

## Abstract

**Aims:** The aim of the present study was, in an open-labelled, randomised, 3-arm parallel-group design including a 1-3 weeks titration period and a 3 months maintenance period to compare in patients with OHA or premix insulin treated type 2 diabetes the efficacy and safety of (1) preprandial insulin aspart (IAsp) (with or without bedtime NPH insulin), (2) preprandial human soluble insulin (HI) (with or without bedtime NPH insulin), (3) with human premix insulin (MIX) (once or twice daily).

**Patients and Methods:** 231 (130 M/ 101 F) type 2 patients from 30 centres with a mean age of 62.2 (SD 8.8) years, Body Mass Index (BMI) 29.3 (SD 3.6) kg/m<sup>2</sup>, HbA1c 7.81 (SD 1.12) %, diabetes duration 10.2 (SD 7.3) years were randomised to either IAsp (n=75), HI (n=80) or MIX (n=76), 204 patients completed the trial according to the protocol. HbA1c, 7-point blood glucose (BG) profiles, fasting blood glucose, insulin dosage, hypoglycaemic episodes, adverse events and standard safety parameters were measured. The primary efficacy endpoint was the change of HbA1c from baseline to the last visit. Analysis for equivalence was performed by T-tests with alpha = 0.83% for each of 3 subtests.

**Results:** Equivalence with regard to HbA1c between the 3 therapies could not be demonstrated. HbA1c decreased by 0.91% (SEM 0.12) in the IAsp group, by 0.73% (SEM 0.10) in the HI group and by 0.65% (SEM 0.13) in the MIX group. Postprandial BG levels decreased most pronounced in the IAsp group: 8 to more than 30 mg/dl when compared to the HI group, and 20 to more than 30 mg/dl when compared to the MIX group. The mean preprandial insulin doses per injection were similar in the IAsp (10-13 units) and the HI group (10-14.5 units). The hypoglycaemia ratio/ month exposed was 0.56 in the HI group, 0.40 in the IAsp group and 0.19 in the MIX group.

**Conclusion:** Equivalence could not be shown between the 3 therapies. However, in this study population IAsp lead to better glycaemic control in terms of HbA1c and postprandial BG levels when compared to HI and MIX. The treatment with IAsp revealed to be very safe and well tolerated.

## Summary

### PRIMARY EFFICACY ENDPOINT

The reduction of HbA1c was in the Insulin Aspart Group -0.91±0.13% compared to -0.73±0.10% and -0.65±0.13% in the Human Soluble Insulin Group and Human Premix Insulin Group, respectively.

### SECONDARY EFFICACY ENDPOINTS

- At the end of the trial, the preprandial and postprandial blood glucose levels were notably improved in all three treatment groups.
- While the preprandial BG levels were found to be comparable between the three treatment groups, the mean postprandial BG levels in the Insulin Aspart Group were always remarkably below the respective mean values of the comparative groups (between 8 and 30 mg/dL).
- Furthermore, the Insulin Aspart Group showed the lowest percentages of patients with postprandial BG levels above 180 mg/dL (10 mmol/L) at the end of the trial.
- The mean preprandial doses of the short-acting insulin injections did not relevantly differ between the Insulin Aspart Group (10-13 IU per injection) and the Human Soluble Insulin Group (10-14.5 U per injection).
- Overall, the treatment groups with the short-acting insulin preparations (IASP, HSI) were found to be comparable regarding percentage of patients who experienced hypoglycemic episodes during the trial period (41% each), whereas in patients treated with HPI the proportion was notably lower (30%).
- The incidence rates of hypoglycemic episodes (ratio hypoglycemia per month exposed) were 0.40, 0.56 and 0.19 for patients treated with IASP, HSI and HPI, respectively.
- Adverse events leading to withdrawals of 1 patient in the IASP group and 2 patients in the HSI group were not related to the study medication.

## Conclusion

This study showed that the treatment with the short-acting insulin analogue, Insulin Aspart (IASP) of patients with type 2 diabetes mellitus led to a more pronounced improvement of HbA1c levels compared with Human Soluble Insulin or Human Premix Insulin. Furthermore, the treatment with IASP led to a more beneficial, circadian blood glucose profile. Interestingly, this happened with less hypoglycemic episodes and no increase of body weight compared to the treatment with Human Soluble Insulin.

