ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
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# Efficacy Assessment of Insulin Glargine Versus LiraglutidE After Oral Agents Failure (EAGLE)

This study has been completed.

| | |
|---|---|
| Sponsor: | Sanofi |
| Collaborators: | |
| Information provided by (Responsible Party): | Sanofi |
| ClinicalTrials.gov Identifier: | NCT01117350 |

## Purpose

Primary objective:

To demonstrate the superiority of insulin glargine over liraglutide in terms of percentage of patients reaching a Glycosylated Haemoglobin (HbA1c) < 7% at the end of the comparative period (24 weeks) in Type 2 diabetic patients failing lifestyle management and oral agents

Secondary objectives of the comparative period (24 weeks):

>To assess the effect of insulin glargine in comparison with liraglutide on:

- HbA1c level
- Percentage of patients whose HbA1c has decreased but remains >= 7% at the end of the comparative period
- Percentage of patients whose HbA1c has increased at the end of the comparative period
- Fasting Plasma Glucose (FPG)
- 7-point Plasma Glucose (PG) profiles
- Hypoglycemia occurrence
- Body weight
- Adverse events

Objectives of the extension period (24 weeks):

>To assess the effect of insulin glargine in patients not adequately controlled with liraglutide on:

- HbA1c level
- FPG
- 7-point PG profiles
- Hypoglycemia occurrence
- Body weight
- Adverse events

| Condition | Intervention | Phase |
|---|---|---|
| Diabetes Mellitus, Type 2 | Drug: Insulin glargine<br>Drug: Liraglutide<br>Drug: Metformin | Phase 4 |

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Open Label, Randomized, Safety/Efficacy Study
Official Title: A 24-week, Multicenter, International, Randomized (1:1), Parallel-group, Open-label, Comparative Study of Insulin Glargine Versus Liraglutide in Insulin-naïve Patients With Type 2 Diabetes Treated With Oral Agents and Not Adequately Controlled, Followed by a 24-week Extension Period With Insulin Glargine for Patients Not Adequately Controlled With Liraglutide

Further study details as provided by Sanofi:

Primary Outcome Measure:

- Percentage of Patients Whose Glycosylated Haemoglobin (HbA1c) <7% at the End of the Comparative Period [Time Frame: week 12, week 24] [Designated as safety issue: No]
  The value at the end of the comparative period was defined as the last available HbA1c value measured during the comparative period plus 14 days after the last dose of Investigational Product (i.e. last-observation-carried-forward [LOCF] value).

Secondary Outcome Measures:

- Percentage of Patients Whose Glycosylated Haemoglobin (HbA1c) Has Decreased But Remains ≥7% at the End of the Comparative Period [Time Frame: baseline (week -2), week 12, week 24] [Designated as safety issue: No]
  Percentage of patients with: * HbA1c value at end of the comparative period (LOCF) lower than HbA1c baseline value AND * HbA1c value at end of the comparative period (LOCF) ≥7%
- Percentage of Patients Whose Glycosylated Haemoglobin (HbA1c) Has Increased at the End of the Comparative Period [Time Frame: baseline (week -2), week 12, week 24] [Designated as safety issue: No]
  Percentage of patients with HbA1c value at end of the comparative period (LOCF) higher than HbA1c baseline value
- Glycosylated Haemoglobin (HbA1c): Change From Baseline to the End of Comparative Period [Time Frame: baseline (week -2), week 12, week 24] [Designated as safety issue: No]
  Change in HbA1C from baseline to the last observation carried forward (LOCF) measured during the comparative period = LOCF value - baseline value
- Glycosylated Haemoglobin (HbA1c): Change From Beginning to the End of the Extension Period [Time Frame: week 24, week 36, week 48] [Designated as safety issue: No]
  Change in HbA1C from beginning of the extension period (week 24) to the last observation carried forward (LOCF) measured during the extension period = LOCF value - week 24 value
- Percentage of Patients Whose Glycosylated Haemoglobin (HbA1c) <7% at the End of the Extension Period [Time Frame: week 36, week 48] [Designated as safety issue: No]
  Value at the end of the extension period defined as last available HbA1c value measured during the extension period (i.e. last observation carried forward (LOCF) value)

- Self-Monitored Fasting Plasma Glucose (SMFPG) Measurements: Change From Baseline to the End of the Comparative Period [Time Frame: baseline (week 0), week 6, week 12, week 18, week 24] [Designated as safety issue: No]
  SMFPG = mean value of Self-Monitored Fasting Plasma Glucose measurements over 3 consecutive days in the week before each visit Value at the end of the comparative period defined as last available value during the comparative period (i.e. last-observation-carried-forward [LOCF] value) Change = LOCF value - baseline value
- Self-Monitored Fasting Plasma Glucose (SMFPG) Measurements: Change From Beginning to the End of the Extension Period [Time Frame: week 24, week 30, week 36, week 48] [Designated as safety issue: No]
  SMFPG = mean value of Self-Monitored Fasting Plasma Glucose measurements over 3 consecutive days in the week before each visit Value at the end of the extension period defined as last available value during the extension period (i.e. last-observation-carried-forward [LOCF] value) Change = LOCF value - week 24 value
- Self-Monitored 7-point Plasma Glucose (PG) Profile: Change From Baseline to the End of the Comparative Period [Time Frame: baseline (week 0), week 12, week 24] [Designated as safety issue: No]
  Self-monitored 7-point plasma glucose profiles (before and 2 hours after the start of breakfast, lunch and dinner, and at bedtime) recorded on 3 consecutive days in the week before each visit Value at the end of the comparative period defined as last available value during the comparative period (i.e. last-observation-carried-forward [LOCF] value) Change = LOCF value - baseline value
- Self-Monitored 7-point Plasma Glucose (PG) Profile: Change From Beginning to the End of the Extension Period [Time Frame: week 24, week 36, week 48] [Designated as safety issue: No]
  Self-monitored 7-point plasma glucose profiles (before and 2 hours after the start of breakfast, lunch and dinner, and at bedtime) recorded on 3 consecutive days in the week before each visit Value at the end of the extension period defined as last available value during the extension period (i.e. last-observation-carried-forward [LOCF] value) Change = LOCF value - week 24 value
- Body Weight: Change From Baseline to the End of the Comparative Period [Time Frame: baseline (week 0), week 2, week 6, week 12, week 18, week 24] [Designated as safety issue: No]
  Change = Last weight value measured during the comparative period (LOCF value) - weight value at baseline
- Body Weight: Change From Beginning to End of the Extension Period [Time Frame: week 24, week 30, week 36, week 48] [Designated as safety issue: No]
  Change = Last weight value measured during the extension period (LOCF value) - weight value at beginning of the Extension Period (Week 24)
- Daily Dose of Insulin Glargine [Time Frame: week 1, week 2, week 6, week 12, week 24] [Designated as safety issue: No]
- Daily Dose of Liraglutide [Time Frame: week 1, week 2, week 6, week 12, week 24] [Designated as safety issue: No]
- Daily Dose of Insulin Glargine Administered During the Extension Period [Time Frame: week 30, week 36, week 48] [Designated as safety issue: No]
- Hypoglycemia Occurence: Number of Patients With at Least One Episode of Symptomatic / Severe Symptomatic Hypoglycemia During the Comparative Period [Time Frame: all across the comparative period (from week 0 to week 24)] [Designated as safety issue: Yes]
  Symptomatic hypoglycemia was defined as an event with clinical symptoms that were considered to result from hypoglycemia. Severe symptomatic hypoglycemia was defined as an event with clinical symptoms that were considered to result from hypoglycemia, requiring the assistance of another person for active administration of carbohydrate, glucagon or other countermeasure because the patient could not treat him/herself due to acute neurological impairment directly resulting from the hypoglycemia (assistance by another person when the patient could have treated him/herself was not considered as requiring assistance)and one of the following criteria: • The event was associated with a measured PG level < 36 mg/dL (2 mmol/L), • Or, in absence of PG value, the event was associated with neurological recovery attributable to the restoration of PG to normal, after oral carbohydrate, intravenous glucose or glucagon administration.
- Hypoglycemia Occurence: Number of Patients With at Least One Episode of Symptomatic / Severe Symptomatic Hypoglycemia During the Extension Period [Time Frame: all across the extension period (from week 24 to week 48)] [Designated as safety issue: Yes]
  Symptomatic hypoglycemia was defined as an event with clinical symptoms that were considered to result from hypoglycemia. Severe symptomatic hypoglycemia was defined as an event with clinical symptoms that were considered to result from hypoglycemia, requiring the assistance of another person for active administration of carbohydrate, glucagon or other countermeasure because the patient could not treat him/herself due to acute neurological impairment directly resulting from the hypoglycemia (assistance by another person when the patient could have treated him/herself was not considered as requiring assistance)and one of the following criteria: • The event was associated with a measured PG level < 36 mg/dL (2 mmol/L), •

