomitant Medications	X	X	X	X	X	X	X	X	
Physical examination	X								
Medical History	X								
ECG	X								
Insulin type and dose	X	X			X			X	
Height	X								
Body weight	X	X	X	X	X	X	X	X	
Screening laboratory analyses[b] ALT, serum creatinine, Hb	X								
Hemoglobin A1c		X			X			X	X
Adverse Events		X	X	X	X	X	X	X	X
Treatment Satisfaction Questionnaire								X	X[c]
Diary dispensing	X	X	X	X	X	X	X		
SBGM and insulin dose		X		X	X		X	X	
Hypoglycemic episodes		X	X	X	X	X	X	X	X
Patient Summary								X	X

X: Performed at this visit.

Abbreviations: SBGM: Self blood glucose monitoring; ALT: alanine transaminase;

Hb: Hemoglobin; ECG: Electrocardiogram

[a]: Performed at early termination in addition to the other activities required for that visit.

[b]: Samples will be collected within 1 week of visit 1 and analyses will be performed at a central laboratory.

[c]: The treatment satisfaction questionnaire will be administered at early termination only if the visit occurs after visit 5.

- * 4 point glucose profile should be done on any 3 separate days out of 7 days, prior to visit 2, 4, 5, 7 & 8.

5.9 Discontinuations

Subjects were discontinued from the study in the following circumstances.

- The investigator felt that for safety subject should be withdrawn because of SAE or clinically significant laboratory value.
- The subject or attending physician's opinion.
- The subject, for any reason, required treatment with another therapeutic agent which was not allowed in the protocol.
- Sponsor's Decision.
- Patients whose metformin dose was changed during the study
- The subject failed to comply with the treatment regimen.
- The subject failed to return for visits as scheduled.

5.10 Assessment of variables:

In this study efficacy as well as safety of the study drug was tested for different treatments, groups and periods, depending on their first treatment assigned.

5.10.1 Assessment of Efficacy variables:

Efficacy assessments were based upon the following measurements, which were collected for each subject

- 4-pt blood glucose profile: Pre-breakfast blood glucose, 2hr-post breakfast blood glucose, pre-dinner blood glucose, 2hr-post dinner blood glucose.

  4-point blood glucose profile was done on any 3 out of 7 days, prior visit 2, 4, 5, 7 & 8.
- HbA_{1c}

  HbA_{1c} measure was taken on Randomization Visit 2.Thereafter, it was done on crossover Visits 5 and final Visit 8
- Insulin dose requirement at the onset and completion of the study.

  The patients were converted to study Insulins on unit-for-unit basis. The dose adjustments were recorded throughout the study.

5.10.2 Assessment of Safety Variables

Safety measures used in the study were

- At the first visit, physical examination and vitals including height, weight, BMI, and ECG was measured. Information about any pre-existing condition(s) was obtained from subject by Study site personnel and was recorded in the Case Report Form.
- At subsequent visits, the information about any change in the pre-existing condition(s), and the occurrence and nature of any adverse events and occurrence of hypoglycemic events was again obtained from subject and were recorded in the Case Report Forms. The weight of the subject was also noted on Case Report Forms for all the visits.

5.10.3 Biochemical Assays

Not applicable

5.10.4 Prior and concomitant medication

At each study visit, the investigators questioned the subject about any medication taken.

Patients were allowed to use metformin and any concomitant medications that they require except for the following: other oral antidiabetic agents (including sulphonylureas, thiazolidinediones, glucosidase inhibitors), chronic systemic glucocorticoid therapy for greater than 2 weeks duration and non-study insulin. Topical and inhaled glucocorticoid preparations were permitted. Any other medication relevant to the protocol, including any specifically contraindicated-administered during the study period was recorded in the case report form-Concomitant Medication Page, with adverse event code, generic name for the medication, start and end dates of treatment and the corresponding pre-existing condition or Adverse Event on Pre-existing Condition Page. The relatedness (Related, Not Related, Possibly related) of this adverse event with respect to study drug was also noted in the Pre-existing Condition Page.

5.10.5 Intervals between study visits

It was the investigator's responsibility to ensure that the intervals between study visits were strictly followed as per visit schedule given for study.

5.11 Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly representatives

- Provided instructional material to the study sites.
- A start-up training session was sponsored to instruct the investigators and study coordinators in order to give instructions on the protocol, completion of the clinical report forms, and study procedures.
- Periodic visits were made to the study site.
- Contact with the study site personnel by mail, telephone, and/or fax for consultation was available.
- Evaluation of clinical report form data and use of standard computer edits to detect errors in data collection was reviewed.
- Quality review of database was conducted.

Adherence to the protocol requirements and verification of data generation accuracy was achieved through monitoring visits to each investigator site to check the subject data recorded against source documents No study specific audits were performed for this study.

5.12 Statistical Methods planned in the protocol

5.12.1 Baseline Characteristics

Baseline characteristics like age, sex, height, weight are summarized by finding Mean, S.D. S.E.M, Median and Range.

5.12.2 Efficacy Analysis

Qualification for efficacy analysis:

- Patients satisfying inclusion / exclusion criteria with baseline, crossover and end of the study efficacy data recorded were deemed fit for efficacy analysis.
- Only those patients were analyzed who had atleast one reading available for efficacy measures.
- For Blood Glucose excursion, HbA1c and 4 – point Blood glucose profile Factorial ANOVA model was used and variation between groups (subjects), between products and between period was tested. For significant efficacy parameters Paired 't' test was performed.
- For treatment effect for combined period Factorial ANOVA model was used.
- Mean, S.D., SEM, Median and Range within each treatment group were summarized for efficacy measures.
- No of hypoglycemic episodes were analyzed using Factorial ANOVA model to find treatment effect.

5.12.3 Analysis of Dose and Exposure

Analysis of Dose: Change in dose and mean dose will be obtained for V2 to V5 and V5 to V8 i.e. for periods and also for treatments and summarized.

5.12.4 Safety Analyses

- Death and SAEs: Listing of Serious Adverse Events and deaths were given investigatorwise.
- Discontinuations: The details of discontinuations will be tabulated with the details.
- Listing of Adverse events were tabulated for the study.
- Number of hypoglycemic episodes by treatment within visits were summarized by calculating the hypo rates. Also overall hypoglycemic episodes by treatment were summarized for period 1, period 2 and combined period i.e. entire study

5.12.5 Concomitant Medications

Percentage of patients on metformin, and concomitant medication for Hypertension, Hyperlipdaemia and Ischemic Heart Disease were summarized.

5.12.6 Lab Evaluations

Not Applicable

5.12.7 Vital Signs (Physical Examination)

Weight and BMI was summarized using descriptive statistic mean, S.D. SEM, Median and Range for each subsequent visit.

5.12.8 Target sample size

Target sample size was 110 elderly subjects suffering from Type 2 Diabetes Mellitus.

5.12.9 Study data sets

Subjects qualified for efficacy analysis were those who met entry criteria enrolled and completed the protocol and having data for efficacy measures. Safety analysis will be done for all the patients who received at least one dose of the study drug.

5.12.10 Analysis of demographics

Patients characteristics obtained at visit 1 were summarized. The summarization included descriptive statistics (Mean, Standard Deviation, sample size, Median, Range) for the continuous parameters like age, height and weight and frequencies and percentages for the remaining categorical parameters such as sex.

5.13 Changes in planned analyses

- No change in the planned analyses.

6. Study Population

6.1 Study dates

The first subject was enrolled in the study on 17th April 2001 and the last study visit was on 10th April 2002.

6.2 Subject eligibility

6.2.1 Number and distribution of subject

A total of 110 subjects were planned to be enrolled in the present clinical study and 114 subjects were actually enrolled.

Table 1 presents the number of subjects enrolled at each center by group.

Table 1: The number of subjects enrolled at each center by group

Centers	No. of subjects Enrolled to study Drug A n1	No. of subjects Enrolled to study Drug B n2	Total no. of subjects enrolled n	%
001	17	18	35	30.70
003	9	11	20	17.54
005	7	9	16	14.04
006	6	8	14	12.28
007	14	15	29	25.44
Total	53	61	114	100.00

N (%): Number (percentage) of subjects enrolled at each center
Drug A: Insulin Lispro LM
Drug B: Human Insulin 30/70

6.2.2 Study completion and drop outs

Of the **130** subjects entered in the study, **4** subjects were excluded from study because of violation of inclusion/exclusion criteria, **12** were drop outs due to primary reasons before enrollment only and only **114** subjects were enrolled in the study. Only **114** patients were taken for safety analysis.

8 subjects were discontinued due to primary reasons and only **106** subjects completed the study and were taken for efficacy analysis.

Table 2 and 3 presents the reasons for dropouts before and after enrollment.

Table 2: Reasons for drop out before enrollment

	Total	Patient Nos
Number of subjects entered	130	-
Exclusions (12)	4	119, 121, 122, 602
Number of Drop Outs	12	114, 127, 307, 312, 323, 324, 510, 413, 419, 430, 606, 614
Number of subjects enrolled	114	-
Reasons for drop-out:		
Adverse event (3)	1	419
SAE : Death (4)	1	114
Lost to follow-up (8)	0	-
Patient Moved (9)	1	609
Personal conflict or patient Decision (10)	9	127, 307, 312, 323, 324, 510, 413, 430, 614
Physician Decision (11)	0	-
Protocol Violations (13)	0	-
Sponsor's Decision (14)	0	-
Total Drop Outs	**12**	

Table 3: Reasons for drop outs / Discontinuations after enrollment

	Total	Patient Nos
Number of subjects enrolled	114	-
Number of Drop outs / Discontinuations	8	128, 301, 303, 315, 423, 431, 608, 611
Number of subjects completed	106	-
Reasons for drop-out / Discontinuations:		
Adverse event (3)	2	423, 315
SAE : Death (4)	2	301, 303
Lost to follow-up (8)	1	608

Patient Moved (9)	1	431
Personal conflict or patient Decision (10)	0	-
Physician Decision (11)	1	128
Protocol Violations (13)	0	-
Sponsor's Decision (14)	1	611
Total Drop Outs	8	

(*): * represents the completion ID

6.2.3 Eligibility for analyses

Out of **114** subjects enrolled **106** subjects were eligible for efficacy analysis and **114** patients were eligible for safety analysis.