Overall, treatment with Insulin Aspart in type 2 diabetics proved efficacious and safe.

# INSULIN ASPART EFFICACY AND SAFETY COMPARED TO HUMAN SOLUBLE INSULIN AND HUMAN PREMIX INSULIN (30/70) IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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## Objectives (1)

- Primary Objective**  
To compare the efficacy of preprandial Insulin Aspart (IASP) as measured by HbA1c in type 2 diabetic subjects with the efficacy of preprandial Human Soluble Insulin (HSI) or with Human Premix Insulin (HPI) (30/70) (once or twice daily). (with or without additional NPH insulin once daily at bedtime)
- Secondary Objectives**  
7-point BG profiles (once weekly); incidence of hypoglycemic episodes; safety profile (adverse events; standard safety parameters)

## Molecular structure of Aspart



## Objectives (2)

- Methodology**  
Multicenter, open-labelled, randomized, 3-arm parallel-group trial, including a screening visit, a 1-3 weeks titration period followed by a 3-months maintenance period (duration of treatment)
- Main criteria for Inclusion**  
Type 2 diabetic patients, aged ≥ 35 years, HbA1c < 10.0%, previous pharmacological antidiabetic treatment (OHA and / or conventional insulin therapy) for more than one year
- Criteria for Evaluation**  
**Efficacy**
  - Change of HbA1c
  - 7-point BG profile\*
  - FSG\*
  - Insulin dosage**Safety**
  - Physical examination
  - Standard safety parameters
  - Hypoglycemic episodes
  - Adverse events
- Main Criteria for Withdrawal**
  - Necessity to have more than 5 visits during the titration period
  - Total daily insulin dose > 1.4 IU/kg
  - Need for 2x daily NPH insulin in the preprandial insulin groups

## Objectives (3)

- Trial Sites**  
A total of 30 clinicians, general practitioners, physicians specialized in internal medicine and / or diabetology, in Germany
- Trial Period:** Aug 27, 1999 to Sep 14, 2000
- Principal Investigator**  
Professor Dr. med. R.G. Bretzel, Chairman and Head of Third Medical Department, University of Giessen, Germany
- Sponsor**  
Novo Nordisk Pharma GmbH, Medical Department, Mainz, Germany  
Dr. med. S. Hirschberger, Medical Advisor  
J. Medding, Statistician

## Trial Profile



## Subjects

A total number of 275 type 2 diabetic patients were screened at 30 trial sites in Germany.



Trial profile

## Subject Characteristics (1)

	Insulin Aspart n = 75	Human Soluble Insulin n = 80	Human Premix Insulin n = 76
Men/Women	44 / 31	40 / 40	46 / 30
Age (yrs)	61.4 ± 9.0	62.0 ± 8.5	63.1 ± 8.9
Height (m)	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1
Weight (kg)	84.3 ± 13.1	84.5 ± 12.3	84.6 ± 15.3
BMI (kg/m <sup>2</sup> )	29.2 ± 3.7	29.3 ± 3.3	29.1 ± 4.0

Values given as mean ± SD.

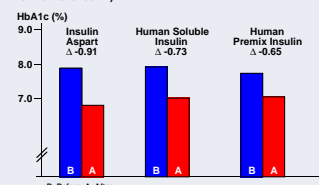
## Subject Characteristics (2)

Percentage of Patients with diabetic secondary complications

	Insulin Aspart (%)	Human Soluble Insulin (%)	Human Premix Insulin (%)
Retinopathy	5.3	10.0	5.3
• Polyneuropathy	24.0	32.5	27.6
• Chronic Ischemic heart disease	21.3	21.3	11.8
• Hypertension	64.0	62.5	73.7
• Hyperlipidemia	25.3	26.3	21.1
• Renal dysfunction (mean S-Creatinine mg/dl)	none 0.87 ±0.02	none 0.94 ±0.06	none 0.87 ±0.02

## Results (1)

Course of HbA1c (%) from baseline to visit M3 (after 3 months of maintenance Rx).