Or, in absence of PG value, the event was associated with neurological recovery attributable to the restoration of PG to normal, after oral carbohydrate, intravenous glucose or glucagon administration.

Enrollment: 978
Study Start Date: July 2010
Primary Completion Date: October 2012
Study Completion Date: March 2013

| Arms | Assigned Interventions |
|---|---|
| Experimental: Insulin Glargine<br>Insulin glargine administered once a day, in the morning or in the evening, at the most convenient time. The time of injection, once chosen was to remain unchanged during the whole duration of the study.<br>The starting dose was 0.2 Unit per kilogram of body weight or 10 Units. Patients were empowered to adjust their insulin doses, under strict investigator's supervision. Insulin titration (by 2 or 4 Units) was done every 3 days according to the median value of Fasting Plasma Glucose (FPG) of the last 3 days. The goal was to achieve 70 < FPG ≤ 100 mg/dL (3.9 < FPG ≤ 5.5 mmol/L). Minor deviations from the titration scheme could be allowed, based on Investigator's judgment and patient's situation. | Drug: Insulin glargine<br>100 Units/mL solution for injection in a pre-filled SoloStar pen<br>Other Names:<br>Lantus®<br>Drug: Metformin<br>Metformin was a background treatment, mandatory for each patient randomized in the study (at the minimum dose of 1g/day). It was not supplied by the sponsor. |
| Active Comparator: Liraglutide<br>Liraglutide administered once a day, in the morning or in the evening, at the most convenient time. The time of injection , once chosen was to remain unchanged during the whole duration of the study.<br>The dose was 0.6 mg/day during the first week, 1.2 mg/day during the second week and 1.8 mg/day until week 24. The dose might be decreased to 1.2 mg for safety reasons (e.g. gastro-intestinal tolerability), based on Investigator's judgment. | Drug: Liraglutide<br>6 mg/mL solution for injection in a 3-mL pre-filled pen (18mg)<br>Other Names:<br>Victoza®<br>Drug: Metformin<br>Metformin was a background treatment, mandatory for each patient randomized in the study (at the minimum dose of 1g/day). It was not supplied by the sponsor. |

Detailed Description:

Maximum estimated study duration per patient: either 27 weeks (patients randomized to insulin glargine arm) or 51 weeks (patients randomized to liraglutide arm) broken down as follow:

- A 2-week of screening period,
- A 24-week comparative period,
- A 24-week extension period (only for patients treated with liraglutide, not adequately controlled at the end of the comparative period),
- A 1-week follow-up period

## Eligibility

Ages Eligible for Study: 35 Years to 75 Years
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

### Criteria

Inclusion criteria (comparative period):

- Patients With Type 2 Diabetes diagnosed for at least 1 year,
- Treated with lifestyle interventions and metformin at the maximum tolerated dosage (with a minimum daily dosage of 1g), either alone or in combination with an oral insulin secretagogue (sulfonylurea, glinide or DiPeptidyl Peptidase IV inhibitor), for more than 3 months,
- 7.5% < HbA1c <= 12%,
- Body Mass Index (BMI) between 25 and 40 kg/m2 inclusively,
- Ability and willingness to perform PG (Plasma Glucose) self monitoring using the sponsor-provided glucose meter and to complete the patient diary,
- Willingness and ability to comply with the study protocol,
- Signed informed consent obtained prior to any study procedure.

Inclusion criteria (extension period):

- Patients treated with liraglutide (at the maximal tolerated dosage), having a mean FPG ≥ 250 mg/dL at visit 10 (Week 12) or visit 11 (Week 18), or a HbA1c≥ 7% at visit 12 (Week 24)
- Dosage of metformin compliant with the inclusion criteria of visit 1 (i.e. maximum tolerated dosage, with a minimum daily dosage of 1g), and maintained stable during the comparative period.

Exclusion criteria:

- Previous treatment with Glucagon Like Peptide-1 analogues or insulin in the past year (except in case of temporary treatment for gestational diabetes, surgery, hospitalization...),
- Treatment with thiazolidinediones or α-Glucosidases inhibitors within 3 months prior to study entry,
- Diabetes other than Type 2 diabetes (e.g. secondary to pancreatic disorders, drug or chemical agents intake),
- Pregnant women (women of childbearing potential must have a negative pregnancy test at study entry and a medically approved contraceptive method),
- Lactating women,
- Hospitalized patients (except hospitalization for routine diabetes check-up),
- Active proliferative retinopathy, as defined by a photocoagulation or vitrectomy occurrence in the 6 months prior to study entry, or any other unstable (rapidly progressing) retinopathy that may require photocoagulation or surgical treatment during the study, documented by a retina examination within 2 years prior to study entry,

- Impaired renal function (creatinine clearance < 60 mL/mn),
- Impaired hepatic function (Alanine Aminotransferase, Aspartate Aminotransferase 2.5 times the upper limit of normal range),
- Personal or family history of medullary thyroid carcinoma,
- Multiple endocrine neoplasia syndrome type 2,
- Severe gastro-intestinal disease (including inflammatory bowel disease or diabetic gastroparesis),
- Congestive heart failure,
- History of acute pancreatitis,
- Treatment with corticosteroids with potential systemic action for more than 10 days within 3 months prior to study entry,
- Alcohol or drug abuse in the past 5 years,
- History of sensitivity to the study drugs or to drugs with a similar chemical structure.
- Night shift worker,
- Presence of any condition (medical, psychological, social or geographical), current or anticipated that would compromise the patients safety or limit the patient successful participation in the study,
- Participation in a clinical trial (drug or device) within 3 months prior to study entry,
- Refusal or inability to give informed consent to participate in the study,
- Patient is the Investigator or any sub-Investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol.