6.2.4 Compliance with protocol specified procedures

Violation Noted	Inv/Pt Number	Remarks
Significant Protocol Violations		
Patient took non-study insulin for more than 7 days because patient underwent a pre-planned gall bladder stone surgery	005/ 507	Patient was included into the study but the information has to be captured on the CRF
Patient did not satisfy inclusion/exclusion criteria but was randomized into the study as site did not receive the lab report before visit 2	006/611	Patient was immediately discontinued from the study
Other GCP Violations		
Randomisation code for patients was opened before the patient came for visit 2	001/134	Since it's an open label study it does not affect data but site was told not to repeat in future
Patient repeatedly was not returning the empty cartridges to site	001/118	Investigator asked to emphasise the same to patient and not to repeat
5 cartridges returned by one patient was included in the stock and dispensed to other patient	005/510	Not repeated after instructing the site
Site did not report 2 SAE's within 24hrs	005/501 , 511	CRA found out on monitoring visit and site was retrained on SAE reporting process
Lead in medication for patient was dispensed after 10 days of visit 1	005/503	Patient was already on intermediate acting insulin so not discontinued from study
Lead in medication for patient was dispensed after 12 days of visit 1	005/504	Patient was already on intermediate acting insulin so not discontinued from study
Visit 8 sample was shipped after 6 days of collection, therefore samples were beyond stability	006/604 , 605	Saite was asked to take samples again
Drug accountability logs were not properly filled 14 cartridges returned by other patients were dispensed to other study patients Shipment was held up at customes for 2 months approx. and site used the drugs inspite of instructions that not to use them	006	Issues were considered during analysis and site will be reassessed for future trials
Visit 2 sample was withdrawn after 3 days	006/608	Could not be repeated as patient had completed the study
ECG was not done at Visit 1	006/608	Could not be repeated as patient had completed the study
For some patients site have transcribed the glucose readings from patient papers to study diaries and original sheets provided to site by patients were not available	006	Site was asked to take signatures of patients
SAE reporting from the affiliate was not done within the PhV timeline	007/406	SAE was reported immediately and closed on the same day
Patient came for visit 2 out of window period	007/411	For further visits patient visits were rescheduled and was asked to come on scheduled dates

Statistical Analyses:

- **All the sites and all the patients entered in the study were analyzed.**

6.3 Demographics characteristics

The demographic profile of the patients enrolled is presented in Table 4 & 5, the male: female ratio was 1.20: 1 The mean age of the subjects was 68.832 years with a standard deviation of 3.7981 years .The mean height of the subjects is 158.6769 cms. with a standard deviation of 9.6438 cms.and mean weight of the subjects is 64.3807 Kgs. with standard deviation 10.2264 Kgs. The study population comprised of 'Elderly Patients with Type 2 Diabetes Mellitus".

Table 4 : Demographics and Physical Examination for Enrolled patients

Visit 1:			
Parameters	**Class**	**Number**	**%**
Sex	M	71	54.62
	F	59	45.38
	Total	130	100
Parameters	**Class**	**Statistic**	**Visit 1**
Age	M	Number	71
		Mean	69.4194
		S. D	4.365
		S. E. M	0.518
		Median	67.7287
		Range	20.452
	F	Number	59
		Mean	68.1251
		S. D	2.8562
		S. E. M	0.3718
		Median	67.3753
		Range	11.7315
	Total	Number	130
		Mean	68.832
		S. D	3.7981
		S. E. M	0.3331
		Median	67.463
		Range	20.452
Height	M	Number	71
		Mean	164.507
		S. D	6.7962
		S. E. M	0.8065
		Median	165
		Range	35
	F	Number	59
		Mean	151.661
		S. D	7.7088
		S. E. M	1.0036
		Median	152
		Range	46
	Total	Number	130
		Mean	158.6769
		S. D	9.6438
		S. E. M	0.8458
		Median	159
		Range	48

Continuation of the above table:

Parameters	Class	Statistic	Visit 1	Visit 3	Visit 4	Visit 6	Visit 7
Weight	M	Number	71	61	61	57	56
		Mean	66.5211	67.2918	67.2622	67.5701	67.8785
		S. D	9.47	9.199	9.1611	9.8429	9.6919
		S. E. M	1.1238	1.1778	1.1729	1.3037	1.2951
		Median	67	68	68.2	67	67.5
		Range	39	37	38	42	42.5
	F	Number	59	50	50	50	49
		Mean	61.805	62.352	63.648	62.696	62.9836
		S. D	10.5769	10.8178	11.3573	11.0081	10.9505
		S. E. M	1.3769	1.5298	1.6061	1.5567	1.5643
		Median	60	62	63	62.5	64
		Range	48	47	52	49.2	48.2
	Total	Number	130	111	111	107	105
		Mean	64.3807	65.0666	65.6342	65.2925	65.5942
		S. D	10.2234	10.2168	10.3198	10.6381	10.5376
		S. E. M	0.8966	0.9697	0.9795	1.0284	1.0283
		Median	65.5	66	66	65	65.00
		Range	48	47	52	50.2	49.2
BMI	M	Number	71	61	61	57	56
		Mean	24.5734	24.8126	24.7982	24.8560	24.9764
		S. D	3.1851	3.1560	3.1194	3.3518	3.3280
		S. E. M	0.3780	0.4040	0.3994	0.4439	0.4447
		Median	24.6097	24.7409	24.7675	24.7675	24.7462
		Range	18.7390	17.9682	18.7390	19.9427	20.1117
	F	Number	59	50	50	50	49
		Mean	26.8554	26.9930	27.6102	27.1553	27.2029
		S. D	4.0249	4.2283	4.9066	4.3972	4.3503
		S. E. M	0.5239	0.5979	0.6939	0.6218	0.6214
		Median	27.6787	27.7335	27.9192	27.5800	27.3881
		Range	18.7076	18.7571	27.2583	19.8081	19.3753
	Total	Number	130	111	111	107	105
		Mean	25.6091	25.7947	26.0649	25.9305	26.0154
		S. D	3.7536	3.8190	4.2435	4.0251	3.9796
		S. E. M	0.3292	0.3624	0.4027	0.3891	0.3883
		Median	25.3074	25.4374	25.5296	25.3154	25.3415
		Range	18.8352	18.9794	27.8187	20.6200	20.7890

Table 5: Demographics

Parameters	Class	Statistic	Visit 2	Period 1 (Visit 5)	Period 2 (Visit 8)
Weight	M	Number	62	60	56
		Mean	67.0806	67.2389	68.0678
		S. D	9.0902	9.8167	9.9850
		S. E. M	1.1544	1.278	1.3343
		Median	67.5	67.6	67.8500
		Range	37	38.5	44.5000
	F	Number	53	50	50
		Mean	61.3396	62.482	63.196
		S. D	10.7978	10.6675	11.0812
		S. E. M	1.4832	1.5086	1.5671
		Median	60	63	63.1500
		Range	46.5	48.6	49.4000
	Total	Number	115	109 (1)	106
		Mean	64.4347	65.0568	65.7698
		S. D	10.2791	10.4428	10.747
		S. E. M	0.9585	1.0002	1.0438
		Median	65	65	65.25
		Range	46.5	48.6	51.9
BMI	M	Number	62	60	56
		Mean	24.7448	24.8243	25.0465
		S. D	3.1495	3.3843	3.4588
		S. E. M	0.3999	0.4406	0.4622
		Median	24.7675	24.7767	24.7257
		Range	18.7390	19.4357	20.3755
	F	Number	53	50	50
		Mean	26.7058	27.0663	27.3732
		S. D	4.1200	4.2733	4.4225
		S. E. M	0.5659	0.6043	0.6254
		Median	27.4076	27.6638	27.6008
		Range	18.2748	19.2826	19.0915
	Total	Number	115	109 (1)	106
		Mean	25.6486	25.8527	26.1440
		S. D	3.7435	3.9618	4.0934
		S. E. M	0.3490	0.3794	0.3975
		Median	25.4028	25.3069	25.5894
		Range	18.8352	19.6307	20.3755

( ) denotes the missing values

Lab Evaluations : HbA1c for Visit 2,Visit 5 , Visit 8 :

Parameters	Class	Statistic	Visit 2	Visit 5	Visit 8
HbA1c	M	Number	62	58 (3)	56
		Mean	7.9713	7.7057	7.7275
		S.D	1.3395	1.0834	1.0297
		SEM	0.1701	0.1423	0.1376
		Median	7.8000	7.5300	7.5300
		Range	5.1900	4.3500	4.3100
	F	Number	52	50	50
		Mean	7.9163	7.8380	7.8320
		S.D	1.1602	1.0427	1.0477
		SEM	0.1609	0.1475	0.1482
		Median	7.8500	7.6500	7.6650
		Range	5.0800	3.5800	4.3500
	Total	Number	114	108(3)	106
		Mean	7.9462	7.7669	7.7768
		S.D	1.2557	1.0619	1.0346
		SEM	0.1176	0.1022	0.1005
		Median	7.8150	7.5550	7.5750
		Range	5.4300	4.3500	4.3800

