ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 08/26/2010

Effect of Insulin Glulisine Compared to Insulin Aspart and Insulin Lispro When Administered by Continuous Subcutaneous Insulin Infusion (CSII) on Specific Pump Parameters in Patient With Type 1 Diabetes Mellitus (PUMP)

This study has been completed.

Sponsor:	Sanofi
Collaborators:	
Information provided by:	Sanofi
ClinicalTrials.gov Identifier:	NCT00607087

Purpose

Primary objective: To demonstrate the superiority of insulin glulisine over insulin aspart and insulin lispro administered by external pump in term of unexplained hyperglycemia and/or infusion set occlusion.

Main Secondary objectives:

To compare insulin glulisine, insulin aspart and insulin lispro on:

- Unexplained hyperglycemia
- Infusion set occlusion
- Hypoglycemic episodes,7-point blood glucose profiles
- Episodes of significant ketosis and/or risk level for impending diabetic ketoacidosis
- Time to change the infusion set
- HbA1c (Glycosylated hemoglobin)
- Overall safety: incidence of adverse events

Condition	Intervention	Phase
Diabetes Mellitus, Type 1	Drug: Insulin glulisine Drug: Insulin lispro Drug: Insulin aspart	Phase 4

Study Type: Interventional
Study Design: Treatment, Crossover Assignment, Open Label, Randomized, Safety/Efficacy Study
Official Title: Effect of Insulin Glulisine Compared to Insulin Aspart and Insulin Lispro When Administered by Continuous Subcutaneous Insulin Infusion (CSII) on Specific Pump Parameters in Patient With Type 1 Diabetes Mellitus

Further study details as provided by Sanofi:

Primary Outcome Measure:

- Percentage of Patients With at Least One Unexplained Hyperglycemia and/ or Confirmed Infusion Set Occlusion [Time Frame: over 13 weeks of each treatment period] [Designated as safety issue: No]
  Unexplained hyperglycemia defined as blood glucose value above 300 mg/dL (16.7 mmol/L) with no apparent medical dietary, insulin dosage or pump failure reason. Pump infusion set occlusion defined by at least one of the following items: >pump occlusion alarm, >patient observation of an occlusion, spontaneously or because of elevated blood glucose value.

Secondary Outcome Measures:

- Monthly Rate of Unexplained Hyperglycemia and/ or Confirmed Infusion Set Occlusion [Time Frame: over 13 weeks of each treatment period] [Designated as safety issue: No]
  Unexplained hyperglycemia defined as blood glucose value above 300 mg/dL (16.7 mmol/L) with no apparent medical dietary, insulin dosage or pump failure reason. Pump infusion set occlusion defined by at least one of the following items: >pump occlusion alarm, >patient observation of an occlusion, spontaneously or because of elevated blood glucose value.
- Percentage of Patients With at Least One Unexplained Hyperglycemia [Time Frame: over 13 weeks of each treatment period] [Designated as safety issue: No]
  Unexplained hyperglycemia defined as blood glucose value above 300 mg/dL (16.7 mmol/L) with no apparent medical dietary, insulin dosage or pump failure reason.
- Monthly Rate of Unexplained Hyperglycemia [Time Frame: over 13 weeks of each treatment period] [Designated as safety issue: No]
- Percentage of Patients With at Least One Confirmed Infusion Set Occlusion [Time Frame: over 13 weeks of each treatment period] [Designated as safety issue: No]
  Pump infusion set occlusion defined by at least one of the following items: >pump occlusion alarm, >patient observation of an occlusion, spontaneously or because of elevated blood glucose value.
- Monthly Rate of Confirmed Infusion Set Occlusion [Time Frame: over 13 weeks of each treatment period] [Designated as safety issue: No]
- Percentage of Patients With at Least One Episode of Significant Ketosis and/ or Risk Level for Impending Diabetic Ketoacidosis [Time Frame: over 13 weeks of each treatment period] [Designated as safety issue: No]
  Diabetic ketoacidosis (DKA) is preceded by an increase in ketone production, resulting in blood ketone value increase (hyperketonemia) and later in ketone urine value (hyperketonuria). Significant hyperketonemia and risk level for impending diabetic ketoacidosis (DKA) are reported respectively as a blood ketone value from 0.6 to 1.5 mmol/L and >1.5 mmol/l
- Monthly Rate of Episode of Significant Ketosis and/ or Risk Level for Impending Diabetic Ketoacidosis [Time Frame: over 13 weeks of each treatment period] [Designated as safety issue: No]
  Diabetic ketoacidosis (DKA) is preceded by an increase in ketone production, resulting in blood ketone value increase (hyperketonemia) and later in ketone urine value (hyperketonuria). Significant hyperketonemia and risk level for impending diabetic ketoacidosis (DKA) are reported respectively as a blood ketone value from 0.6 to 1.5 mmol/L and >1.5 mmol/l
- Rate of Symptomatic Hypoglycemia With a Plasma Glucose (PG) ≤ 70 mg/dL Per Patient-year [Time Frame: over 13 weeks of each treatment period] [Designated as safety issue: No]
  Symptomatic hypoglycemia is defined as an event with clinical symptoms that are considered to results from hypoglycemia (confirmed or not by a glucose measurement) and associated with prompt recovery after oral carbohydrate administration.
- Rate of Severe Symptomatic Hypoglycemia Per Patient-year [Time Frame: over 13 weeks of each treatment period] [Designated as safety issue: No]

Severe symptomatic hypoglycemia is defined as an event with clinical symptoms that are considered to results from hypoglycemia in which the patient required assistance of another person and one of the following: >the event was associated with a measured blood glucose level below 36 mg/dL >or event was associated with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.