Additional exclusion criteria for the extension period:

- Treatment with oral antidiabetic drugs other than metformin and patient's usual sulfonylurea if any, or with insulin during the comparative period (except in case of an emergency, for a period of time less than 7 days),
- Treatment with corticosteroids with potential systemic action within the last 3 months of the comparative period.
- History of sensitivity to insulin glargine.

## Contacts and Locations

Locations

United States, Alabama
investigational site number 840023
Birmingham, Alabama, United States, 35294
United States, Arizona
investigational site number 840002
Goodyear, Arizona, United States, 85395
investigational site number 840047
Phoenix, Arizona, United States, 85020
United States, California
investigational site number 840017
La Jolla, California, United States, 92037
investigational site number 840036
La Mesa, California, United States, 91942
investigational site number 840037
Loma Linda, California, United States, 92357
investigational site number 840045
Long Beach, California, United States, 90822

investigational site number 840048
Mission Hills, California, United States, 91345
investigational site number 840033
Mission Viejo, California, United States, 92691
investigational site number 840019
Palm Springs, California, United States, 92262
investigational site number 840042
San Diego, California, United States, 92161
investigational site number 840039
San Diego, California, United States, 92101
investigational site number 840043
Tustin, California, United States, 92780
United States, Colorado
investigational site number 840028
Denver, Colorado, United States, 80220
investigational site number 840034
Grand Junction, Colorado, United States, 81501
investigational site number 840026
Longmont, Colorado, United States, 80501
United States, Georgia
investigational site number 840022
Lawrenceville, Georgia, United States
investigational site number 840029
Roswell, Georgia, United States, 30076
United States, Illinois
investigational site number 840009
Arlington Heights, Illinois, United States, 60004
investigational site number 840051
Springfield, Illinois, United States, 62704
United States, Indiana
investigational site number 840050
Indianapolis, Indiana, United States, 46222
United States, Kansas
investigational site number 840031
Kansas City, Kansas, United States, 66160
United States, Kentucky
investigational site number 840004
Paducah, Kentucky, United States, 42003
United States, Maryland
investigational site number 840010
Rockville, Maryland, United States, 20850
United States, Minnesota
investigational site number 840038
Eagan, Minnesota, United States, 55122
investigational site number 840030

Minneapolis, Minnesota, United States, 55414
United States, Missouri
investigational site number 840012
St Louis, Missouri, United States, 63128
investigational site number 840044
St. Louis, Missouri, United States, 63141
United States, New Jersey
investigational site number 840015
Atco, New Jersey, United States, 08004
investigational site number 840008
Blackwood, New Jersey, United States, 08012
United States, New York
investigational site number 840027
Mineola, New York, United States, 11501
investigational site number 840011
Staten Island, New York, United States, 10301-3914
United States, North Carolina
investigational site number 840005
Hickory, North Carolina, United States, 28601
investigational site number 840052
Winston-Salem, North Carolina, United States, 27103
United States, North Dakota
investigational site number 840049
Fargo, North Dakota, United States, 58103
United States, Ohio
investigational site number 840006
Bryan, Ohio, United States, 43506
investigational site number 840035
Cincinnati, Ohio, United States, 45220
United States, Pennsylvania
investigational site number 840016
Carnegie, Pennsylvania, United States, 15106
investigational site number 840020
Uniontown, Pennsylvania, United States, 15401
United States, South Dakota
investigational site number 840024
Rapid City, South Dakota, United States, 57701
United States, Texas
investigational site number 840007
Dallas, Texas, United States, 75246
investigational site number 840001
Dallas, Texas, United States, 75230
investigational site number 840013
Houston, Texas, United States, 77030
United States, Washington

investigational site number 840014
Renton, Washington, United States, 98057
investigational site number 840046
Spokane, Washington, United States, 99220-3649
Austria
investigational site number 040-007
Salzburg, Austria, 5020
investigational site number 040-006
Salzburg, Austria, 5010
investigational site number 040-003
Stockerau, Austria, A-2000
investigational site number 040-005
Vienna, Austria, A-1010
investigational site number 040-004
Vienna, Austria, A-1220
investigational site number 040-001
Vienna, Austria, A-1130
investigational site number 040-002
Vienna, Austria, A-1090
Brazil
investigational site number 076-004
Belém, Brazil, 66073-000
investigational site number 076-007
Fortaleza, Brazil, 60015-052
investigational site number 076-001
Fortaleza, Brazil, 60115-282
investigational site number 076-006
Fortaleza, Brazil, 60430-370
investigational site number 076-005
Marília, Brazil, 17519-101
investigational site number 076-002
São Paulo, Brazil, 01244-030
Canada
investigational site number 124-003
Mississauga, Canada, L5M2V8
investigational site number 124-001
Montreal, Canada, H2W1T8
investigational site number 124-006
Montreal, Canada, H3A1A1
investigational site number 124-004
Toronto, Canada, M5C 2T2
investigational site number 124-008
Vancouver, Canada, V5Z1M9
investigational site number 124-007
Victoria, Canada, V8R1J8

Czech Republic
- investigational site number 203001
  - Hradec Kralove, Czech Republic, 50005
- investigational site number 203003
  - Krnov, Czech Republic, 79401
- investigational site number 203005
  - Kromeriz, Czech Republic, 76701
- investigational site number 203002
  - Olomouc, Czech Republic, 77900
- investigational site number 203006
  - Praha 5, Czech Republic, 15000

Finland
- investigational site number 246003
  - Harjavalta, Finland, 29200
- investigational site number 246001
  - Kuopio, Finland, 70210
- investigational site number 246002
  - Oulu, Finland, 90100
- investigational site number 246004
  - Turku, Finland, 20100