B: Before; A: After

## Results (2)

Mean Preprandial Blood Glucose levels (mg/dL) at baseline and at visit M3 (after 3 months of maintenance Rx)

	Insulin Aspart at baseline after 3 mo	Human Soluble Insulin at baseline after 3 mo	Human Premix Insulin at baseline after 3 mo
Before Breakfast	154.3 ±43.6	130.5 ±36.2	161.0 ±50.7
Before Lunch	143.4 ±53.5	120.2 ±43.9	149.1 ±64.1
Before Dinner	148.0 ±42.7	136.0 ±50.7	155.8 ±52.3
At baseline	133.5 ±39.4	128.2 ±46.2	155.8 ±57.7
At visit M3	127.6 ±36.4	121.5 ±31.5	141.9 ±40.3

Values given as mean ± SD.

## Results (3)

Mean Postprandial Blood Glucose levels (mg/dL) at baseline and at visit M3 (after 3 months of maintenance Rx)

	Insulin Aspart at baseline after 3 mo	Human Soluble Insulin at baseline after 3 mo	Human Premix Insulin at baseline after 3 mo
90 min after Breakfast	212.0 ±64.5	161.1 ±55.9	220.4 ±68.1
90 min after Lunch	178.6 ±58.3	144.3 ±32.0	178.8 ±59.8
90 min after Dinner	182.4 ±58.6	144.1 ±40.7	184.3 ±73.3
At baseline	169.1 ±55.9	159.8 ±48.6	188.2 ±61.4
At visit M3	174.6 ±43.2	164.3 ±40.4	168.9 ±43.6

Values given as mean ± SD.

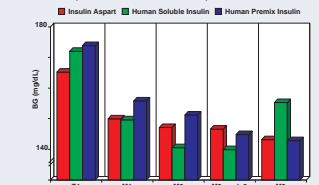
## Results (4)

Proportion of Patients (percentage, %) with Postprandial Blood Glucose Levels > 180 mg/dL (> 10 mmol/L)

	Insulin Aspart at baseline after 3 mo	Human Soluble Insulin at baseline after 3 mo	Human Premix Insulin at baseline after 3 mo
90 min after Breakfast	40.0	26.7	40.0
90 min after Lunch	23.8	14.3	21.4
90 min after Dinner	27.9	13.3	29.0
At baseline	29.0	29.0	29.0
At visit M3	49.3	40.0	40.0

## Results (5)

Course of Blood Glucose Levels (mg/dL) at Bedtime from baseline to visit M3 (after 3 months of maintenance Rx).



## Results (6)

Incidence of Hypoglycemic Episodes (Symptoms and / or BG ≤ 45 mg/dL resp. ≤ 2.5 mmol/L)

	Insulin Aspart n mean	Human Soluble Insulin n mean	Human Premix Insulin n mean
Patients with hypoglycemic episodes (n)	31 (41.3%)	33 (41.3%)	23 (30.3%)
Total number of hypoglycemic episodes (n)	103	160	55
Hypoglycemic episodes / patient	1.4	2.0	0.7
Hypoglycemic episodes / month exposed	0.4	0.56	0.19
HbA1c (%) at baseline	7.82	7.83	7.78
at end of study	6.87	7.08	7.09

## Results (7)

Blood Glucose levels (mg/dL) at Visit M3 in Patients with and without additional NPH insulin

	Insulin Aspart never NPH mean n	Insulin Aspart NPH continued mean n	Human Soluble Insulin never NPH mean n	Human Soluble Insulin NPH continued mean n
Visit M3 before breakfast	106.5	137.6	119.8	127.5
Visit M3 after breakfast	150.3	135.0	156.6	241.0
Visit M3 before lunch	107.1	140.7	115.0	96.0
Visit M3 after lunch	138.3	138.8	140.8	90.0
Visit M3 before dinner	123.2	164.0	117.0	127.0
Visit M3 after dinner	148.5	156.6	149.2	156.0
Visit M3 NPH at bedtime	116.9	177.0	126.3	110.0

## Results (8)

Course of Body weight from baseline to visit M3 (after 3 months of maintenance Rx)

Patients treated with	Mean Increase of BodyWeight (kg) within 3 months
• Insulin Aspart	± 0.0 kg
• Human Soluble Insulin	± 0.5 kg
• Human Premix Insulin	± 1.0 kg