- Rate of Nocturnal Symptomatic Hypoglycemia With a Plasma Glucose (PG) ≤70 mg/dL Per Patient-year [Time Frame: over 13 weeks of each treatment period] [Designated as safety issue: No]
  Nocturnal Symptomatic hypoglycemia was defined as an event with clinical symptoms that are considered to result from hypoglycemia (confirmed or not by a glucose measurement) and associated with prompt recovery after oral carbohydrate administration which occurs while the patient is asleep, after bedtime and before getting up in the morning.
- Patients With at Least One Site Infection, Site Inflammation/Erythema, Pruritus or Isolated Pain at Injection Site [Time Frame: over 13 weeks of each treatment period] [Designated as safety issue: No]
  Infection: local reaction at the infusion site requiring local or systemic antibiotherapy, or local drainage as per Investigator judgment. Site inflammation or erythema: local reaction at the infusion site with no need for local or systemic antibiotherapy as per Investigator judgment. Pruritis at injection site: presence of pruritis at the infusion site without any symptom of inflammation or erythema and/or infection. Isolated pain at injection site: presence of pain at the infusion site without any symptom of inflammation or erythema and/or infection.
- Time Interval Between Infusion Set Changes: All Changes [Time Frame: over 13 weeks of each treatment period] [Designated as safety issue: No]
  Patients treated with insulin pump have to change their infusion set regularly (i.e.change was recommended every 48h). The patients were asked to report any change of their infusion set and the reason for change (routine basis or because of occurrence of a specific event such as occlusion, unexplained hyperglycemia or adverse event). "All changes" include all the changes whatever the reason such as routine or requested by occurrence of events.
- Time Interval Between Infusion Set Changes in Routine [Time Frame: over 13 weeks of each treatment period] [Designated as safety issue: No]
  Patients treated with insulin pump have to change their infusion set regularly (i.e.change was recommended every 48h). The patients were asked to report any change of their infusion set and the reason for change (routine basis or because of occurrence of a specific event such as occlusion, unexplained hyperglycemia or adverse event). Changes in routine correspond to interval between changes according to patient use.
- Glycosylated Hemoglobin: HbA1c [Time Frame: over 13 weeks of each treatment period] [Designated as safety issue: No]
  Glycolysated Haemoglobin (HbA1c) is a biological parameter that reflects the blood glucose concentration over a long period of time. It is the standard parameter for glycemic control follow-up in diabetic patients. This parameter is expressed in percentage (%) and the target in diabetes management is to reach a HbA1c <7%
- Total Daily Basal Insulin Infusion [Time Frame: over 13 weeks of each treatment period] [Designated as safety issue: No]
  dose of the basal insulin regimen administered throughout the 24-hour period
- Total Daily Bolus Insulin Dose [Time Frame: over 13 weeks of each treatment period] [Designated as safety issue: No]
  dose of every increment administered for example before meals

Enrollment: 289
Study Start Date: January 2008
Primary Completion Date: June 2009
Study Completion Date: June 2009

Arms	Assigned Interventions
Experimental: sequence 1 sequence 1: insulin glulisine / insulin aspart / insulin lispro.	Drug: Insulin glulisine 100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump Drug: Insulin lispro 100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump

Arms	Assigned Interventions
	Drug: Insulin aspart 100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Experimental: Sequence 2 Sequence 2: insulin aspart / insulin lispro / insulin glulisine	Drug: Insulin glulisine 100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump Drug: Insulin lispro 100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump Drug: Insulin aspart 100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Experimental: Sequence 3 Sequence 3: insulin lispro / insulin glulisine / insulin aspart	Drug: Insulin glulisine 100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump Drug: Insulin lispro 100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump Drug: Insulin aspart 100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump

Detailed Description:

The maximal duration of the study participation for patients was 41 weeks and one day, split in:

- a 2-week screening period,
- a 39-week treatment period: 3 treatment periods of 13 weeks with a crossover alternative regimen, including a dose adjustment period of 1 week at the beginning of each period (sequence1: insulin glulisine, then insulin aspart, then insulin lispro; sequence2: insulin aspart, then insulin lispro, then insulin glulisine; sequence 3: insulin lispro, then insulin glulisine, then insulin aspart)
- and a follow-up period of 24 hours.

Eligibility

Ages Eligible for Study: 18 Years to 75 Years
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Type 1 diabetic subjects
- Treated with insulin for at least 2 years and by CSII for at least 6 months
- Using the same insulin (insulin glulisine, insulin aspart or insulin lispro) in CSII for at least 3 months with the same external pump compatible with the 3 short acting insulin analogues used in the study
- Using the same type of infusion set (catheter and cannula) for at least 3 months
- Performing at least 3 blood glucose controls per day
- HbA1c < 8.5%
- Body mass index (BMI) < 35 kg/m²
- Ability and willingness to perform blood glucose and ketone monitoring using the Sponsor-provided combined glucose and ketone meter and patient diary at home

Exclusion Criteria:

- Diabetes other than Type 1
- Total daily dose of insulin greater than 90 U/day
- Using an insulin pump requiring pre-filled cartridges
- History of infection at infusion site requiring a drainage in the last 3 months
- History of severe episodes of ketosis requiring hospitalization in the last 6 months
- Active proliferative retinopathy, as defined by a photocoagulation or vitrectomy occurrence in the 6 months prior to visit 1, or any other unstable (rapidly progressing) retinopathy that may require photocoagulation or surgical treatment during the study. An ophthalmoscopic examination should have been performed in the 2 years prior to study entry
- Pregnancy (women of childbearing potential must have a negative pregnancy test at study entry and a medically approved contraception method) or breastfeeding
- Treatment with systemic corticosteroids or medication known to influence insulin sensitivity in the 3 months prior to visit 1
- Treatment with antidiabetic drug other than insulin in the 3 months prior to visit 1
- Likelihood of requiring treatments during the study which are not permitted
- Treatment with an investigational product in the 30 days prior to visit 1
- History of sensitivity to the study drugs or to drugs with a similar chemical structure
- Presence of any condition (medical, including clinically significant abnormal laboratory test, psychological, social or geographical) actual or anticipated that the Investigator feels would compromise the patient safety or limit his/her successful participation in the study
- Night shift workers
- Impaired renal function as shown by serum creatinine ≥1.5 mg/dL (133 µmol/L) or ≥1.4 mg/dL (124 µmol/L) in men and women, respectively
- Impaired hepatic function as shown by Alanine aminotransferase (ALT) and/or Aspart aminotransferase (AST) greater than three times the upper limit of normal range)
- Alcohol or drug abuse in the last year
- Mental condition rendering the patient unable to understand the nature, scope and possible consequences of the study

The above information is not intended to contain all considerations relevant to a patient's potential participation in a clinical trial.