France
- investigational site number 250-007
  - Annecy, France, 74000
- investigational site number 250-017
  - Bois Guillaume Cedex, France, 76233
- investigational site number 250-003
  - Boulogne Billancourt, France, 92100
- investigational site number 250-011
  - Brest, France, 29000
- investigational site number 250-008
  - Cahors Cedex 9, France, 46005
- investigational site number 250-012
  - Corbeil Essonnes, France, 91100
- investigational site number 250-009
  - La Rochelle Cedex 1, France, 17019
- investigational site number 250-004
  - Le Creusot, France, 71200
- investigational site number 250-006
  - Mantes La Jolie, France, 78200
- investigational site number 250-021
  - Nanterre, France, 92014
- investigational site number 250-020
  - Strasbourg, France, 67091
- investigational site number 250022
  - Strasbourg, France, 67000

investigational site number 250-002
Toulouse, France, 31300
investigational site number 250-016
Venissieux, France, 69200
Greece
investigational site number 300003
Athens, Greece
investigational site number 300004
Athens, Greece
investigational site number 300001
Haidari, Athens, Greece, 12462
Ireland
investigational site number 372001
Dublin 4, Ireland
Israel
investigational site number 376004
Hadera, Israel
investigational site number 376002
Petah Tiqwa, Israel, 49361
investigational site number 376003
Tel-Aviv, Israel
Mexico
investigational site number 484004
Guadalajara, Mexico, 44630
investigational site number 484002
Mexico, Mexico, 14000
investigational site number 484001
Mexico, Mexico, 07760
investigational site number 484003
Zapopan, Mexico, 45200
Netherlands
investigational site number 528001
Beek, Netherlands, 6191JW
investigational site number 528006
Enschede, Netherlands, 7523JJ
investigational site number 528002
Hoogeveen, Netherlands, 7909AA
investigational site number 528007
Nijverdal, Netherlands, 7442LS
investigational site number 528003
Rotterdam, Netherlands
investigational site number 528005
Woerden, Netherlands
investigational site number 528004
s-Hertogenbosch, Netherlands

Russian Federation
- investigational site number 643-009
  - Kazan, Russian Federation
- investigational site number 643008
  - Kirov, Russian Federation, 610014K
- investigational site number 643001
  - Moscow, Russian Federation, 117036
- investigational site number 643006
  - Samara, Russian Federation
- investigational site number 643007
  - Samara, Russian Federation
- investigational site number 643005
  - Saratov, Russian Federation
- investigational site number 643004
  - St-Petersburg, Russian Federation, 195257
- investigational site number 643003
  - St-Ptetersburg, Russian Federation, 194354

Slovakia
- investigational site number 703002
  - Bratislava, Slovakia, 81102
- investigational site number 703004
  - Kosice, Slovakia, 04013
- investigational site number 703001
  - Nitra, Slovakia, 94911
- investigational site number 703005
  - Nove Mesto nad Vahom, Slovakia, 091501
- investigational site number 703003
  - Zilina, Slovakia, 01001

Spain
- investigational site number 724007
  - Bilbao, Spain, 48013
- investigational site number 724006
  - Cádiz, Spain, 11009
- investigational site number 724005
  - LLeida, Spain
- investigational site number 724001
  - Las Palmas de Gran Canaria, Spain, 35020
- investigational site number 724008
  - Madrid, Spain, 28040
- investigational site number 724003
  - Málaga, Spain, 29010
- investigational site number 724009
  - Sabadell, Spain, 08208
- investigational site number 724004
  - Valencia, Spain, 46015

investigational site number 721002
Valencia, Spain, 46014
investigational site number 724010
Vigo, Spain, 36211
Sweden
investigational site number 752-002
Göteborg, Sweden, 41665
investigational site number 752-005
Karlskoga, Sweden, 69181
investigational site number 752-006
Motala, Sweden, 59185
investigational site number 752-001
Stockholm, Sweden, 17176
investigational site number 752-03
Ängelholm, Sweden, 26281
investigational site number 752-007
Örebro, Sweden, 70235
Turkey
investigational site number 792-001
Antalya, Turkey, 07070
investigational site number 792-002
Istanbul, Turkey, 34890

Investigators

| | | |
|---|---|---|
| Study Director: | Clinical Sciences & Operations | sanofi-aventis |

## More Information

| | |
|---|---|
| Responsible Party: | Sanofi |
| Study ID Numbers: | LANTU_C_03680<br>2010-018437-21 [EudraCT Number]<br>U1111-1116-9684 [UTN] |
| Health Authority: | Czech Republic: State Institute for Drug Control<br>United States: Food and Drug Administration |

# Study Results

## Participant Flow

| | |
|---|---|
| Recruitment Details | The first patient was enrolled on July 23, 2010. The 24-week comparative period was completed on October 5, 2012. |

| | |
|---|---|
| | The extension period was initiated on March 24, 2011 and completed on March 6, 2013. |
| Pre-Assignment Details | A total of 1456 patients were screened in 136 centers, in 17 countries (Austria, Brazil, Canada, Czech Republic, Finland, France, Greece, Ireland, Israel, Mexico, Netherlands, Russian Federation Slovakia, Spain, Sweden, Turkey, USA). Among them, 478 (32.8%) patients were not randomized (main reason was Glycosylated Haemoglobin A1c out of range). |

Reporting Groups

| | Description |
|---|---|
| Insulin Glargine | Insulin glargine starting dose: 0.2 Unit per kilogram of body weight or 10 Units. Insulin titration (by 2 or 4 Units) every 3 days according to the median value of Fast Plasma Glucose of the last 3 days |
| Liraglutide (Comparative Period)/ Insulin Glargine (Extension) | Liraglutide dose: 0.6 mg/day during the first week, 1.2 mg/day during the second week and 1.8 mg/day until week 24 (comparative period)<br>For patients included in the extension period: Insulin Glargine (dosing same as above) |

Comparative Period

| | Insulin Glargine | Liraglutide (Comparative Period)/ Insulin Glargine (Extension) |
|---|---|---|
| Started | 489 [1] | 489 |
| TREATED = Safety Population | 484 [2] | 481 |
| mITT Population | 474 [3] | 470 |
| Completed | 447 | 414 |
| Not Completed | 42 | 75 |
| Not Treated | 5 | 8 |
| Adverse Event | 6 | 33 |
| Lost to Follow-up | 11 | 7 |
| Withdrawal by Subject | 9 | 13 |
| Protocol Violation | 8 | 12 |
| Lack of Efficacy | 1 | 0 |
| Physician Decision | 0 | 1 |
| Move to another city/country | 2 | 1 |

[1] STARTED: randomized

[2] Safety population: all randomized and treated patients (received at least one dose)

[3] modified Intent-To-Treat population: treated patients with at least one efficacy post-baseline value

Extension Period

| | Insulin Glargine | Liraglutide (Comparative Period)/ Insulin Glargine (Extension) |
|---|---|---|
| Started | 0 | 210 [1] |
| TREATED = Safety Population (Extension) | 0 | 160 [2] |
| mITT Population (Extension) | 0 | 154 [3] |
| Completed | 0 | 147 |
| Not Completed | 0 | 63 |
| Not included in extension, not treated | 0 | 50 |
| Adverse Event | 0 | 2 |
| Protocol Violation | 0 | 2 |
| Lost to Follow-up | 0 | 2 |
| Withdrawal by Subject | 0 | 3 |
| Lack of Efficacy | 0 | 2 |
| Inclusion criteria not respected | 0 | 1 |
| Prohibited medication | 0 | 1 |