( ) represents missing values

Dose Analysis : Morning Dose for Visit 2,Visit 5 , Visit 8 :

Parameters	Class	Statistic	Visit 2	Visit 5	Visit 8
Morning Dose	M	Number	62	59 (2)	56
		Mean	24.7366	27.0169	28.1012
		S.D	8.7489	8.0388	9.8504
		SEM	1.1111	1.0466	1.3163
		Median	25.00	26.00	25.50
		Range	45.00	35.00	42.00
	F	Number	52	50	49 (1)
		Mean	23.9167	27.5533	28.7619
		S.D	9.0767	9.9915	11.2618
		SEM	1.2587	1.4130	1.6088
		Median	23.50	28.00	30.00
		Range	38.3333	35.6667	50.00
	Total	Number	114	109 (2)	105 (1)
		Mean	24.3626	27.2630	28.4095
		S.D	8.8697	8.9482	10.4862
		SEM	0.8307	0.8571	1.0233
		Median	25.00	28.00	28.00
		Range	49.3333	40.6667	50.00

Parameters	Class	Statistic	Visit 2	Visit 5	Visit 8
Evening Dose	M	Number	62	59 (2)	56
		Mean	16.0968	18.2034	17.8571

Dose		S.D	7.6602	8.1299	8.8491
		SEM	0.9728	1.0584	1.1825
		Median	15.00	18.00	16.00
		Range	34.00	36.00	38.00
	F	Number	52	50	49 (1)
		Mean	17.4423	20.5800	21.7551
		S.D	8.6804	10.1420	11.2241
		SEM	1.2038	1.4343	1.6034
		Median	16.00	18.00	20.00
		Range	34.00	41.00	43.00
	Total	Number	114	109 (2)	105 (1)
		Mean	16.7105	19.2936	19.6762
		S.D	8.1324	9.1422	10.1673
		SEM	0.7617	0.8757	0.9922
		Median	15.00	18.00	17.00
		Range	34.00	41.00	44.00
Parameters	**Class**	**Statistic**	**Visit 2**	**Visit 5**	**Visit 8**
Total Dose	M	Number	62	59 (2)	56
		Mean	40.8387	45.2373	45.9643
		S.D	15.2812	14.6268	16.8609
		SEM	1.9407	1.9042	2.2531
		Median	40.00	42.00	43.50
		Range	64.00	62.00	72.00
	F	Number	52	50	49 (1)
		Mean	41.3846	48.1200	50.5306
		S.D	16.7509	18.8611	21.0298
		SEM	2.3229	2.6674	3.0043
		Median	39.50	49.50	50.00
		Range	64.00	66.00	90.00
	Total	Number	114	109 (2)	105 (1)
		Mean	41.0877	46.5596	48.0952
		S.D	15.8988	16.6847	18.9658
		SEM	1.4891	1.5981	1.8509
		Median	40.00	43.00	46.00
		Range	69.00	66.00	90.00

( ) represents missing values

Table 6: Demographics: Treatment Effect Testing (ANOVA):

Parameter: Weight				
H_0 There is no significant difference between the two treatments LM and HI 30 / 70.				
H_1 There is significant difference between the two treatments LM and HI 30 / 70.				
Statistic	Combined Periods		P-Value	(Treatment Effect) Statistical Significance
	LM	HI 30 / 70		
Mean	65.382	65.3566	0.7653	Non Significant
S.D.	10.5943	10.6265		
SEM	1.029	1.0321		
N	106	106		
Min Weight	38.6	37.9		
Max Weight	89	90.5		
Range	50.4	52.6		
Med.	65	65		

Parameter: BMI				
H_0 There is no significant difference between the two treatments LM and HI 30 / 70.				
H_1 There is significant difference between the two treatments LM and HI 30 / 70.				
Statistic	Combined Periods		P-Value	(Treatment Effect) Statistical Significance
	LM	HI 30 / 70		
Mean	25.9941	25.9767	0.8540	Non Significant
S.D.	4.0481	4.0379		
SEM	0.3931	0.3922		
N	106	106		
Med.	25.5894	25.2947		
Range	20.2496	19.8685		

Table 7: Demographics: ANOVA results of the parameters

Parameter: Weight		
H_0 There is no significant difference between the two treatments LM and HI 30/70.		
H_1 There is significant difference between the two treatments LM and HI 30/70.		
Source	P-Value	Statistical Significance
Sequence	0.9258	Non Significant
Patients	<0.0001	Significant
Period	<0.0001	Significant
Treatment	0.7653	Non Significant

Parameter: BMI		
H_0 There is no significant difference between the two treatments LM and HI 30/70.		
H_1 There is significant difference between the two treatments LM and HI 30/70.		
Source	P-Value	Statistical Significance
Sequence	0.6972	Non Significant
Patients	<0.0001	Significant
Period	<0.0001	Significant
Treatment	0.8540	Non Significant

Table 8: Efficacy Analysis:Treatment Effect Testing (Anova)

Parameter:Morning Blood Glucose Excursion				
H_0 There is no significant difference between the two treatments LM and HI 30/70.				
H_1 There is significant difference between the two treatments LM and HI 30/70.				
Statistic	Combined Periods		P-Value	(Treatment Effect) Statistical Significance
	LM	HI 30 / 70		
Mean	64.5566	71.6603	0.0952	Non Significant
S.D.	42.5636	48.6046		
SEM	4.1341	4.7209		
N	106	106		
Med.	61.3333	68.8333		
Range	225.6666	273.3333		

Postprandial Blood Glucose Excursion = (2 Hr Postprandial Blood Glucose Level) - (Pre Meal Blood Glucose Level)				
Parameter: Evening Blood Glucose Excursion				
H_0 There is no significant difference between the two treatments LM and HI 30/70.				
H_1 There is significant difference between the two treatments LM and HI 30/70.				
Statistic	Combined Periods		P-Value	(Treatment Effect) Statistical Significance
	LM	HI 30 / 70		
Mean	26.3616	38.9669	0.0078	**Significant**
S.D.	40.3241	44.5918		
SEM	3.9166	4.3311		
N	106	106		
Med.	24.8333	38		
Range	211	280.6666		

Parameter:Pre Morning Meal Blood Glucose Level				
H_0 There is no significant difference between the two treatments LM and HI 30/70.				
H_1 There is significant difference between the two treatments LM and HI 30/70.				
Statistic	Combined Periods		P-Value	(Treatment Effect) Statistical Significance
	LM	HI 30 / 70		
Mean	142.8663	129.9905	0.0012	**Significant**
S.D.	41.7206	36.8133		
SEM	4.0522	3.5756		
N	106	106		
Med.	137.6666	122.8333		
Range	210.6666	191.3333		

Parameter:2 Hr. Postprandial Morning Blood Glucose Level				
H_0 There is no significant difference between the two treatments LM and HI 30/70.				
H_1 There is significant difference between the two treatments LM and HI 30/70.				
Statistic	Combined Periods		P-Value	(Treatment Effect) Statistical Significance
	LM	HI 30 / 70		
Mean	207.4229	201.6509	0.2962	Non Significant
S.D.	50.5837	56.3334		
SEM	4.9131	5.4715		
N	106	106		
Med.	203.1666	192.5		
Range	287.6666	279.6666		

Parameter: Pre Evening Meal Blood Glucose Level				
H_0 There is no significant difference between the two treatments LM and HI 30/70.				
H_1 There is significant difference between the two treatments LM and HI 30/70.				
Statistic	Combined Periods		P-Value	(Treatment Effect) Statistical Significance
	LM	HI 30 / 70		
Mean	176.2893	164.2798	0.0157	**Significant**
S.D.	53.8232	47.7925		
SEM	5.2277	4.642		
N	106	106		
Med.	171.8333	165.1666		
Range	331.00	206.3333		

Parameter: 2 - hrs Post Prandial Evening Blood Glucose Level				
H_0 There is no significant difference between the two treatments LM and HI 30/70.				
H_1 There is significant difference between the two treatments LM and HI 30/70.				
Statistic	Combined Periods		P-Value	(Treatment Effect) Statistical Significance
	LM	HI 30 / 70		
Mean	202.6509	203.2468	0.9643	Non Significant
S.D.	54.1772	54.3355		
SEM	5.2621	5.2775		
N	106	106		
Med.	193.8333	193.3333		
Range	279.6666	276		

Parameter: HbA1c				
H_0 There is no significant difference between the two treatments LM and HI 30/70.				
H_1 There is significant difference between the two treatments LM and HI 30/70.				
Statistic	Combined Periods		P-Value	(Treatment Effect) Statistical Significance
	LM	HI 30 / 70		
Mean	7.7883	7.7209	0.3119	Non Significant
S.D.	1.0249	1.0447		
SEM	0.0995	0.1014		
N	106	106		
Med.	7.54	7.575		
Range	4.36	4.37		

Parameter: 4-Point (Average Daily) Blood Sugar Between LM and Hum 30/70				
H_0 There is no significant difference between the two treatments LM and HI 30/70.				
H_1 There is significant difference between the two treatments LM and HI 30/70.				
Statistic	Combined Periods		P-Value	(Treatment Effect) Statistical Significance
	LM	HI 30 / 70		
Mean	182.3616	174.6391	**0.0451**	**Significant**
S.D.	43.0367	40.1871		
SEM	4.18	3.9033		
N	106	106		
Med.	175.375	170.5		
Range	262.5833	193.25		