Contacts and Locations

Locations

United States, New Jersey

sanofi-aventis administrative office

Bridgewater, New Jersey, United States

Australia
- sanofi-aventis administrative office
  - Macquarie Park, Australia

Austria
- sanofi-aventis administrative office
  - Vienna, Austria

France
- sanofi-aventis administrative office
  - Paris, France

Hungary
- sanofi-aventis administrative office
  - Budapest, Hungary

Israel
- sanofi-aventis administrative office
  - Natanya, Israel

Italy
- sanofi-aventis administrative office
  - Milan, Italy

Korea, Republic of
- sanofi-aventis administrative office
  - Seoul, Korea, Republic of

Netherlands
- sanofi-aventis administrative office
  - PE Gouda, Netherlands

Spain
- sanofi-aventis administrative office
  - Barcelona, Spain

Sweden
- sanofi-aventis administrative office
  - Bromma, Sweden

United Kingdom
- sanofi-aventis administrative office
  - Guildford Surrey, United Kingdom

Investigators

Study Director:	Medical Affairs	sanofi-aventis

More Information

Responsible Party:	sanofi-aventis (Medical Affairs Study Director)
Study ID Numbers:	APIDR_C_02083 2007-003579-38 [EudraCT Number]
Health Authority:	Sweden: Regional Ethical Review Board

Study Results

Participant Flow

Recruitment Details	Multicenter study: 44 active centers from 12 countries in Europe, USA and Asia Pacific region. Study Initiation date: January 8, 2008, Study Completion Date: June 15, 2009.
Pre-Assignment Details	359 participants screened; 289 randomized; 288 patients treated (1 patient not treated per physician's decision): 274 with insulin glulisine, 269 with insulin lispro, 266 with insulin aspart. The safety population, (N=288 patients randomized and treated) is described in the participant flow and baseline characteristics.

Reporting Groups

	Description
Sequence 1	insulin glulisine / insulin aspart / insulin lispro
Sequence 2	insulin aspart / insulin lispro / insulin glulisine
Sequence 3	insulin lispro / insulin glulisine / insulin aspart

Overall Study

	Sequence 1	Sequence 2	Sequence 3
Started	99	95	94
Completed	84	84	84
Not Completed	15	11	10
Withdrawal by Subject	9	4	4
Adverse Event	3	2	3
Other reason	1	5	2
Poor compliance to protocol	1	0	1
Lost to Follow-up	1	0	0

Period 1

	Sequence 1	Sequence 2	Sequence 3
Started	99	95	94

	Sequence 1	Sequence 2	Sequence 3
Completed	87	89	89
Not Completed	12	6	5
Withdrawal by Subject	7	2	3
Adverse Event	3	0	0
Poor compliance to protocol	1	0	0
Lost to Follow-up	1	0	0
Other reason	0	4	2

Period 2

	Sequence 1	Sequence 2	Sequence 3
Started	87	89	89
Completed	86	86	84
Not Completed	1	3	5
Withdrawal by Subject	0	1	1
Other reason	1	1	0
Adverse Event	0	1	3
Poor compliance to protocol	0	0	1

Period 3

	Sequence 1	Sequence 2	Sequence 3
Started	86	86	84
Completed	84	84	84
Not Completed	2	2	0
Withdrawal by Subject	2	1	0
Adverse Event	0	1	0

Baseline Characteristics

Reporting Groups

	Description
Sequence 1	insulin glulisine / insulin aspart / insulin lispro
Sequence 2	insulin aspart / insulin lispro / insulin glulisine
Sequence 3	insulin lispro / insulin glulisine / insulin aspart

Baseline Measures

	Sequence 1	Sequence 2	Sequence 3	Total
Number of Participants	99	95	94	288
Age, Continuous [units: years] Mean (Standard Deviation)	43.45 (13.71)	45.84 (13.59)	44.04 (12.87)	44.43 (13.39)
Gender, Male/Female [units: participants]				
Female	49	54	48	151
Male	50	41	46	137
Region of Enrollment [units: participants]				
United States	22	21	21	64
France	8	9	10	27
Hungary	4	4	6	14
Spain	11	9	10	30
Austria	7	9	8	24
Australia	4	4	3	11
Israel	11	11	10	32
Netherlands	8	8	7	23
United Kingdom	5	4	4	13
Italy	9	7	7	23
Sweden	9	8	7	24

	Sequence 1	Sequence 2	Sequence 3	Total
Korea, Republic of	1	1	1	3
Previous insulin at study entry [1] [units: participants]				
Insulin glulisine	4	2	2	8
Insulin aspart	32	43	42	117
Insulin lispro	63	49	50	162
Duration of treatment with previous insulin at study entry [2] [units: years] Mean (Standard Deviation)	4.84 (3.58)	4.37 (3.05)	4.79 (3.00)	4.67 (3.22)
Duration of treatment with insulin at study entry [units: years] Mean (Standard Deviation)	22.39 (13.53)	23.07 (13.33)	22.75 (11.08)	22.73 (12.67)
Total daily bolus insulin dose [3] [units: Units] Mean (Standard Deviation)	19.61 (9.40)	18.58 (10.34)	19.35 (7.78)	19.18 (9.22)
Duration of treatment with CSII (continuous subcutaneous insulin infusion) at study entry [units: years] Mean (Standard Deviation)	5.99 (4.83)	5.52 (5.27)	6.31 (4.95)	5.94 (5.01)
Total daily basal insulin infusion [3] [units: Units] Mean (Standard Deviation)	20.98 (8.84)	19.99 (9.38)	22.03 (9.17)	21.00 (9.13)
Body Mass Index (BMI) [units: kg/m²] Mean (Standard Deviation)	25.01 (3.53)	25.25 (3.91)	25.92 (3.98)	25.39 (3.81)
Central fasting plasma glucose [4] [units: mg/dL] Mean (Standard Deviation)	149.84 (59.03)	147.45 (61.63)	151.18 (64.06)	149.48 (61.37)
Glycosylated Haemoglobin (HbA1c) [units: Percent] Mean (Standard Deviation)	7.38 (0.69)	7.36 (0.61)	7.41 (0.69)	7.38 (0.66)