[1] STARTED: patients having completed the comparative period and eligible for the extension period
[2] Safety population (extension): treated with insulin glargine during the extension period
[3] mITT (extension): treated patients with at least 1 efficacy value both at entry and during extension

## Baseline Characteristics

Analysis Population Description

Modified-Intent-to-treat (mITT) population: all patients who were randomized, received at least one dose of Interventional Product (IP), and had at least one post-baseline assessment during comparative period of any primary or secondary efficacy variables

Reporting Groups

| | Description |
|---|---|
| Insulin Glargine | Insulin glargine starting dose: 0.2 Unit per kilogram of body weight or 10 Units. Insulin titration (by 2 or 4 Units) every 3 days according to the median value of Fast Plasma Glucose of the last 3 days. |

| | Description |
|---|---|
| Liraglutide | Liraglutide dose: 0.6 mg/day during the first week, 1.2 mg/day during the second week and 1.8 mg/day until week 24. |

Baseline Measures

| | Insulin Glargine | Liraglutide | Total |
|---|---|---|---|
| Number of Participants | 474 | 470 | 944 |
| Age, Continuous<br>[units: years]<br>Mean (Standard Deviation) | 57.07 (8.78) | 57.44 (8.85) | 57.25 (8.81) |
| Gender, Male/Female<br>[units: participants] | | | |
| Female | 224 | 207 | 431 |
| Male | 250 | 263 | 513 |
| Body Mass Index (BMI) at week -2<br>[units: kg/m²]<br>Mean (Standard Deviation) | 32.00 (4.24) | 31.75 (4.12) | 31.88 (4.18) |
| Duration of Type 2 diabetes<br>[units: years]<br>Median (Inter-Quartile Range) | 8.54 (5.20 to 12.38) | 8.41 (4.80 to 11.69) | 8.49 (4.94 to 12.17) |
| At least one diabetic late complication [1]<br>[units: participants] | | | |
| Yes | 212 | 223 | 435 |
| No | 262 | 247 | 509 |
| Glycosylated Hemoglobin A1c (HbA1c) at week -2<br>[units: percent]<br>Mean (Standard Deviation) | 9.04 (1.10) | 9.11 (1.09) | 9.07 (1.09) |

[1] Diabetic late complications: myocardial infarction, angina pectoris, coronary artery disease, heart failure, stroke, transient ischemic attack, peripheral vascular disease, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy

## Outcome Measures

1. Primary Outcome Measure:

| | |
|---|---|
| Measure Title | Percentage of Patients Whose Glycosylated Haemoglobin (HbA1c) <7% at the End of the Comparative Period |
| Measure Description | The value at the end of the comparative period was defined as the last available HbA1c value measured during the comparative period plus 14 days after the last dose of Investigational Product (i.e. last-observation-carried-forward [LOCF] value). |
| Time Frame | week 12, week 24 |
| Safety Issue? | No |

Analysis Population Description

The population analyzed for this outcome measure consisted of the subset of mITT patients who had at least one HbA1c value on treatment during the comparative period.

Reporting Groups

| | Description |
|---|---|
| Insulin Glargine | Insulin glargine starting dose: 0.2 Unit per kilogram of body weight or 10 Units. Insulin titration (by 2 or 4 Units) every 3 days according to the median value of Fast Plasma Glucose of the last 3 days. |
| Liraglutide | Liraglutide dose: 0.6 mg/day during the first week, 1.2 mg/day during the second week and 1.8 mg/day until week 24. |

Measured Values

| | Insulin Glargine | Liraglutide |
|---|---|---|
| Number of Participants Analyzed | 467 | 458 |
| Percentage of Patients Whose Glycosylated Haemoglobin (HbA1c) <7% at the End of the Comparative Period<br>[units: percentage of participants] | 48.4 | 45.9 |

Statistical Analysis 1 for Percentage of Patients Whose Glycosylated Haemoglobin (HbA1c) <7% at the End of the Comparative Period

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Groups | Insulin Glargine, Liraglutide |

| | | |
|---|---|---|
| | Comments | Superiority testing<br>H0: Rate measured with insulin glargine = rate measured with liraglutide<br>H1: Rate measured with insulin glargine ≠ rate measured with liraglutide<br>Sample size calculation (465 randomized patients per arm) was based on the assumption of an expected success rate of 46% with insulin glargine and 35% with liraglutide, an alpha risk of 5% (2-sided) and a power of 90%, taking into account an estimated non evaluability rate of 10%. |
| | Non-Inferiority or Equivalence Analysis? | No |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Statistical Test of Hypothesis | P-Value | 0.439 |
| | Comments | If superiority not demonstrated, switching from superiority to non-inferiority considered.<br>Conclusion of non-inferiority reached if lower limit of 2-sided 95% confidence interval of the difference (insulin glargine – liraglutide) > or = to - 3.5% |
| | Method | Chi-squared |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Method of Estimation | Estimation Parameter | Mean Difference (Final Values) |
| | Estimated Value | 2.54 |
| | Confidence Interval | (2-Sided) 95%<br>-3.88 to 8.93 |
| | Estimation Comments | [Not specified] |

2. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Percentage of Patients Whose Glycosylated Haemoglobin (HbA1c) Has Decreased But Remains ≥7% at the End of the Comparative Period |
| Measure Description | Percentage of patients with:<br>* HbA1c value at end of the comparative period (LOCF) lower than HbA1c baseline value<br>AND<br>* HbA1c value at end of the comparative period (LOCF) ≥7% |
| Time Frame | baseline (week -2), week 12, week 24 |

| | |
|---|---|
| Safety Issue? | No |

Analysis Population Description

The population analyzed for this outcome measure consisted of the subset of mITT patients who had at least one HbA1c value on treatment during the comparative period.

Reporting Groups

| | Description |
|---|---|
| Insulin Glargine | Insulin glargine starting dose: 0.2 Unit per kilogram of body weight or 10 Units. Insulin titration (by 2 or 4 Units) every 3 days according to the median value of Fast Plasma Glucose of the last 3 days. |
| Liraglutide | Liraglutide dose: 0.6 mg/day during the first week, 1.2 mg/day during the second week and 1.8 mg/day until week 24. |

Measured Values

| | Insulin Glargine | Liraglutide |
|---|---|---|
| Number of Participants Analyzed | 467 | 458 |
| Percentage of Patients Whose Glycosylated Haemoglobin (HbA1c) Has Decreased But Remains ≥7% at the End of the Comparative Period<br>[units: percentage of participants] | 47.1 | 46.3 |

3. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Percentage of Patients Whose Glycosylated Haemoglobin (HbA1c) Has Increased at the End of the Comparative Period |
| Measure Description | Percentage of patients with HbA1c value at end of the comparative period (LOCF) higher than HbA1c baseline value |
| Time Frame | baseline (week -2), week 12, week 24 |
| Safety Issue? | No |

Analysis Population Description

The population analyzed for this outcome measure consisted of the subset of mITT patients who had at least one HbA1c value on treatment during the comparative period.