Parameter: No. of Hypoglycemic Events				
H_0 There is no significant difference between the two treatments LM and HI 30/70.				
H_1 There is significant difference between the two treatments LM and HI 30/70.				
Statistic	Combined Periods		P-Value	(Treatment Effect) Statistical Significance
	LM	HI 30 / 70		
Mean	0.3679	0.3018	0.5492	Non Significant
S.D.	0.9887	1.0251		
SEM	0.0960	0.0995		
N	106	106		
Med.	0	0		
Range	7	8		

Parameter: Morning Dose				
H_0 There is no significant difference between the two treatments LM and HI 30/70.				
H_1 There is significant difference between the two treatments LM and HI 30/70.				
Statistic	Combined Periods		P-Value	(Treatment Effect) Statistical Significance
	LM	HI 30 / 70		
Mean	27.5125	28.0888	**0.0348**	**Significant**
S.D.	9.9847	9.6162		
SEM	0.9698	0.9384		
N	106	106		
Med.	26.5	28		
Range	50	42		

Parameter: Evening Dose				
H_0 There is no significant difference between the two treatments LM and HI 30/70.				
H_1 There is significant difference between the two treatments LM and HI 30/70.				
Statistic	Combined Periods		P-Value	(Treatment Effect) Statistical Significance
	LM	HI 30 / 70		
Mean	19.4779	19.3555	0.7616	Non Significant
S.D.	9.9974	9.3227		
SEM	0.971	0.9098		
N	106	106		
Med.	17	18		
Range	41	44		

Parameter: Change in Morning Dose				
H_0 There is no significant difference between the two treatments LM and HI 30/70.				
H_1 There is significant difference between the two treatments LM and HI 30/70.				
Statistic	Combined Periods		P-Value	(Treatment Effect) Statistical Significance
	LM	HI 30 / 70		
Mean	1.5	2.8761	**0.0335**	**Significant**
S.D.	4.4171	4.9694		
SEM	0.429	0.4849		
N	106	106		
Med.	1	2.3333		
Range	25.3333	32.3333		

Parameter: Change in Evening Dose				
H_0 There is no significant difference between the two treatments LM and HI 30/70.				
H_1 There is significant difference between the two treatments LM and HI 30/70.				
Statistic	Combined Periods		P-Value	(Treatment Effect) Statistical Significance
	LM	HI 30 / 70		
Mean	1.4088	1.8698	0.6079	Non Significant
S.D.	4.3960	4.3788		
SEM	0.4269	0.4273		
N	106	106		
Med.	0	1		
Range	34	24		

Parameter: Change in HbA1c				
H_0 There is no significant difference between the two treatments LM and HI 30/70.				
H_1 There is significant difference between the two treatments LM and HI 30/70.				
Statistic	Combined Periods		P-Value	(Treatment Effect) Statistical Significance
	LM	HI 30 / 70		
Mean	-0.0072	-0.1103	0.3837	Non Significant
S.D.	0.7282	0.6970		
SEM	0.0707	0.0677		
N	106	106		
Med.	-0.14	-0.125		
Range	4.33	3.21		

Table 9: ANOVA Results of the Parameters

Parameter:Morning Blood Glucose Excursion		
H_0 There is no significant difference between the two treatments LM and HI 30/70.		
H_1 There is significant difference between the two treatments LM and HI 30/70.		
Source	P-Value	Statistical Significance
Sequence	0.9916	Non Significant
Patients	<0.0001	Significant
Period	0.1735	Non Significant
Treatment	0.0952	Non Significant

Parameter: Evening Blood Glucose Excursion		
H_0 There is no significant difference between the two treatments LM and HI 30/70.		
H_1 There is significant difference between the two treatments LM and HI 30/70.		
Source	P-Value	Statistical Significance
Sequence	0.5442	Non Significant
Patients	<0.0001	Significant
Period	0.9148	Non Significant
Treatment	**0.0078**	**Significant**

Parameter:Pre Morning Meal Blood Glucose Level		
H_0 There is no significant difference between the two treatments LM and HI 30/70.		
H_1 There is significant difference between the two treatments LM and HI 30/70.		
Source	P-Value	Statistical Significance
Sequence	0.5364	Non Significant
Patients	<0.0001	Significant
Period	0.7588	Non Significant
Treatment	0.0012	**Significant**

Parameter:2 Hr. Postprandial Morning Blood Glucose Level		
H_0 There is no significant difference between the two treatments LM and HI 30/70.		
H_1 There is significant difference between the two treatments LM and HI 30/70.		
Source	P-Value	Statistical Significance
Sequence	0.7854	Non Significant
Patients	<0.0001	Significant
Period	0.3182	Non Significant
Treatment	0.2962	Non Significant

Parameter:Pre Evening Meal Blood Glucose Level		
H_0 There is no significant difference between the two treatments LM and HI 30/70.		
H_1 There is significant difference between the two treatments LM and HI 30/70.		
Source	P-Value	Statistical Significance
Sequence	0.7510	Non Significant
Patients	<0.0001	Significant
Period	0.5020	Non Significant
Treatment	**0.0157**	**Significant**

Parameter: 2 - hrs Post Prandial Evening Blood Glucose Level

H_0 There is no significant difference between the two treatments LM and HI 30/70.

H_1 There is significant difference between the two treatments LM and HI 30/70.

Source	P-Value	Statistical Significance
Sequence	0.8748	Non Significant
Patients	<0.0001	Significant
Period	0.4521	Non Significant
Treatment	0.9643	Non Significant

Parameter: HbA1c

H_0 There is no significant difference between the two treatments LM and HI 30/70.

H_1 There is significant difference between the two treatments LM and HI 30/70.

Source	P-Value	Statistical Significance
Sequence	0.2982	Non Significant
Patients	<0.0001	Significant
Period	0.5443	Non Significant
Treatment	0.3119	Non Significant

Parameter: 4-Point (Average Daily) Blood Sugar Between LM and HI 30/70.

H_0 There is no significant difference between the two treatments LM and HI 30/70.

H_1 There is significant difference between the two treatments LM and HI 30/70.

Source	P-Value	Statistical Significance
Sequence	0.8721	Non Significant
Patients	<0.0001	Significant
Period	0.8322	Non Significant
Treatment	**0.0451**	**Significant**

Parameter: No. of Hypoglycemic Events

H_0 There is no significant difference between the two treatments LM and HI 30/70.

H_1 There is significant difference between the two treatments LM and HI 30/70.

Source	P-Value	Statistical Significance
Sequence	0.8100	Non Significant
Patients	<0.0001	Significant
Period	0.5492	Non Significant
Treatment	0.5492	Non Significant

Parameter: Change in HbA1c

H_0 There is no significant difference between the two treatments LM and HI 30/70.

H_1 There is significant difference between the two treatments LM and HI 30/70.

Source	P-Value	Statistical Significance
Sequence	0.6633	Non Significant
Patients	0.3925	Non Significant
Period	0.0425	Non Significant
Treatment	0.3837	Non Significant

Parameter: Morning Dose

H_0 There is no significant difference between the two treatments LM and HI 30/70.

H_1 There is significant difference between the two treatments LM and HI 30/70.

Source	P-Value	Statistical Significance
Sequence	0.8134	Non Significant
Patients	<0.0001	Significant
Period	0.0004	Significant
Treatment	**0.0348**	**Significant**

Parameter: Evening Dose

H_0 There is no significant difference between the two treatments LM and HI 30/70.

H_1 There is significant difference between the two treatments LM and HI 30/70.

Source	P-Value	Statistical Significance
Sequence	0.7628	Non Significant
Patients	<0.0001	Significant
Period	0.0332	Significant
Treatment	0.7616	Non Significant

Parameter: Change in Morning Dose

H_0 There is no significant difference between the two treatments LM and HI 30/70.

H_1 There is significant difference between the two treatments LM and HI 30/70.

Source	P-Value	Statistical Significance
Sequence	0.5407	Non Significant
Patients	0.018	Significant
Period	0.0053	Significant
Treatment	0.0335	**Significant**

Parameter: Change in Evening Dose

H_0 There is no significant difference between the two treatments LM and HI 30/70.

H_1 There is significant difference between the two treatments LM and HI 30/70.

Source	P-Value	Statistical Significance
Sequence	0.9431	Non Significant
Patients	0.0391	Significant
Period	0.0008	Significant
Treatment	0.6079	Non Significant

Table 10: Efficacy Analysis Paired 't' Test Results

Treatment Effect Testing Using Paired 't' Test for the parameters which show ANOVA results Significant for Treatment effect

Postprandial Blood Glucose Excursion = (2 Hr Postprandial Blood Glucose Level) - (Pre Meal Blood Glucose Level)

Parameter: Evening Blood Glucose Excursion

H_0: Treatment HI 30 / 70 is better than LM
[I.e. Mean of (Evening excursion LM - Evening Excursion HI) => 0]

H_1: Treatment LM is better than HI 30/70
[I.e. Mean of (Evening excursion LM - Evening Excursion HI) < 0]

Statistic	Combined Periods		P-Value	(Treatment Effect) Statistical Significance
	LM	HI 30 / 70		
Mean	26.3616	38.9669	0.0035	Significant
S.D.	40.3241	44.5918		
SEM	3.9166	4.3311		
N	106	106		
Med.	24.8333	38		
Range	211	280.6666		

This result goes in the favour of LM

Parameter:Pre Morning Meal Blood Glucose Level

H_0: Treatment LM is better than HI 30/70
[I.e. Mean of (Pre Morning BGL LM - Pre Morning BGL HI) <= 0]

H_1: Treatment HI 30/70 is better than LM
[I.e. Mean of (Pre Morning BGL - Pre Morning BGL HI) > 0]

Statistic	Combined Periods		P-Value	(Treatment Effect) Statistical Significance
	LM	HI 30 / 70		
Mean	142.8664	129.9906	0.0006	Significant
S.D.	41.721	36.813		
SEM	4.0523	3.5756		
N	106	106		
Med.	137.6666	122.8333		
Range	210.6666	191.3333		