[1] Total patients analyzed n=287 due to one missing data in the "sequence 2" group

[2] Total patients analyzed n=286 due to one missing data in the "sequence 1" and in the "sequence 2" groups

[3] Total patients analyzed n=285 due to 3 missing data: 2 in the "sequence 1" and 1 in the "sequence 2" groups

[4] Total patients analyzed n=284 due to 4 missing data: 2 in the "sequence 1" and 2 in the "sequence 3" groups

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Percentage of Patients With at Least One Unexplained Hyperglycemia and/ or Confirmed Infusion Set Occlusion
Measure Description	Unexplained hyperglycemia defined as blood glucose value above 300 mg/dL (16.7 mmol/L) with no apparent medical dietary, insulin dosage or pump failure reason. Pump infusion set occlusion defined by at least one of the following items: • pump occlusion alarm, • patient observation of an occlusion, spontaneously or because of elevated blood glucose value.
Time Frame	over 13 weeks of each treatment period
Safety Issue?	No

Analysis Population Description

Analysis was performed on the Intention To Treat (ITT) population. The Intent-To-Treat population is composed of all randomized patients having received the 3 insulins (Insulin glulisine, aspart and lispro) N=256 patients: (sequence 1: N=86, sequence 2: N=86; sequence 3: N=84 patients).

Reporting Groups

	Description
Insulin Glulisine	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Aspart	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Lispro	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump

Measured Values

	Insulin Glulisine	Insulin Aspart	Insulin Lispro
Number of Participants Analyzed	256	256	256
Percentage of Patients With at Least One Unexplained Hyperglycemia and/ or Confirmed Infusion Set Occlusion [units: percentage of patients] Number (95% Confidence Interval)	68.4 (62.7 to 74.1)	62.1 (56.2 to 68.1)	61.3 (55.4 to 67.3)

Statistical Analysis 1 for Percentage of Patients With at Least One Unexplained Hyperglycemia and/ or Confirmed Infusion Set Occlusion

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Aspart
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.039
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	McNemar
	Comments	[Not specified]

Statistical Analysis 2 for Percentage of Patients With at Least One Unexplained Hyperglycemia and/ or Confirmed Infusion Set Occlusion

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Lispro
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.031
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025.
	Method	McNemar
	Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Monthly Rate of Unexplained Hyperglycemia and/ or Confirmed Infusion Set Occlusion

Measure Description	Unexplained hyperglycemia defined as blood glucose value above 300 mg/dL (16.7 mmol/L) with no apparent medical dietary, insulin dosage or pump failure reason. Pump infusion set occlusion defined by at least one of the following items: • pump occlusion alarm, • patient observation of an occlusion, spontaneously or because of elevated blood glucose value.
Time Frame	over 13 weeks of each treatment period
Safety Issue?	No

Analysis Population Description

Analysis was performed on the Intention To Treat (ITT) population. The Intent-To-Treat population is composed of all randomized patients having received the 3 insulins (Insulin glulisine, aspart and lispro) N=256 patients: (sequence 1: N=86, sequence 2: N=86; sequence 3: N=84 patients).

Reporting Groups

	Description
Insulin Glulisine	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Aspart	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Lispro	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump

Measured Values

	Insulin Glulisine	Insulin Aspart	Insulin Lispro
Number of Participants Analyzed	256	256	256
Monthly Rate of Unexplained Hyperglycemia and/ or Confirmed Infusion Set Occlusion [units: events per patient per month] Mean (Standard Error)	2.02 (0.15)	1.32 (0.15)	1.54 (0.15)

Statistical Analysis 1 for Monthly Rate of Unexplained Hyperglycemia and/ or Confirmed Infusion Set Occlusion

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Aspart
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	Mixed Models Analysis
	Comments	[Not specified]

Statistical Analysis 2 for Monthly Rate of Unexplained Hyperglycemia and/ or Confirmed Infusion Set Occlusion

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Lispro
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	Mixed Models Analysis
	Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Percentage of Patients With at Least One Unexplained Hyperglycemia
Measure Description	Unexplained hyperglycemia defined as blood glucose value above 300 mg/dL (16.7 mmol/L) with no apparent medical dietary, insulin dosage or pump failure reason.
Time Frame	over 13 weeks of each treatment period
Safety Issue?	No

Analysis Population Description

Analysis was performed on the Intention To Treat (ITT) population. The Intent-To-Treat population is composed of all randomized patients having received the 3 insulins (Insulin glulisine, aspart and lispro) N=256 patients: (sequence 1: N=86, sequence 2: N=86; sequence 3: N=84 patients).

Reporting Groups

	Description
Insulin Glulisine	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Aspart	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Lispro	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump

Measured Values

	Insulin Glulisine	Insulin Aspart	Insulin Lispro
Number of Participants Analyzed	256	256	256
Percentage of Patients With at Least One Unexplained Hyperglycemia [units: percentage of patients] Number (95% Confidence Interval)	61.3 (55.4 to 67.3)	55.9 (49.8 to 61.9)	56.3 (50.2 to 62.3)

Statistical Analysis 1 for Percentage of Patients With at Least One Unexplained Hyperglycemia

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Aspart
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.080
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	McNemar
	Comments	[Not specified]

Statistical Analysis 2 for Percentage of Patients With at Least One Unexplained Hyperglycemia

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Lispro
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.107
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	McNemar
	Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Monthly Rate of Unexplained Hyperglycemia
Measure Description	
Time Frame	over 13 weeks of each treatment period
Safety Issue?	No

Analysis Population Description

Analysis was performed on the Intention To Treat (ITT) population. The Intent-To-Treat population is composed of all randomized patients having received the 3 insulins (Insulin glulisine, aspart and lispro) N=256 patients: (sequence 1: N=86, sequence 2: N=86; sequence 3: N=84 patients).