Reporting Groups

| | Description |
|---|---|
| Insulin Glargine | Insulin glargine starting dose: 0.2 Unit per kilogram of body weight or 10 Units. Insulin titration (by 2 or 4 Units) every 3 days according to the median value of Fast Plasma Glucose of the last 3 days. |
| Liraglutide | Liraglutide dose: 0.6 mg/day during the first week, 1.2 mg/day during the second week and 1.8 mg/day until week 24. |

Measured Values

| | Insulin Glargine | Liraglutide |
|---|---|---|
| Number of Participants Analyzed | 467 | 458 |
| Percentage of Patients Whose Glycosylated Haemoglobin (HbA1c) Has Increased at the End of the Comparative Period<br>[units: percentage of participants] | 4.1 | 6.6 |

4. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Glycosylated Haemoglobin (HbA1c): Change From Baseline to the End of Comparative Period |
| Measure Description | Change in HbA1C from baseline to the last observation carried forward (LOCF) measured during the comparative period = LOCF value - baseline value |
| Time Frame | baseline (week -2), week 12, week 24 |
| Safety Issue? | No |

Analysis Population Description

The population analyzed for this outcome measure consisted of the subset of mITT patients who had at least one HbA1c value on treatment during the comparative period.

Reporting Groups

| | Description |
|---|---|
| Insulin Glargine | Insulin glargine starting dose: 0.2 Unit per kilogram of body weight or 10 Units. Insulin titration (by 2 or 4 Units) every 3 days according to the median value of Fast Plasma Glucose of the last 3 days. |
| Liraglutide | Liraglutide dose: 0.6 mg/day during the first week, 1.2 mg/day during the second week and 1.8 mg/day until week 24. |

Measured Values

| | Insulin Glargine | Liraglutide |
|---|---|---|
| Number of Participants Analyzed | 467 | 458 |
| Glycosylated Haemoglobin (HbA1c): Change From Baseline to the End of Comparative Period<br>[units: percent]<br>Mean (Standard Deviation) | -1.92 (1.22) | -1.81 (1.33) |

5. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Glycosylated Haemoglobin (HbA1c): Change From Beginning to the End of the Extension Period |
| Measure Description | Change in HbA1C from beginning of the extension period (week 24) to the last observation carried forward (LOCF) measured during the extension period = LOCF value - week 24 value |
| Time Frame | week 24, week 36, week 48 |
| Safety Issue? | No |

Analysis Population Description

The population analyzed for this outcome measure consisted of the subset of mITT population (extension) who had HbA1c value both at beginning of the extension and at least one value on treatment during the extension period.

Reporting Groups

| | Description |
|---|---|
| Insulin Glargine (Extension Period) | Insulin glargine starting dose: 0.2 Unit per kilogram of body weight or 10 Units. Insulin titration (by 2 or 4 Units) every 3 days according to the median value of Fast Plasma Glucose of the last 3 days |

Measured Values

| | Insulin Glargine (Extension Period) |
|---|---|
| Number of Participants Analyzed | 152 |
| Glycosylated Haemoglobin (HbA1c): Change From Beginning to the End of the Extension Period<br>[units: percent]<br>Mean (Standard Deviation) | -0.26 (1.11) |

6. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Percentage of Patients Whose Glycosylated Haemoglobin (HbA1c) <7% at the End of the Extension Period |
| Measure Description | Value at the end of the extension period defined as last available HbA1c value measured during the extension period (i.e. last observation carried forward (LOCF) value) |
| Time Frame | week 36, week 48 |
| Safety Issue? | No |

Analysis Population Description

The population analyzed for this outcome measure consisted of the mITT patients who had at least one HbA1c value on treatment during the extension period.

Reporting Groups

| | Description |
|---|---|
| Insulin Glargine (Extension Period) | Insulin glargine starting dose: 0.2 Unit per kilogram of body weight or 10 Units. Insulin titration (by 2 or 4 Units) every 3 days according to the median value of Fast Plasma Glucose of the last 3 days |

Measured Values

| | Insulin Glargine (Extension Period) |
|---|---|
| Number of Participants Analyzed | 154 |
| Percentage of Patients Whose Glycosylated Haemoglobin (HbA1c) <7% at the End of the Extension Period<br>[units: percentage of participants] | 22.7 |

7. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Self-Monitored Fasting Plasma Glucose (SMFPG) Measurements: Change From Baseline to the End of the Comparative Period |
| Measure Description | SMFPG = mean value of Self-Monitored Fasting Plasma Glucose measurements over 3 consecutive days in the week before each visit<br><br>Value at the end of the comparative period defined as last available value during the comparative period (i.e. last-observation-carried-forward [LOCF] value)<br><br>Change = LOCF value - baseline value |
| Time Frame | baseline (week 0), week 6, week 12, week 18, week 24 |
| Safety Issue? | No |

Analysis Population Description

The population analyzed for this outcome measure consisted of the subset of mITT patients who had at least one SMFPG value on treatment during the comparative period.

Reporting Groups

| | Description |
|---|---|
| Insulin Glargine | Insulin glargine starting dose: 0.2 Unit per kilogram of body weight or 10 Units. Insulin titration (by 2 or 4 Units) every 3 days according to the median value of Fast Plasma Glucose of the last 3 days. |
| Liraglutide | Liraglutide dose: 0.6 mg/day during the first week, 1.2 mg/day during the second week and 1.8 mg/day until week 24. |

Measured Values

| | Insulin Glargine | Liraglutide |
|---|---|---|
| Number of Participants Analyzed | 468 | 452 |
| Self-Monitored Fasting Plasma Glucose (SMFPG) Measurements: Change From Baseline to the End of the Comparative Period<br>[units: mg/dL]<br>Mean (Standard Deviation) | -65.25 (50.95) | -37.23 (47.31) |

8. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Self-Monitored Fasting Plasma Glucose (SMFPG) Measurements: Change From Beginning to the End of the Extension Period |
| Measure Description | SMFPG = mean value of Self-Monitored Fasting Plasma Glucose measurements over 3 consecutive days in the week before each visit<br><br>Value at the end of the extension period defined as last available value during the extension period (i.e. last-observation-carried-forward [LOCF] value)<br><br>Change = LOCF value - week 24 value |
| Time Frame | week 24, week 30, week 36, week 48 |
| Safety Issue? | No |

Analysis Population Description

The population analyzed for this outcome measure consisted of the subset of mITT (extension) patients who had SMFPG value both at beginning of the extension and at least one value on treatment during the extension period.