This result is in favour of HI 30/70

Parameter:Pre Evening Meal Blood Glucose Level

H_0: Treatment LM is better than HI 30/70
[I.e. Mean of (Pre Evening BGL LM - Pre Evening BGL HI) <= 0]

H_1: Treatment HI 30/70 is better than LM
[I.e. Mean of (Pre Evening BGL - Pre Evening BGL HI) > 0]

Statistic	Combined Periods		P-Value	(Treatment Effect) Statistical Significance
	LM	HI 30 / 70		
Mean	176.2893	164.2798	0.0088	Significant
S.D.	53.8232	47.7925		
SEM	5.2277	4.642		
N	106	106		
Med.	171.8333	165.1666		
Range	331	206.3333		

This result is in favour of HI 30/70

Parameter: 4-Point (Average Daily) Blood Sugar Between LM and Hum 30/70

H_0: Treatment LM is better than HI 30/70
[I.e. Mean of (4 pt BGL LM - 4 pt BGL HI) <= 0]

H_1: Treatment HI 30/70 is better than LM
[I.e. Mean of (4 pt BGL LM - 4 pt BGL HI) > 0]

Statistic	Combined Periods		P-Value	(Treatment Effect) Statistical Significance
	LM	HI 30 / 70		
Mean	182.3616	174.6392	0.0226	Significant
S.D.	43.037	40.187		
SEM	4.1801	3.9033		
N	106	106		
Med.	175.375	170.5		
Range	262.5833	193.25		

This result is in favour of HI 30/70

Parameter: Morning Dose

H_0: Treatment LM is better than HI 30/70
[I.e. Mean of (Morning Dose LM - Morning Dose HI) => 0]

H_1: Treatment HI 30/70 is better than LM
[I.e. Mean of (Morning Dose LM - Morning Dose HI) < 0]

Statistic	Combined Periods		P-Value	(Treatment Effect) Statistical Significance
	LM	HI 30 / 70		
Mean	27.4222	28.0888	0.0492	Significant
S.D.	9.989	9.6163		
SEM	0.9748	0.9385		
N	105	105		
Med.	26.5	28		
Range	28	42		

This result is in favour of LM

Parameter: Change in Morning Dose

H_0: Treatment LM is better than HI 30/70
[I.e. Mean of (Change in Morning Dose LM - Change in Morning Dose HI) => 0]

H_1: Treatment HI 30/70 is better than LM
[I.e. Mean of (Change in Morning Dose LM - Change in Morning Dose HI) < 0]

Statistic	Combined Periods		P-Value	(Treatment Effect) Statistical Significance
	LM	HI 30 / 70		
Mean	1.5000	2.8762	0.0094	Significant
S.D.	4.4172	4.9694		
SEM	0.4290	0.4850		
N	106	105(1)		
Med.	1.0000	2.3333		
Range	25.3333	32.3333		

This result is in favour of LM

- Morning Blood Glucose Excursion, 2hr. Post morning blood glucose level, 2hr. post evening blood glucose level, HbA1c, Change in HbA1c, Evening Dose and Change in Evening Dose, No. of Hypoglycemic Episodes, weight and BMI
  - There is no significant difference in above-mentioned variables between groups, between periods and between treatments : insulin lispro low mixture(LM) and Human Insulin 30/70

- Evening Blood Glucose Excursion, pre-morning blood glucose level, pre-evening blood glucose level, 4-point blood glucose profiles, Morning Dose and Change in Morning Dose and treatment satisfaction questionnaire: Q3, Q5
  - There is **significant** difference in above-mentioned variable between treatments insulin lispro low mixture(LM) and Human Insulin 30/70 using Crossover ANOVA model.
  - Out of these significant results Evening Excursion (p-value: 0.0035) and Morning Dose (p-value: 0.0492) and change in morning dose (p-value: 0.0094) goes in the favour of Study drug Insulin Lispro (LM) and Pre morning blood glucose level (p-value: 0.0006), Pre evening blood glucose level (p-value: 0.0088), 4-point blood glucose profile (p-value: 0.0226) goes in the favour of drug Human insulin 30/70. (These p-values are from Paired 't' test).
  - Treatment preference questionnaire Q3 (p-value: 0.0243) and Q5 (p-value: 0.0253) goes in the favor of drug Human insulin 30/70. These p-values are from Macnamer's paired Chi square test.

Table 11: Efficacy Analysis: Summary of Blood Glucose Levels for all possible visits

Parameter:Pre Morning Meal Blood Glucose Level					
Statistic	V2	V4	V5	V7	V8
Mean	149.3490	138.6761	136.4182	134.4937	136.4386
S.D.	46.5601	39.0711	40.6622	41.2481	39.0652
SEM	4.5223	3.7949	3.9494	4.0063	3.7943
N	106	106	106	106	106
Med.	136.5000	126.5000	128.1666	128.6666	129.6666
Range	232.3333	190.6666	199.0000	210.0000	223.3333

Parameter:2 Hr. Postprandial Morning Blood Glucose Level					
Statistic	V2	V4	V5	V7	V8
Mean	228.5125	204.3349	201.7578	201.849	207.316
S.D.	62.6788	66.1089	56.2226	59.9643	50.7189
SEM	6.0879	6.4210	5.4608	5.8242	4.9262
N	106	106	106	106	106
Med.	222.3333	197	198.5000	189.3333	199.5000
Range	289.0000	301.3333	290.6666	320.0000	276.6666

Parameter:Pre Evening Meal Blood Glucose Level					
Statistic	V2	V4	V5	V7	V8
Mean	188.1336	172.5251	171.3930	178.6650	169.1761
S.D.	57.7643	54.5425	51.5798	54.5701	50.9009
SEM	5.6105	5.2976	5.0098	5.3003	4.9439
N	106	106	106	106	106
Med.	176.5000	160.8333	171.1666	172.5000	165.1666
Range	272.1666	317.6666	331.0000	254.6666	283.6666

Parameter: 2 - hrs Post Prandial Evening Blood Glucose Level					
Statistic	V2	V4	V5	V7	V8
Mean	219.1031	198.4654	204.8977	206.2625	201
S.D.	65.4148	59.8302	57.5905	56.5882	50.6296
SEM	6.3838	5.8112	5.5936	5.4963	4.9175
N	105 (1)	106	106	106	106
Med.	203.3333	190.5000	196.6666	197.3333	191.1666
Range	308.0000	323.3333	315.0000	319.6666	239.6666

( ) denotes missing value.

Efficacy Analyses

Table 12: Treatment Preference Questionnaire

Treatment Satisfaction Questionnaire 1: In your opinion, which insulin therapy used in this study made you feel better?		
H0: There is no significant difference between the two treatments as per the treatment Preference questionnaire 1		
H1: There is significant difference between the two treatments as per the treatment Preference questionnaire 1		
For this Macnamer's Chi Square test is used		
P Value	0.7324	
Statistical Significance	Non Significant	

Treatment Satisfaction Questionnaire 2: In your opinion, which insulin therapy used in this study provided you greater ability to manage your diabetes?:		
H0: There is no significant difference between the two treatments as per the treatment Preference questionnaire 2		
H1: There is significant difference between the two treatments as per the treatment Preference questionnaire 2		
For this Macnamer's Chi Square test is used		
P Value	0.9081	
Statistical Significance	Non Significant	

Treatment Satisfaction Questionnaire 3: In your opinion, which insulin therapy used in this study allowed you to better concentrate shortly after meals?		
H0: There is no significant difference between the two treatments as per the treatment Preference questionnaire 3		
H1: There is significant difference between the two treatments as per the treatment Preference questionnaire 3		
For this Macnamer's Chi Square test is used		
P Value	0.0243	
Statistical Significance	**Significant**	
Huminsulin 30/70 is better than Insulin Lispro LM as per the Treatment satisfaction Questionnaire: Q3		

Treatment Satisfaction Questionnaire 4: In your opinion, which insulin therapy used in this study allowed to have a greater energy level shortly after meals?		
H0: There is no significant difference between the two treatments as per the treatment Preference questionnaire 4		
H1: There is significant difference between the two treatments as per the treatment Preference questionnaire 4		
For this Macnamer's Chi Square test is used		
P Value	0.1025	
Statistical Significance	Non Significant	

Treatment Satisfaction Questionnaire 5: In your opinion, which insulin therapy used in this study allowed your to feel less sleepy shortly after meals?		
H0: There is no significant difference between the two treatments as per the treatment Preference questionnaire 5		
H1: There is significant difference between the two treatments as per the treatment Preference questionnaire 5		
For this Macnamer's Chi Square test is used		
P Value	0.0253	
Statistical Significance	**Significant**	
Huminsulin 30/70 is better than Insulin Lispro LM as per the Treatment satisfaction Questionnaire: Q5		

Treatment Satisfaction Questionnaire 6: In your opinion, which insulin therapy used in this study provided you greater convenience?		
H0: There is no significant difference between the two treatments as per the treatment Preference questionnaire 6		
H1: There is significant difference between the two treatments as per the treatment Preference questionnaire 6		
For this Macnamer's Chi Square test is used		
P Value	0.1151	
Statistical Significance	Non Significant	

Treatment Satisfaction Questionnaire 7: Which insulin therapy did you like better?		
H0: There is no significant difference between the two treatments as per the treatment Preference questionnaire 7		
H1: There is significant difference between the two treatments as per the treatment Preference questionnaire 7		
For this Macnamer's Chi Square test is used		
P Value	0.9115	
Statistical Significance	Non Significant	