Reporting Groups

	Description
Insulin Glulisine	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Aspart	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Lispro	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump

Measured Values

	Insulin Glulisine	Insulin Aspart	Insulin Lispro
Number of Participants Analyzed	256	256	256
Monthly Rate of Unexplained Hyperglycemia [units: events per patient per month] Mean (Standard Error)	1.61 (0.13)	1.04 (0.13)	1.23 (0.13)

Statistical Analysis 1 for Monthly Rate of Unexplained Hyperglycemia

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Aspart
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	Mixed Models Analysis
	Comments	[Not specified]

Statistical Analysis 2 for Monthly Rate of Unexplained Hyperglycemia

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Lispro
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	McNemar
	Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Percentage of Patients With at Least One Confirmed Infusion Set Occlusion
Measure Description	Pump infusion set occlusion defined by at least one of the following items: • pump occlusion alarm, • patient observation of an occlusion, spontaneously or because of elevated blood glucose value.
Time Frame	over 13 weeks of each treatment period

Safety Issue?	No

Analysis Population Description

Analysis was performed on the Intention To Treat (ITT) population. The Intent-To-Treat population is composed of all randomized patients having received the 3 insulins (Insulin glulisine, aspart and lispro) N=256 patients: (sequence 1: N=86, sequence 2: N=86; sequence 3: N=84 patients).

Reporting Groups

	Description
Insulin Glulisine	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Aspart	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Lispro	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump

Measured Values

	Insulin Glulisine	Insulin Aspart	Insulin Lispro
Number of Participants Analyzed	256	256	256
Percentage of Patients With at Least One Confirmed Infusion Set Occlusion [units: percentage of patients] Number (95% Confidence Interval)	32.8 (27.1 to 38.6)	27.0 (21.5 to 32.4)	27.0 (21.5 to 32.4)

Statistical Analysis 1 for Percentage of Patients With at Least One Confirmed Infusion Set Occlusion

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Aspart
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.079
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	McNemar
	Comments	[Not specified]

Statistical Analysis 2 for Percentage of Patients With at Least One Confirmed Infusion Set Occlusion

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Lispro
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.063
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	McNemar
	Comments	[Not specified]

6. Secondary Outcome Measure:

Measure Title	Monthly Rate of Confirmed Infusion Set Occlusion
Measure Description	
Time Frame	over 13 weeks of each treatment period
Safety Issue?	No

Analysis Population Description

Analysis was performed on the Intention To Treat (ITT) population. The Intent-To-Treat population is composed of all randomized patients having received the 3 insulins (Insulin glulisine, aspart and lispro) N=256 patients: (sequence 1: N=86, sequence 2: N=86; sequence 3: N=84 patients).

Reporting Groups

	Description
Insulin Glulisine	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Aspart	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Lispro	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump

Measured Values

	Insulin Glulisine	Insulin Aspart	Insulin Lispro
Number of Participants Analyzed	256	256	256
Monthly Rate of Confirmed Infusion Set Occlusion	0.41 (0.06)	0.28 (0.06)	0.31 (0.06)

	Insulin Glulisine	Insulin Aspart	Insulin Lispro
[units: events per patient per month] Mean (Standard Error)			

Statistical Analysis 1 for Monthly Rate of Confirmed Infusion Set Occlusion

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Aspart
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.015
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	Mixed Models Analysis
	Comments	[Not specified]

Statistical Analysis 2 for Monthly Rate of Confirmed Infusion Set Occlusion

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Lispro
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.073
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	Mixed Models Analysis
	Comments	[Not specified]

7. Secondary Outcome Measure:

Measure Title	Percentage of Patients With at Least One Episode of Significant Ketosis and/ or Risk Level for Impending Diabetic Ketoacidosis
Measure Description	Diabetic ketoacidosis (DKA) is preceded by an increase in ketone production, resulting in blood ketone value increase (hyperketonemia) and later in ketone urine value (hyperketonuria). Significant hyperketonemia and risk level for impending diabetic ketoacidosis (DKA) are reported respectively as a blood ketone value from 0.6 to 1.5 mmol/L and >1.5 mmol/l
Time Frame	over 13 weeks of each treatment period
Safety Issue?	No

Analysis Population Description

Analysis was performed on the Intention To Treat (ITT) population. The Intent-To-Treat population is composed of all randomized patients having received the 3 insulins (Insulin glulisine, aspart and lispro) N=256 patients: (sequence 1: N=86, sequence 2: N=86; sequence 3: N=84 patients).

Reporting Groups

	Description
Insulin Glulisine	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Aspart	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Lispro	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump

Measured Values

	Insulin Glulisine	Insulin Aspart	Insulin Lispro
Number of Participants Analyzed	256	256	256
Percentage of Patients With at Least One Episode of Significant Ketosis and/ or Risk Level for Impending Diabetic Ketoacidosis [units: percentage of patients] Number (95% Confidence Interval)	17.6 (12.9 to 22.2)	10.9 (7.1 to 14.8)	11.7 (7.8 to 15.7)

Statistical Analysis 1 for Percentage of Patients With at Least One Episode of Significant Ketosis and/ or Risk Level for Impending Diabetic Ketoacidosis

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Aspart
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.017
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	McNemar
	Comments	[Not specified]

Statistical Analysis 2 for Percentage of Patients With at Least One Episode of Significant Ketosis and/ or Risk Level for Impending Diabetic Ketoacidosis

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Lispro
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.032
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	McNemar
	Comments	[Not specified]

8. Secondary Outcome Measure:

Measure Title	Monthly Rate of Episode of Significant Ketosis and/ or Risk Level for Impending Diabetic Ketoacidosis
Measure Description	Diabetic ketoacidosis (DKA) is preceded by an increase in ketone production, resulting in blood ketone value increase (hyperketonemia) and later in ketone urine value (hyperketonuria). Significant hyperketonemia and risk level for impending diabetic ketoacidosis (DKA) are reported respectively as a blood ketone value from 0.6 to 1.5 mmol/L and >1.5 mmol/l
Time Frame	over 13 weeks of each treatment period
Safety Issue?	No

Analysis Population Description

Analysis was performed on the Intention To Treat (ITT) population. The Intent-To-Treat population is composed of all randomized patients having received the 3 insulins (Insulin glulisine, aspart and lispro) N=256 patients: (sequence 1: N=86, sequence 2: N=86; sequence 3: N=84 patients).