Reporting Groups

| | Description |
|---|---|
| Insulin Glargine (Extension Period) | Insulin glargine starting dose: 0.2 Unit per kilogram of body weight or 10 Units. Insulin titration (by 2 or 4 Units) every 3 days according to the median value of Fast Plasma Glucose of the last 3 days |

Measured Values

| | Insulin Glargine (Extension Period) |
|---|---|
| Number of Participants Analyzed | 147 |
| Self-Monitored Fasting Plasma Glucose (SMFPG) Measurements: Change From Beginning to the End of the Extension Period<br>[units: mg/dL]<br>Mean (Standard Deviation) | -44.63 (45.47) |

9. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Self-Monitored 7-point Plasma Glucose (PG) Profile: Change From Baseline to the End of the Comparative Period |
| Measure Description | Self-monitored 7-point plasma glucose profiles (before and 2 hours after the start of breakfast, lunch and dinner, and at bedtime) recorded on 3 consecutive days in the week before each visit<br>Value at the end of the comparative period defined as last available value during the comparative period (i.e. last-observation-carried-forward [LOCF] value)<br>Change = LOCF value - baseline value |
| Time Frame | baseline (week 0), week 12, week 24 |
| Safety Issue? | No |

Analysis Population Description

The population considered was the mITT population but due to missing values, different subsets of this mITT population were analyzed for each time point of the profile.

Reporting Groups

| | Description |
|---|---|
| Insulin Glargine | Insulin glargine starting dose: 0.2 Unit per kilogram of body weight or 10 Units. Insulin titration (by 2 or 4 Units) every 3 days according to the median value of Fast Plasma Glucose of the last 3 days. |
| Liraglutide | Liraglutide dose: 0.6 mg/day during the first week, 1.2 mg/day during the second week and 1.8 mg/day until week 24. |

Measured Values

| | Insulin Glargine | Liraglutide |
|---|---|---|
| Number of Participants Analyzed | 474 | 470 |
| Self-Monitored 7-point Plasma Glucose (PG) Profile: Change From Baseline to the End of the Comparative Period<br>[units: mg/dL]<br>Mean (Standard Deviation) | | |
| Before breakfast (N ig = 448 & N l = 409) | -65.92 (50.29) | -38.64 (46.17) |
| After breakfast (N ig = 440 & N l = 397) | -66.70 (63.29) | -55.35 (61.56) |
| Before lunch (N ig = 438 & N l = 404) | -50.16 (59.53) | -39.13 (58.78) |
| After lunch (N ig = 433 & N l = 406) | -43.00 (58.42) | -41.82 (61.16) |
| Before dinner (N ig = 434 & N l = 400) | -40.84 (58.88) | -36.88 (58.49) |
| After dinner (N ig = 426 & N l = 396) | -42.6 (61.74) | -45.04 (60.42) |
| At bedtime (N ig = 380 & N l = 351) | -43.11 (60.37) | -44.06 (59.80) |

10. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Self-Monitored 7-point Plasma Glucose (PG) Profile: Change From Beginning to the End of the Extension Period |
| Measure Description | Self-monitored 7-point plasma glucose profiles (before and 2 hours after the start of breakfast, lunch and dinner, and at bedtime) recorded on 3 consecutive days in the week before each visit<br><br>Value at the end of the extension period defined as last available value during the extension period (i.e. last-observation-carried-forward [LOCF] value)<br><br>Change = LOCF value - week 24 value |
| Time Frame | week 24, week 36, week 48 |
| Safety Issue? | No |

Analysis Population Description

The population considered was the mITT population (extension) but due to missing values, different subsets of this population were analyzed for each time point of the profile.

Reporting Groups

| | Description |
|---|---|
| Insulin Glargine (Extension Period) | Insulin glargine starting dose: 0.2 Unit per kilogram of body weight or 10 Units. Insulin titration (by 2 or 4 Units) every 3 days according to the median value of Fast Plasma Glucose of the last 3 days |

Measured Values

| | Insulin Glargine (Extension Period) |
|---|---|
| Number of Participants Analyzed | 154 |
| Self-Monitored 7-point Plasma Glucose (PG) Profile: Change From Beginning to the End of the Extension Period<br>[units: mg/dL]<br>Mean (Standard Deviation) | |
| Before breakfast (N=143) | -46.13 (44.89) |
| After breakfast (N=134) | -27.67 (52.37) |
| Before lunch (N=131) | -20.32 (57.58) |
| After lunch (N=134) | -11.50 (58.37) |
| Before dinner (N=133) | -12.56 (54.57) |
| After dinner (N=130) | -2.28 (54.55) |
| At bedtime (N=127) | -14.94 (52.67) |

11. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Body Weight: Change From Baseline to the End of the Comparative Period |
| Measure Description | Change = Last weight value measured during the comparative period (LOCF value) - weight value at baseline |
| Time Frame | baseline (week 0), week 2, week 6, week 12, week 18, week 24 |
| Safety Issue? | No |

Analysis Population Description

The population analyzed for this outcome measure consisted of the subset of mITT patients who had at least one weight value on treatment during the comparative period.

Reporting Groups

| | Description |
|---|---|
| Insulin Glargine | Insulin glargine starting dose: 0.2 Unit per kilogram of body weight or 10 Units. Insulin titration (by 2 or 4 Units) every 3 days according to the median value of Fast Plasma Glucose of the last 3 days. |
| Liraglutide | Liraglutide dose: 0.6 mg/day during the first week, 1.2 mg/day during the second week and 1.8 mg/day until week 24. |

Measured Values

| | Insulin Glargine | Liraglutide |
|---|---|---|
| Number of Participants Analyzed | 474 | 468 |
| Body Weight: Change From Baseline to the End of the Comparative Period<br>[units: kg]<br>Mean (Standard Deviation) | 1.98 (3.95) | -2.99 (3.64) |

12. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Body Weight: Change From Beginning to End of the Extension Period |
| Measure Description | Change = Last weight value measured during the extension period (LOCF value) - weight value at beginning of the Extension Period (Week 24) |
| Time Frame | week 24, week 30, week 36, week 48 |
| Safety Issue? | No |

Analysis Population Description

The population analyzed for this outcome measure consisted of the mITT population (extension).

Reporting Groups

| | Description |
|---|---|
| Insulin Glargine (Extension Period) | Insulin glargine starting dose: 0.2 Unit per kilogram of body weight or 10 Units. Insulin titration (by 2 or 4 Units) every 3 days according to the median value of Fast Plasma Glucose of the last 3 days |

Measured Values

| | Insulin Glargine (Extension Period) |
|---|---|
| Number of Participants Analyzed | 154 |

| | Insulin Glargine (Extension Period) |
|---|---|
| Body Weight: Change From Beginning to End of the Extension Period<br>[units: kg]<br>Mean (Standard Deviation) | 4.35 (3.39) |

13. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Daily Dose of Insulin Glargine |
| Measure Description | |
| Time Frame | week 1, week 2, week 6, week 12, week 24 |
| Safety Issue? | No |

Analysis Population Description

The population considered was the mITT population but due to missing values, different subsets of this mITT population were analyzed at each week.