Treatment Satisfaction Questionnaire 8: Which insulin therapy would you prefer to use in the future?		
H0: There is no significant difference between the two treatments as per the treatment Preference questionnaire 8		
H1: There is significant difference between the two treatments as per the treatment Preference questionnaire 8		
For this Macnamer's Chi Square test is used		
P Value	1.0000	
Statistical Significance	Non Significant	

7.1 Adverse Events

Table 13: Listing of Adverse Events: (Applicable to those patients for whom AE occurred during the study)

Inv_ No	Pt_ No	Code	Description of Condition / Event	Visit No
001	101	E01	Ischemic Heart Disease	1
001	102	E01	Hypertension	1
001	103	E01	Ischemic Heart Disease	1
001	104	E01	Hypertension	1
001	105	E01	Ischemic Heart Disease	1
001	106	E01	Ischemic Heart Disease	1
001	107	E01	Hypertension	1
001	108	E01	Neuropathy	1
001	109	E01	Coronary Artery Disease	1
001	110	E01	Neuropathy	5
001	111	E01	Coronary Artery Disease	1
001	112	E01	Ischemic Heart Disease	1
001	113	E01	Coronary Artery Disease	1
001	114	E01	Hypothyroidism	1
001	115	E01	Hypertension	1
001	116	E01	Hypertension	1
001	117	E01	Hypertension	1
001	118	E01	Hypertension	1
001	119	E01	Dyslipidemia	1
001	120	E01	Chronic Backache	1
001	121	E01	Hypertension	1
001	122	E01	Hypertension	1
001	123	E01	Hypertension	1
001	124	E01	Neuropathy	2
001	125	E01	Neuropathy	1
001	126	E01	Hypertension	1
001	127	E01	Coronary Artery Disease	1
001	128	E01	Hypertension	1
001	129	E01	Hypertension	1
001	130	E01	Hypertension	1
001	131	E01	Constipation	1
001	132	E01	Ischemic Heart Disease	1
001	133	E01	Hypertension	1
001	134	E01	Periarthritis Left Shoulder	6
001	135	E01	Coronary Artery Disease	1
001	136	E01	Neuropathy	1
001	137	E01	Coronary Artery Disease	1
001	138	E01	Hypertension	1

Inv_ No	Pt_ No	Code	Description of Condition / Event	Visit No
001	139	E01	Acid Peptic Disease	5
001	140	E01	Hypertension	1
003	301	E01	Hypertension	1
003	302	E01	Hyper Cholestrolemin	1
003	303	E01	Hypertension	1
003	304	E01	Ischemic Heart Disease	1
003	305	E01	Cervical and Lumbar Spondylosis	1
003	306	E01	Hypertension	1
003	307	E01	Hyperthyroidism	1
003	308	E01	Spondylysis	1
003	310	E01	Hypertension	1
003	311	E01	Hypercholestrolemia	1
003	312	E01	Hypertension	1
003	313	E01	Ischemic Heart Disease	1
003	314	E01	hypertension	1
003	315	E01	Hypertension	1
003	316	E01	Right Nerve palsy	1
003	317	E01	hypertension	1
003	318	E01	Hypertension	1
003	319	E01	Hypertension	1
003	320	E01	Hypertension	1
003	321	E01	Ischemic Heart Disease	1
003	322	E01	Hypertension	1
003	323	E01	Cervical Spondylosis	1
003	324	E01	Hypertension	1
005	501	E01	Hypertension	1
005	502	E01	Hypertension	1
005	503	E01	Background Retinopathy	1
005	504	E01	Hypertension	1
005	505	E01	Shortness of Breath	1
005	506	E01	Constipation	3
006	601	E01	Hypertension	1
006	602	E01	Stable Angina	1
006	603	E01	Hypertension	1
006	605	E01	Hypertension	1
006	607	E01	Hypertension	1
006	608	E01	Osteoporosis	1
006	609	E01	Hypertension	1
006	610	E01	Cataract	1
006	611	E01	Background Retinopathy	1
006	612	E01	Hypertension	4
006	613	E01	Hypertension	1

Inv_ No	Pt_ No	Code	Description of Condition / Event	Visit No
006	614	E01	Peripheral Vascular Disease	1
006	615	E01	Dyspepsia	1
006	616	E01	Bronchial Asthama	1
006	617	E01	Hypertension	1
007	401	E01	Hypertension	1
007	402	E01	Ischemic Heart Disease	1
007	403	E01	Background Retinopathy	1
007	404	E01	Hypertension	1
007	405	E01	Osteoarthritis	1
007	406	E01	Asthma	1
007	407	E01	Hypertension	1
007	408	E01	Hypertension	1
007	409	E01	Hypertension	1
007	411	E01	Cataract Both Eyes	1
007	412	E01	Non-Prolifuative Diabetic Retinopathy (Maculopathy)	1
007	413	E01	Hypertension	1
007	414	E01	Hypertension	1
007	415	E01	Hypertension	1
007	416	E01	Hypertension	1
007	417	E01	Non-Prolifuative Diabetic Retinopathy	1
007	419	E01	Ischemic Heart Disease	1
007	420	E01	Hyperlipidemia	1
007	421	E01	Cataract ® Eye	1
007	422	E01	Hypercholestrolemia	1
007	423	E01	Background Diabetic Retinopathy	1
007	424	E01	Cataract Both Eyes	1
007	425	E01	Hypertension	1
007	426	E01	Hypertension	1
007	427	E01	Hypertension	1
007	428	E01	Cataract Both Eyes	1
007	429	E01	Hypertension	1
007	430	E01	Hypertension	1
007	431	E01	Ischemic Heart Disease	1
007	432	E01	Ischemic Heart Disease	1
001	101	E02	Dyslipidemia	1
001	102	E02	Urinary Urgency	1
001	103	E02	Abrasion LT Little Finger	4
001	104	E02	Stroke Rt. Hemiparesis	1
001	108	E02	Pain	1
001	109	E02	Parkinsonism	1
001	111	E02	Upper Respiratory Tract Infection	6
001	112	E02	Hypertension	1

Inv_ No	Pt_ No	Code	Description of Condition / Event	Visit No
001	113	E02	Constipation	1
001	114	E02	Ischemic Heart Disease	1
001	116	E02	Indigestion	1
001	117	E02	Ischemic Heart Disease	1
001	118	E02	Coronary Artery Disease	1
001	119	E02	Coronary Artery Disease	1
001	120	E02	Hypertension	1
001	122	E02	Allergy	1
001	124	E02	Pain	2
001	125	E02	Nephropathy edema	2
001	126	E02	Dyslipidemia	1
001	127	E02	Dyslipidemia	1
001	128	E02	Coronary Artery Disease	1
001	130	E02	1 Degree Hypothyroidism	1
001	131	E02	Glaucoma Right Eye	1
001	132	E02	Vitiligo	1
001	133	E02	Ischemic Heart Disease	1
001	135	E02	Peripheral Vascular Disease	1
001	137	E02	Giddiness	8
001	138	E02	Cerebrovascular Disease	1
001	140	E02	? Coronary Artery Disease	1
003	301	E02	Chest pain	3
003	303	E02	Tenea corporis and Xerotic Eczema	3
003	304	E02	Enlagrged Prostrate	1
003	305	E02	Parkinsons	1
003	306	E02	Ischemic Heart Disease	1
003	310	E02	Ischemic Heart Disease	1
003	312	E02	Ischemic Heart Disease	1
003	314	E02	Leg pain	5
003	315	E02	Background Diabetic Retinopathy	1
003	317	E02	Ischemic Heart Disease	1
003	318	E02	Ischemic Heart Disease	1
003	319	E02	Lumber spondylosis	1
003	320	E02	Hyperthyroidism	1
003	322	E02	Background Diabetic Retinopathy	1
003	323	E02	Chronic Vulvovaginitis	1
003	324	E02	Ischemic Heart Disease	1

Inv_ No	Pt_ No	Code	Description of Condition / Event	Visit No
005	501	E02	Melaena	2
005	503	E02	Insomnia	1
005	504	E02	Hyperlipidemia	1
005	505	E02	Peripheral Neuropathy	1
006	601	E02	Burning Epigestrial & Chest pain (Dyspepsia)	1
006	602	E02	Hypertension	1
006	603	E02	Peripheral Neuropathy	1
006	607	E02	Herpes Infection	7
006	608	E02	Hypertension	1
006	609	E02	Peripheral Neuropathy	1
006	610	E02	Peripheral Neuropathy	1
006	611	E02	Peripheral Neuropathy	1
006	613	E02	Ischemic Heart Disease	1
006	614	E02	Hypertension	1
006	616	E02	Hypertension	1
007	401	E02	Cataract	1
007	402	E02	Back Pain	3
007	403	E02	Hypertension	1
007	405	E02	Cataract Both Eyes	1
007	406	E02	PedalEdema	1
007	407	E02	Cataract	1
007	408	E02	Ischemic Heart Disease	1
007	409	E02	Ischemic Heart Disease	1
007	410	E02	Bronchial Asthama	1
007	411	E02	Knee Pain (Leg)	1
007	412	E02	Watering in Both Eyes	3
007	413	E02	Arthritis	1
007	414	E02	Vertigo	1
007	415	E02	Hyperlipidemia	1
007	416	E02	Ischemic Heart Disease	1
007	417	E02	Neuropathy	1
007	418	E02	Cataract ® Eye	1
007	419	E02	Acid Peptic Disease	1
007	420	E02	Ischemic Heart Disease	1
007	421	E02	Ischemic Heart Disease	1