Reporting Groups

	Description
Insulin Glulisine	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Aspart	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Lispro	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump

Measured Values

	Insulin Glulisine	Insulin Aspart	Insulin Lispro
Number of Participants Analyzed	256	256	256
Monthly Rate of Episode of Significant Ketosis and/ or Risk Level for Impending Diabetic Ketoacidosis [units: events per patient per month] Mean (Standard Error)	0.14 (0.43)	0.06 (0.22)	0.06 (0.18)

Statistical Analysis 1 for Monthly Rate of Episode of Significant Ketosis and/ or Risk Level for Impending Diabetic Ketoacidosis

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Aspart
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.009
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	Mixed Models Analysis
	Comments	[Not specified]

Statistical Analysis 2 for Monthly Rate of Episode of Significant Ketosis and/ or Risk Level for Impending Diabetic Ketoacidosis

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Lispro
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.019
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	Mixed Models Analysis
	Comments	[Not specified]

9. Secondary Outcome Measure:

Measure Title	Rate of Symptomatic Hypoglycemia With a Plasma Glucose (PG) ≤ 70 mg/dL Per Patient-year
Measure Description	Symptomatic hypoglycemia is defined as an event with clinical symptoms that are considered to results from hypoglycemia (confirmed or not by a glucose measurement) and associated with prompt recovery after oral carbohydrate administration.
Time Frame	over 13 weeks of each treatment period
Safety Issue?	No

Analysis Population Description

Analysis was performed on the Intention To Treat (ITT) population. The Intent-To-Treat population is composed of all randomized patients having received the 3 insulins (Insulin glulisine, aspart and lispro) N=256 patients: (sequence 1: N=86, sequence 2: N=86; sequence 3: N=84 patients).

Reporting Groups

	Description
Insulin Glulisine	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Aspart	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Lispro	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump

Measured Values

	Insulin Glulisine	Insulin Aspart	Insulin Lispro
Number of Participants Analyzed	256	256	256
Rate of Symptomatic Hypoglycemia With a Plasma Glucose (PG) ≤ 70 mg/dL Per Patient-year [units: events in patient-year] Mean (Standard Error)	73.88 (4.74)	65.06 (4.74)	62.74 (4.74)

Statistical Analysis 1 for Rate of Symptomatic Hypoglycemia With a Plasma Glucose (PG) ≤ 70 mg/dL Per Patient-year

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Aspart
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.008
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	Mixed Models Analysis
	Comments	[Not specified]

Statistical Analysis 2 for Rate of Symptomatic Hypoglycemia With a Plasma Glucose (PG) ≤ 70 mg/dL Per Patient-year

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Lispro
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	Mixed Models Analysis
	Comments	[Not specified]

10. Secondary Outcome Measure:

Measure Title	Rate of Severe Symptomatic Hypoglycemia Per Patient-year

Measure Description	Severe symptomatic hypoglycemia is defined as an event with clinical symptoms that are considered to results from hypoglycemia in which the patient required assistance of another person and one of the following: • the event was associated with a measured blood glucose level below 36 mg/dL • or event was associated with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.
Time Frame	over 13 weeks of each treatment period
Safety Issue?	No

Analysis Population Description

Analysis was performed on the Intention To Treat (ITT) population. The Intent-To-Treat population is composed of all randomized patients having received the 3 insulins (Insulin glulisine, aspart and lispro) N=256 patients: (sequence 1: N=86, sequence 2: N=86; sequence 3: N=84 patients).

Reporting Groups

	Description
Insulin Glulisine	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Aspart	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Lispro	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump

Measured Values

	Insulin Glulisine	Insulin Aspart	Insulin Lispro
Number of Participants Analyzed	256	256	256
Rate of Severe Symptomatic Hypoglycemia Per Patient-year [units: events in patient-year] Mean (Standard Error)	1.63 (0.35)	1.39 (0.35)	1.07 (0.35)

Statistical Analysis 1 for Rate of Severe Symptomatic Hypoglycemia Per Patient-year

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Aspart
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.563
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	Mixed Models Analysis
	Comments	[Not specified]

Statistical Analysis 2 for Rate of Severe Symptomatic Hypoglycemia Per Patient-year

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Lispro
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.186
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	Mixed Models Analysis
	Comments	[Not specified]

11. Secondary Outcome Measure:

Measure Title	Rate of Nocturnal Symptomatic Hypoglycemia With a Plasma Glucose (PG) ≤70 mg/dL Per Patient-year
Measure Description	Nocturnal Symptomatic hypoglycemia was defined as an event with clinical symptoms that are considered to result from hypoglycemia (confirmed or not by a glucose measurement) and associated with prompt recovery after oral carbohydrate administration which occurs while the patient is asleep, after bedtime and before getting up in the morning.
Time Frame	over 13 weeks of each treatment period
Safety Issue?	No

Analysis Population Description

Analysis was performed on the Intention To Treat (ITT) population. The Intent-To-Treat population is composed of all randomized patients having received the 3 insulins (Insulin glulisine, aspart and lispro) N=256 patients: (sequence 1: N=86, sequence 2: N=86; sequence 3: N=84 patients).

Reporting Groups

	Description
Insulin Glulisine	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Aspart	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Lispro	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump

Measured Values

	Insulin Glulisine	Insulin Aspart	Insulin Lispro
Number of Participants Analyzed	256	256	256
Rate of Nocturnal Symptomatic Hypoglycemia With a Plasma Glucose (PG) ≤70 mg/dL Per Patient-year [units: events in patient-year] Mean (Standard Error)	12.80 (0.95)	9.66 (0.95)	9.48 (0.95)

Statistical Analysis 1 for Rate of Nocturnal Symptomatic Hypoglycemia With a Plasma Glucose (PG) ≤70 mg/dL Per Patient-year

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Aspart
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	Mixed Models Analysis
	Comments	[Not specified]

Statistical Analysis 2 for Rate of Nocturnal Symptomatic Hypoglycemia With a Plasma Glucose (PG) ≤70 mg/dL Per Patient-year

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Lispro
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	Mixed Models Analysis
	Comments	[Not specified]

12. Secondary Outcome Measure:

Measure Title	Patients With at Least One Site Infection, Site Inflammation/Erythema, Pruritus or Isolated Pain at Injection Site
Measure Description	Infection: local reaction at the infusion site requiring local or systemic antibiotherapy, or local drainage as per Investigator judgment. Site inflammation or erythema: local reaction at the infusion site with no need for local or systemic antibiotherapy as per Investigator judgment. Pruritis at injection site: presence of pruritis at the infusion site without any symptom of inflammation or erythema and/or infection. Isolated pain at injection site: presence of pain at the infusion site without any symptom of inflammation or erythema and/or infection.
Time Frame	over 13 weeks of each treatment period
Safety Issue?	No

Analysis Population Description

Analysis was performed on the Intention To Treat (ITT) population. The Intent-To-Treat population is composed of all randomized patients having received the 3 insulins (Insulin glulisine, aspart and lispro) N=256 patients: (sequence 1: N=86, sequence 2: N=86; sequence 3: N=84 patients).

Reporting Groups

	Description
Insulin Glulisine	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Aspart	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Lispro	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump

Measured Values

	Insulin Glulisine	Insulin Aspart	Insulin Lispro
Number of Participants Analyzed	256	256	256
Patients With at Least One Site Infection, Site Inflammation/Erythema, Pruritus or Isolated Pain at Injection Site [units: patients]	110	110	107

Statistical Analysis 1 for Patients With at Least One Site Infection, Site Inflammation/Erythema, Pruritus or Isolated Pain at Injection Site

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Aspart
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	1.000
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	McNemar
	Comments	[Not specified]

Statistical Analysis 2 for Patients With at Least One Site Infection, Site Inflammation/Erythema, Pruritus or Isolated Pain at Injection Site

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Lispro
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.701
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	McNemar

	Comments	[Not specified]

13. Secondary Outcome Measure:

Measure Title	Time Interval Between Infusion Set Changes: All Changes
Measure Description	Patients treated with insulin pump have to change their infusion set regularly (i.e.change was recommended every 48h). The patients were asked to report any change of their infusion set and the reason for change (routine basis or because of occurrence of a specific event such as occlusion, unexplained hyperglycemia or adverse event). "All changes" include all the changes whatever the reason such as routine or requested by occurrence of events.
Time Frame	over 13 weeks of each treatment period
Safety Issue?	No

Analysis Population Description

Analysis was performed on the Intention To Treat (ITT) population. The Intent-To-Treat population is composed of all randomized patients having received the 3 insulins (Insulin glulisine, aspart and lispro) N=256 patients: (sequence 1: N=86, sequence 2: N=86; sequence 3: N=84 patients).

Reporting Groups

	Description
Insulin Glulisine	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Aspart	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Lispro	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump

Measured Values

	Insulin Glulisine	Insulin Aspart	Insulin Lispro
Number of Participants Analyzed	254	254	254
Time Interval Between Infusion Set Changes: All Changes [units: hours] Mean (Standard Deviation)	69.1 (20.70)	69.44 (19.22)	69.98 (21.64)

14. Secondary Outcome Measure:

Measure Title	Time Interval Between Infusion Set Changes in Routine

Measure Description	Patients treated with insulin pump have to change their infusion set regularly (i.e.change was recommended every 48h). The patients were asked to report any change of their infusion set and the reason for change (routine basis or because of occurrence of a specific event such as occlusion, unexplained hyperglycemia or adverse event). Changes in routine correspond to interval between changes according to patient use.
Time Frame	over 13 weeks of each treatment period
Safety Issue?	No

Analysis Population Description

Analysis was performed on the Intention To Treat (ITT) population. The Intent-To-Treat population is composed of all randomized patients having received the 3 insulins (Insulin glulisine, aspart and lispro) N=256 patients: (sequence 1: N=86, sequence 2: N=86; sequence 3: N=84 patients).

Reporting Groups

	Description
Insulin Glulisine	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Aspart	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Lispro	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump

Measured Values

	Insulin Glulisine	Insulin Aspart	Insulin Lispro
Number of Participants Analyzed	254	254	254
Time Interval Between Infusion Set Changes in Routine [units: hours] Mean (Standard Deviation)	70.72 (21.47)	71.00 (20.68)	71.07 (21.65)

15. Secondary Outcome Measure:

Measure Title	Glycosylated Hemoglobin: HbA1c
Measure Description	Glycolysated Haemoglobin (HbA1c) is a biological parameter that reflects the blood glucose concentration over a long period of time. It is the standard parameter for glycemic control follow-up in diabetic patients. This parameter is expressed in percentage (%) and the target in diabetes management is to reach a HbA1c <7%
Time Frame	over 13 weeks of each treatment period
Safety Issue?	No

Analysis Population Description

Analysis was performed on the Intention To Treat (ITT) population. The Intent-To-Treat population is composed of all randomized patients having received the 3 insulins (Insulin glulisine, aspart and lispro) N=256 patients: (sequence 1: N=86, sequence 2: N=86; sequence 3: N=84 patients).

Reporting Groups

	Description
Insulin Glulisine	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Aspart	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Lispro	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump

Measured Values

	Insulin Glulisine	Insulin Aspart	Insulin Lispro
Number of Participants Analyzed	256	256	256
Glycosylated Hemoglobin: HbA1c [units: percentage] Mean (Standard Deviation)			
First week (week 1) (n=253, n=254, n=255)	7.31 (0.71)	7.33 (0.71)	7.28 (0.71)
Last week (week 13) (n=252, n=255, n=251)	7.32 (0.03)	7.25 (0.03)	7.33 (0.03)

Statistical Analysis 1 for Glycosylated Hemoglobin: HbA1c

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Aspart
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.078
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	ANCOVA
	Comments	ANCOVA adjusted on HbA1c value at the start of the first period

Statistical Analysis 2 for Glycosylated Hemoglobin: HbA1c

Statistical Analysis Overview	Comparison Groups	Insulin Glulisine, Insulin Lispro
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.938
	Comments	The p-value is adjusted for multiple comparisons. Each comparison is performed at the alpha level=2.5% (instead of 5%). Consequently a difference between 2 treatments is statistically significant if the corresponding p-value is <0.025
	Method	ANCOVA
	Comments	ANCOVA adjusted on HbA1c level at the start of the first period

16. Secondary Outcome Measure:

Measure Title	Total Daily Basal Insulin Infusion
Measure Description	dose of the basal insulin regimen administered throughout the 24-hour period
Time Frame	over 13 weeks of each treatment period
Safety Issue?	No

Analysis Population Description

Analysis was performed on the Intention To Treat (ITT) population. The Intent-To-Treat population is composed of all randomized patients having received the 3 insulins (Insulin glulisine, aspart and lispro) N=256 patients: (sequence 1: N=86, sequence 2: N=86; sequence 3: N=84 patients).