Inv_ No	Pt_ No	Code	Description of Condition / Event	Visit No

Inv_ No	Pt_ No	Code	Description of Condition / Event	Visit No
007	422	E02	Gastritis	1
007	423	E02	Neuropathy	1
007	424	E02	Hypercholestrolemia	1
007	425	E02	Gastritis	1
007	426	E02	Hyperkerotosis	1
007	427	E02	Non - Proliferative Diabetic Retinopathy	1
007	428	E02	Burning Feet	2
007	429	E02	Anaemia	1
007	431	E02	Hyperlipidemia	1
007	432	E02	Arthritis	1
001	102	E03	Gastroenteritis	2
001	103	E03	Neuropathy Peripheral	7
001	104	E03	Dyslipidemia	1
001	107	E03	Pain	1
001	109	E03	Cataract Both Eyes	1
001	112	E03	Cataract Both Eyes	1
001	114	E03	Hypertension	1
001	118	E03	Osteoarthritis	1
001	120	E03	Dyslipidemia	1
001	125	E03	Paronychia Rt. Toe	2
001	126	E03	Neuropathy	4
001	128	E03	Insomnia	1
001	130	E03	Coronary Artery Disease	1
001	131	E03	Cataract Left Eye	1
001	132	E03	Joint Pains	1
001	133	E03	Dyslipidemia	1
001	135	E03	Neuropathy	1
001	138	E03	Unstable Angina Ischemic Heart Disease	3
001	140	E03	Dyslipidemia	1
003	301	E03	Breathlessness	3
003	303	E03	Ischemic Heart Disease	4
003	304	E03	Hernia	1
003	305	E03	Ischemic Heart Disease	1
003	306	E03	GOUT	1
003	315	E03	Enlargement of Prostrate	7
003	317	E03	Hypertriglyceridimia	1
003	320	E03	Ischemic Heart Disease	1
005	501	E03	Portal Hypertension	2
005	503	E03	Constipation	1
005	504	E03	Lumber canal stenosis with left L5 Rediculopathy	1
005	505	E03	Hypoglycaemic Coma	5
006	601	E03	Pain in Right knee joint -	5

Inv_ No	Pt_ No	Code	Description of Condition / Event	Visit No
			Osteoarthritis	
006	603	E03	Osteoarthritis	1
006	609	E03	Neuropathic Ulcer	1
006	611	E03	Hypertension	1
006	613	E03	Xanthalesmata over Eyelids	1
006	614	E03	Ischemic Heart Disease	1
006	616	E03	Left sided Frozen Shoulder	1
007	401	E03	Neuropathy	1
007	402	E03	Body pain	3
007	403	E03	Ischemic Heart Disease	1
007	404	E03	Periarthritis (R) Shpulder	1
007	406	E03	Benign Hypertrophic Prostatis	1
007	407	E03	Ischemic Heart Disease	1
007	408	E03	Cataract ® Eye	1
007	409	E03	Peripheral Vascular Disease	1
007	410	E03	Leg - Pain	1
007	411	E03	Leg - Pain	6
007	412	E03	Hypertension	3
007	413	E03	Neuropathy	1
007	414	E03	Neuropathy	1
007	415	E03	Neuropathy	1
007	416	E03	Atherosclerotic Disease	1
007	417	E03	Hypercholestrolemia	1
007	418	E03	Hypertriglycerdemia	1
007	419	E03	Hypertension	1
007	420	E03	Cardiomegaly	1
007	421	E03	Neuropathy	1
007	422	E03	Neuropathy	1
007	423	E03	Ischemic Heart Disease	1
007	424	E03	Hypertension	1
007	425	E03	Background Diabetic Retinopathy	1
007	426	E03	Hypercholestrolemia	1
007	427	E03	Bronchial Asthama	1
007	428	E03	Ischemic Heart Disease	3
007	429	E03	Cataract	1
007	430	E03	Cataract	1
007	431	E03	Proteinuria	1
007	432	E03	Hyperlipidemia	1
001	102	E04	UTI Urinary Tract Infection	3

Inv_ No	Pt_ No	Code	Description of Condition / Event	Visit No
001	103	E04	Diarrhea	7
001	104	E04	Abrasion LT 1st Toe (Great Toe)	4
001	109	E04	Background Retinopathy	1
001	112	E04	Non Profliferaive Retinopathy	1
001	118	E04	Retinopathy (Background)	1
001	120	E04	Vertigo	1
001	125	E04	Pain	1
001	128	E04	Neuropathy	1
001	130	E04	Cerebro Vascular Disease	1
001	131	E04	Vertigo	4
001	132	E04	Cataract	1
001	133	E04	Bronchial Asthama	1
001	138	E04	Seizure	3
001	140	E04	Anaemia	2
003	301	E04	Sweating	3
003	303	E04	Cerebro vascular Accident	5
003	317	E04	Urinary tract Infection	3
005	501	E04	Cirrhosis of liver with splenom egaly and oesophageal varices	2
005	503	E04	Diabetic Peripheral Neuropathy	1
005	504	E04	Diabetic Lumbosacral plexopathy	1
006	601	E04	Dry Cough - Captorial Induces	1
006	603	E04	Dyspepsia	1
006	609	E04	Mild Cataract in Both Eyes	1
006	611	E04	Cataract	1
006	616	E04	Itching & Redness of palms & Face (Focal Allergy)	3
007	401	E04	Leg pain	2
007	402	E04	(R) Thumb infection	8
007	403	E04	Knee Pain	3
007	404	E04	Neuropathy	1
007	405	E04	Peripheral Vascular Disease	1
007	406	E04	Early Non- Proliferative Diabetic Retinopathy	1
007	407	E04	Varicose Veins	1
007	409	E04	Diabetic Neuropathy	1
007	410	E04	Body - Pain	2
007	411	E04	Cramps in legs	6
007	412	E04	Cough & Cold	2

Inv_ No	Pt_ No	Code	Description of Condition / Event	Visit No
007	413	E04	Early Retinopathy ® Eye	1
007	414	E04	Cataract	1
007	415	E04	Microalbunuria	1
007	416	E04	Eczema Feet	1
007	417	E04	Bronchial Asthama	1
007	418	E04	Proteinuria	1
007	419	E04	Diabetic Retinopathy	1
007	420	E04	Neuropathy	1
007	421	E04	Gastritis	1
007	422	E04	Heaviness in the Chest	4
007	423	E04	Hypertension	1
007	424	E04	Early Non - Proliferative Diabetic Retinopathy	1
007	425	E04	Cataract	1
007	426	E04	Atherosclerosis Carotid Vessels	1
007	427	E04	Nephropathy	1
007	428	E04	Acid Peptic Disease	3
007	429	E04	Non - Proliferative Diabetic Retinopathy	1
007	430	E04	Ischemic Heart Disease	1
007	431	E04	Hypertension	1
001	102	E05	Urinary Tract Infection Fever Infection	5
001	103	E05	Acidity	7
001	112	E05	Urinary Tract Infection	5
001	118	E05	Edema	2
001	120	E05	Ischemic Heart Disease	1
001	128	E05	Acid Peptic Disease	1
001	130	E05	Allergic Cough	2
001	133	E05	LT Branchial Radiculopathy	3
001	138	E05	Chest pain	3
003	301	E05	Cardio respiratory arrest	3
003	303	E05	Peripheral Neuropathy	1
003	320	E05	Shoulder pain	3
005	501	E05	Ascites	2
006	601	E05	Puffes up Abdomen	6
006	603	E05	Bilateral Ankle Oedema	7
006	611	E05	Impotence	1
006	616	E05	Dysuria (Urinary Tract Infection)	6
007	402	E05	Itching sensation	8
007	404	E05	Irritation in Eyes	3

Inv_ No	Pt_ No	Code	Description of Condition / Event	Visit No
007	405	E05	Neuropathy	1
007	406	E05	Knee Pain	1
007	407	E05	Numbness	2
007	408	E05	Hyperlipidemia	1
007	409	E05	Hyperlipidemia	1
007	413	E05	Early Neuropathy	1
007	414	E05	Numbness	2
007	415	E05	Moderate to Severe Non-Proliferative Diabetic Retinopathy	1
007	416	E05	Ulcer - mouth	1
007	417	E05	Corn Both Feet (Mild) Paronychia	1
007	418	E05	Neuropathy	1
007	419	E05	Neuropathy	2
007	420	E05	Breathlessness	2
007	421	E05	Polyuria	5
007	422	E05	Pain in the (L)Leg	6
007	423	E05	Hypoglycemia	6
007	425	E05	Glaucoma	1
007	426	E05	Hepatomegaly	1
007	427	E05	Cataract	1
007	428	E05	Fever	3
007	429	E05	® Foot Pain	2
007	432	E05	Cataract	1
001	103	E06	Fever Associated with Diarrhea	7
001	128	E06	Pain	1
003	303	E06	Vomiting	5
005	501	E06	Melaena	4
006	616	E06	Dyspepsia	4
007	404	E06	Gastritis	7
007	406	E06	Depression	3
007	407	E06	Cough-Persistant	2
007	408	E06	Gastritis	1
007	409	E06	Glaucoma	1
007	414	E06	Giddiness	3
007	415	E06	Burning Feet	3
007	417	E06	Mouth - Ulcers	1
007	419	E06	Focal Seizure ® side	2
007	420	E06	Concentric Hypertrophy of LV	2
007	421	E06	Palpitation	6
007	425	E06	Leg - Pain	1
007	426	E06	Gall Stones	1
007	427	E06	Giddiness	6
007	428	E06	Abdominal Pain	5
007	429	E06	Shoulder Pain	2
007	431	E06	Neuropathy	1
007	432	E06	Nephropathy	1