Reporting Groups

	Description
Insulin Glulisine	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Aspart	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Lispro	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump

Measured Values

	Insulin Glulisine	Insulin Aspart	Insulin Lispro
Number of Participants Analyzed	256	256	256
Total Daily Basal Insulin Infusion			

	Insulin Glulisine	Insulin Aspart	Insulin Lispro
[units: Units] Mean (Standard Deviation)			
First week (week 1) (n=251, n=249, n=250)	20.83 (9.05)	20.93 (9.45)	20.85 (9.16)
Last week (week 13) (n=251, n=249, n=251)	20.86 (9.24)	20.81 (9.73)	21.11 (9.38)

17. Secondary Outcome Measure:

Measure Title	Total Daily Bolus Insulin Dose
Measure Description	dose of every increment administered for example before meals
Time Frame	over 13 weeks of each treatment period
Safety Issue?	No

Analysis Population Description

Analysis was performed on the Intention To Treat (ITT) population. The Intent-To-Treat population is composed of all randomized patients having received the 3 insulins (Insulin glulisine, aspart and lispro) N=256 patients: (sequence 1: N=86, sequence 2: N=86; sequence 3: N=84 patients).

Reporting Groups

	Description
Insulin Glulisine	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Aspart	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Lispro	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump

Measured Values

	Insulin Glulisine	Insulin Aspart	Insulin Lispro
Number of Participants Analyzed	256	256	256
Total Daily Bolus Insulin Dose [units: Units] Mean (Standard Deviation)			
First week (week 1) (n=249, n=247, n=250)	18.63 (9.22)	18.49 (9.00)	18.40 (8.69)
Last week (week 13) (n=248, n=244, n=249)	18.58 (8.49)	18.64 (9.60)	19.19 (9.13)

Reported Adverse Events

Time Frame	Adverse events are collected from the first to the last drug intake (3 periods x 13 weeks) + 1 week after the administration of the last intake i.e. end of the study.
Additional Description	The safety analyses are performed on the safety population which includes all randomized and treated patients. Safety population is defined based on actual treatment received.

Reporting Groups

	Description
Insulin Glulisine	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Aspart	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump
Insulin Lispro	100 U/ml, administration by Continuous Subcutaneous Insulin Infusion with external pump

Serious Adverse Events

	Insulin Glulisine	Insulin Aspart	Insulin Lispro
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	29/274 (10.58%)	18/266 (6.77%)	11/269 (4.09%)
Cardiac disorders			
arteritis coronary [A] *	0/274 (0%)	1/266 (0.38%)	0/269 (0%)
cardiovascular disorders [A] *	1/274 (0.36%)	0/266 (0%)	0/269 (0%)
coronary artery stenosis [A] *	0/274 (0%)	1/266 (0.38%)	0/269 (0%)
myocardial infarction [A] *	0/274 (0%)	1/266 (0.38%)	0/269 (0%)
Ear and labyrinth disorders			
vertigo [A] *	0/274 (0%)	0/266 (0%)	1/269 (0.37%)
General disorders			
chest pain [A] *	1/274 (0.36%)	1/266 (0.38%)	0/269 (0%)
Injury, poisoning and procedural complications			
forearm fracture [A] *	0/274 (0%)	0/266 (0%)	1/269 (0.37%)
overdose [A] *	1/274 (0.36%)	1/266 (0.38%)	0/269 (0%)

	Insulin Glulisine	Insulin Aspart	Insulin Lispro
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Metabolism and nutrition disorders			
diabetic ketoacidosis [A] *	1/274 (0.36%)	0/266 (0%)	0/269 (0%)
hypoglycaemia [A] *	3/274 (1.09%)	0/266 (0%)	0/269 (0%)
hypoglycaemic seizure [A] *	8/274 (2.92%)	3/266 (1.13%)	4/269 (1.49%)
hypoglycaemic unconsciousness [A] *	4/274 (1.46%)	6/266 (2.26%)	2/269 (0.74%)
ketosis [A] *	9/274 (3.28%)	4/266 (1.5%)	2/269 (0.74%)
Musculoskeletal and connective tissue disorders			
back pain [A] *	1/274 (0.36%)	0/266 (0%)	0/269 (0%)
Nervous system disorders			
headache [A] *	0/274 (0%)	1/266 (0.38%)	0/269 (0%)
hemianopia [A] *	0/274 (0%)	0/266 (0%)	1/269 (0.37%)
hypoglycaemic coma [A] *	0/274 (0%)	1/266 (0.38%)	0/269 (0%)
Pregnancy, puerperium and perinatal conditions			
pregnancy [A] *	1/274 (0.36%)	0/266 (0%)	0/269 (0%)
Psychiatric disorders			
depression [A] *	1/274 (0.36%)	0/266 (0%)	0/269 (0%)
Respiratory, thoracic and mediastinal disorders			
dyspnoea [A] *	1/274 (0.36%)	0/266 (0%)	0/269 (0%)
nasal congestion [A] *	1/274 (0.36%)	0/266 (0%)	0/269 (0%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA 12.1

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Insulin Glulisine	Insulin Aspart	Insulin Lispro
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	47/274 (17.15%)	24/266 (9.02%)	30/269 (11.15%)
Metabolism and nutrition disorders			
Ketosis [A] *	47/274 (17.15%)	24/266 (9.02%)	30/269 (11.15%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA 12.1

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

If no publication has occurred within 12 months of the completion of the study, the Investigator shall have the right to publish/present independently the results of the study. The Investigator shall provide the Sponsor with a copy of any such presentation/publication for comment at least 30 days before any presentation/submission for publication. If requested by the Sponsor, any presentation/submission shall be delayed up to 90 days, to allow the Sponsor to preserve its proprietary rights.

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