Inv_ No	Pt_ No	Code	Description of Condition / Event	Visit No
001	128	E07	Unstable Angina	3
003	303	E07	Confusion	5
005	501	E07	Duodenal ulcer	5
006	616	E07	Dry cough (Enalapril Induced)	4
007	404	E07	chest discomfort	7
007	406	E07	Acidity	3
007	407	E07	Swelling Left Leg	2
007	408	E07	Proteinuria	1
007	409	E07	Had A fall	2
007	414	E07	Itching all over the Body	4
007	416	E07	Gastritis	1
007	417	E07	Pain in the toes	7
007	418	E07	Excess Hunger	5
007	420	E07	Hepatomegaly	2
007	425	E07	Right - Knee Pain	4
007	428	E07	Pain (L) Foot	6
007	432	E07	Hypertension	1
001	128	E08	Pseudomonas Septicaemic Shock	3
003	303	E08	Weakness	5
007	404	E08	nocturia	8
007	406	E08	Burning Feet	3
007	407	E08	Hypercholestrolemia	1
007	408	E08	irritation in the Stomach	4
007	409	E08	Pain in the ® Shoulder & Leg	3
007	414	E08	Itching	7
007	416	E08	Cold	3
007	418	E08	Irritation & pain in the (R) eye corneal ulcer	6
007	420	E08	General Tiredness	6
007	426	E08	Mild non - Profilerative Diabetic Retinopathy (L) Eye	1
007	428	E08	Burning sensation	3
007	432	E08	Stomatitis	2
001	128	E09	Total Leucocyte Count	3
003	303	E09	Chest pain and Discomfort	4
007	404	E09	sweating	8
007	407	E09	Cold	3
007	408	E09	Cold	5
007	409	E09	Gastritis	2
007	416	E09	Hip Pain	4
007	420	E09	Coronary Artery spasm	2
007	426	E09	Cataract Left Eye	1
007	432	E09	Leg - Pain	1

Inv_ No	Pt_ No	Code	Description of Condition / Event	Visit No
001	128	E10	Respiratory Tract Infection	3
003	303	E10	Dyspnoea	4
007	404	E10	shooting pain - (R) shoulder	8
007	406	E10	Congestion of Breathlessness	4
007	409	E10	Right knee pain	6
007	426	E10	Neuropathy	1
007	432	E10	Cold	6
003	303	E11	Thrombocytopenia	5
007	406	E11	Insomnia	4
007	426	E11	Cold	3
007	432	E11	Dysentry	2
007	406	E12	Polyphagia	4
007	426	E12	Cough	3
007	406	E13	Cough	5
007	426	E13	Giddiness	3
007	406	E14	fracture vertebral column	7
007	426	E14	Acidity	4
007	426	E15	Swelling both feet	6

7.2 Serious Adverse Events (SAE)

***Table 14: Listing of Serious Adverse Events*: (Applicable to those patients for whom SAE occurred during the study**

Inv. No.	Pat. No.	Visit No.	Description of event	Onset date	Stop date	Visit No.	Severity	Relatedness to study Device	Relatedness to study drug	Serious Codes
001	128	3	Unstable Angina	12/06/01	-	3	3	2	2	4
001	128	3	Pseudomonas Septicaemic Shock	30/06/01	-	3	3	2	2	1
001	138	8	Coronary Artery Disease	28/09/01	29/09/01	3	1	2	2	4
003	301	3	Myocardial Infarction	17/07/01	-	3	3	2	2	1
003	303	5	Ischemic Heart Disease	07/08/01	-	4	2	2	2	4
003	303	5	Cerebro vascular Accident	04/09/01	-	5	3	2	2	1
003	303	5	Vomiting	04/09/01	-	5	3	2	2	4
003	303	5	Thrombocytopenia	04/09/01	-	5	3	2	2	4
003	315	7	Enlargement of Prostrate	15/12/01	26/12/01	7	3	2	2	4
005	501	8	Duodenal ulcer	03/10/01	12/11/01	5	2	2	2	4
005	505	8	Hypoglycaemic Coma	21/10/01	21/10/01	5	3	2	1	4
005	511	8	Transient Ischaemic Attack	10/10/01	11/10/01	4	1	2	2	4
007	406	8	Fracture- Vertebral Column	08/03/02	-	7	2	2	2	4
007	423	6	Hypoglycemia	27/01/02	27/01/02	6	3	2	2	4

Table 15: Number of SAE's Investigatorwise

Investigator No	Patients having SAE	SAE Code	Total No of SAE
001	128	1 (Fatal)	2
	138	4 (Hospitalization)	
003	301	1 (Death)	4
	303	4 (Hospitalization)	
	303	1 (Death)	
	315	4 (Hospitalization)	
005	501	4 (Hospitalization)	3
	505	4 (Hospitalization)	
	511	4 (Hospitalization)	
006	--	--	0
007	406	4 (Hospitalization)	2
	423	4 (Hospitalization)	
Total No. of SAEs: 11			
No. of Deaths:2			
No of Hospitalizations: 9			

In the entire study ,out of 11 SAEs, 2 were deaths and 9 hospitalization.

7.3 Hypoglycemic Event

7.3 Hypoglycemic Events

Table 16: Hypoglycemic Rate Per month Treatmentwise

Treatment:		A		B	
		Total No of episodes	Hypo Rate	Total No of episodes	Hypo Rate
Combined:		39	14.10	32	11.57
	Avg. No. of days for Entire study	83		83	

Hypoglycemic Rate Per month per patient Treatmentwise

Treatment:		A		B	
		Total No of episodes	Hypo Rate	Total No of episodes	Hypo Rate
Combined:		39	0.1294	32	0.1061
	Avg. No. of days for Entire study	83		83	

Note: Patients 301 , 608 are not included for finding duration of study as no data is available for visit 3.

A: Lispro Low Mixture (LM)
B: Human Insulin 30/ 70 (HI 30/70)

As we can see there is no difference in the Hypoglycemic Rate per month over the treatments Insulin Lispro Low Mixture and Huminsulin 30/70.

7.4 Pre-existing Conditions

Table 17: % of Patients having Pre-existing Conditions

Type of Pre-existing Conditions	Classification	For the Entire Duration	
		Statistic	
		number (n)	%
Hypertension	M	34	47.8873
	F	36	61.0169
	Total	70	53.8462
Ischemic Heart Disease	M	18	25.3521
	F	18	30.5085
	Total	36	27.6923
Hyperlipidemia	M	5	7.0422
	F	9	15.2542
	Total	14	10.7692
No. of Patients who had at least one Pre-existing Condition	M	49	69.0141
	F	59	100
	total	108	83.0769
Total No. of Patients entered	M	71	
	F	59	
	total	130	

Out of total 130 patients entered 108 patients (83.0769 %) had at least one pre-existing condition. Out of 130 patients 70 patients (53.8462 %) had Hypertension,36 patients (27.6923%) had Ischemic Heart Disease and 14 patients (10.7692%) had Hyperlipidemia as one of the pre-existing condition .

7.5 Concomitant Medications

Table 18: Percentages of Pts on ConComitant Medications

Concomitant Medications	Classification	Statistic	
		number Of Patients (n)	%
		Entire Duration	
Blood Pressure Controlling Drug	M	34	47.8873
	F	29	49.1525
	total	63	48.4615
Cholestrol Controlling Drugs	M	3	4.2254
	F	7	11.8644
	total	10	7.6923
Total No. of Patients entered	M	71	
	F	59	
	total	130	

Out of total 130 patients entered, 63 were on Blood pressure controlling drugs (48.4615%), 10 were on Cholestrol controlling drugs (7.6923%).

Table 19: No. of Patients On Metformin obtained From Oral Therapy Module :

Concomitant Medications	Classification	Statistic	
		number Of Patients (n)	%
		Entire Duration	
Metformin	M	36	50.7042
	F	28	47.4576
	total	64	49.2308
Patients Not On Metformin	M	35	49.2958
	F	31	52.5424
	total	66	50.7692
Total Patients Entered in the Study	M	71	100
	F	59	100
	total	130	100

Out of total 130 patients entered in the study, 64 patients were on Metformin (49.2308%) and 66 patients were not on Metformin (50.7692%)

7.6 Discussion

The drug Insulin Lispro low mixture better as compared to Human insulin 30/70 in controlling glycemic control measured by

- Evening Blood Glucose Excursion

The drug Insulin Lispro low mixture is not statistically significant as compared to Human insulin 30/70 in controliing glycemic control measured by

- Morning Blood Glucose Excursion
- 2-hr. Post Breakfast Blood Glucose Leve
- 2-hr. Post Dinner Blood Glucose Level
- Number of Hypoglycemic Episodes
- HbA1c

The drug Human insulin 30/70 better as compared to Insulin Lispro low mixture in controliing glycemic control measured by

- Pre Breakfast Blood Glucose Level
- Pre Dinner Blood Glucose Level
- 4-Point Average Blood Glucose Level

- Treatment Preference Questionnaire Overall also goes in favour of Insulin Lispro Low mixture

8. Overall Conclusions

The evening glycemic excursion in elderly patients (≥65years) with type 2 diabetes was significantly lower in patients on Low Mixture as compared to Human Insulin 30/70. It is possible that morning excursion was not found to be significantly different in case of LM because the morning dose of LM was significantly lower as compared to HI 30/70. Low mix and HI 30/70 were similarly effective in controlling morning and evening post-prandial blood glucose levels. Pre-morning, pre-evening and average blood sugar levels were better in case of HI 30/70 but no difference was seen in HbA1c levels.

Though treatment satisfaction questionnaire showed patients can concentrate more after meals and they feel less sleepy after meals when on Human Insulin 30/70 there was no difference in LM and HI 30/70 as far as management of diabetes and convenience was considered.

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