Reporting Groups

| | Description |
|---|---|
| Insulin Glargine | Insulin glargine starting dose: 0.2 Unit per kilogram of body weight or 10 Units. Insulin titration (by 2 or 4 Units) every 3 days according to the median value of Fast Plasma Glucose of the last 3 days. |

Measured Values

| | Insulin Glargine |
|---|---|
| Number of Participants Analyzed | 474 |
| Daily Dose of Insulin Glargine<br>[units: Unit (U)]<br>Mean (Standard Deviation) | |
| Start of treatment (N=472) | 13.39 (4.87) |
| Week 1 (N=470) | 17.74 (6.52) |
| Week 2 (N=470) | 22.06 (8.40) |
| Week 6 (N=470) | 34.67 (17.03) |
| Week 12 (N=463) | 44.40 (26.63) |
| Week 18 (N=454) | 48.65 (31.03) |
| Week 24 (N=459) | 51.67 (34.05) |

| | Insulin Glargine |
|---|---|
| End comparative period (LOCF) (N=474) | 51.24 (33.93) |

14. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Daily Dose of Liraglutide |
| Measure Description | |
| Time Frame | week 1, week 2, week 6, week 12, week 24 |
| Safety Issue? | No |

Analysis Population Description

The population considered was the mITT population but due to missing values, different subsets of this mITT population were analyzed at each week.

Reporting Groups

| | Description |
|---|---|
| Liraglutide | Liraglutide dose: 0.6 mg/day during the first week, 1.2 mg/day during the second week and 1.8 mg/day until week 24. |

Measured Values

| | Liraglutide |
|---|---|
| Number of Participants Analyzed | 470 |
| Daily Dose of Liraglutide<br>[units: mg]<br>Mean (Standard Deviation) | |
| Start of treatment (N=470) | 0.60 (0.00) |
| Week 1 (N=463) | 0.91 (0.31) |
| Week 2 (N=458) | 1.49 (0.33) |
| Week 6 (N=444) | 1.72 (0.21) |
| Week 12 (N=426) | 1.73 (0.19) |
| Week 18 (N=415) | 1.74 (0.18) |
| Week 24 (N=431) | 1.73 (0.21) |
| End comparative period (LOCF) (N=470) | 1.71 (0.24) |

15. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Daily Dose of Insulin Glargine Administered During the Extension Period |
| Measure Description | |
| Time Frame | week 30, week 36, week 48 |
| Safety Issue? | No |

Analysis Population Description

The population considered was the mITT population (extension) but due to missing values, different subsets of this mITT population were analyzed at each week.

Reporting Groups

| | Description |
|---|---|
| Insulin Glargine (Extension Period) | Insulin glargine starting dose: 0.2 Unit per kilogram of body weight or 10 Units. Insulin titration (by 2 or 4 Units) every 3 days according to the median value of Fast Plasma Glucose of the last 3 days |

Measured Values

| | Insulin Glargine (Extension Period) |
|---|---|
| Number of Participants Analyzed | 154 |
| Daily Dose of Insulin Glargine Administered During the Extension Period<br>[units: Unit (U)]<br>Mean (Standard Deviation) | |
| Start of treatment (N=154) | 15.77 (4.53) |
| Week 30 (N=151) | 37.49 (15.70) |
| Week 36 (N=150) | 46.21 (23.06) |
| Week 48 (N=151) | 50.68 (27.33) |

16. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Hypoglycemia Occurence: Number of Patients With at Least One Episode of Symptomatic / Severe Symptomatic Hypoglycemia During the Comparative Period |

| | |
|---|---|
| Measure Description | Symptomatic hypoglycemia was defined as an event with clinical symptoms that were considered to result from hypoglycemia.<br><br>Severe symptomatic hypoglycemia was defined as an event with clinical symptoms that were considered to result from hypoglycemia, requiring the assistance of another person for active administration of carbohydrate, glucagon or other countermeasure because the patient could not treat him/herself due to acute neurological impairment directly resulting from the hypoglycemia (assistance by another person when the patient could have treated him/herself was not considered as requiring assistance)and one of the following criteria:<br><br>• The event was associated with a measured PG level < 36 mg/dL (2 mmol/L),<br>• Or, in absence of PG value, the event was associated with neurological recovery attributable to the restoration of PG to normal, after oral carbohydrate, intravenous glucose or glucagon administration. |
| Time Frame | all across the comparative period (from week 0 to week 24) |
| Safety Issue? | Yes |

Analysis Population Description

The population analyzed was the safety population i.e. all randomized and treated patients.

Reporting Groups

| | Description |
|---|---|
| Insulin Glargine | Insulin glargine starting dose: 0.2 Unit per kilogram of body weight or 10 Units. Insulin titration (by 2 or 4 Units) every 3 days according to the median value of Fast Plasma Glucose of the last 3 days. |
| Liraglutide | Liraglutide dose: 0.6 mg/day during the first week, 1.2 mg/day during the second week and 1.8 mg/day until week 24. |

Measured Values

| | Insulin Glargine | Liraglutide |
|---|---|---|
| Number of Participants Analyzed | 484 | 481 |
| Hypoglycemia Occurence: Number of Patients With at Least One Episode of Symptomatic / Severe Symptomatic Hypoglycemia During the Comparative Period<br>[units: participants] | | |
| symptomatic hypoglycemia | 219 | 85 |
| severe symptomatic hypoglycemia | 0 | 2 |

17. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Hypoglycemia Occurence: Number of Patients With at Least One Episode of Symptomatic / Severe Symptomatic Hypoglycemia During the Extension Period |
| Measure Description | Symptomatic hypoglycemia was defined as an event with clinical symptoms that were considered to result from hypoglycemia.<br><br>Severe symptomatic hypoglycemia was defined as an event with clinical symptoms that were considered to result from hypoglycemia, requiring the assistance of another person for active administration of carbohydrate, glucagon or other countermeasure because the patient could not treat him/herself due to acute neurological impairment directly resulting from the hypoglycemia (assistance by another person when the patient could have treated him/herself was not considered as requiring assistance)and one of the following criteria:<br><br>• The event was associated with a measured PG level < 36 mg/dL (2 mmol/L),<br>• Or, in absence of PG value, the event was associated with neurological recovery attributable to the restoration of PG to normal, after oral carbohydrate, intravenous glucose or glucagon administration. |
| Time Frame | all across the extension period (from week 24 to week 48) |
| Safety Issue? | Yes |

Analysis Population Description

The population analyzed was the safety population (extension) i.e. all treated patients during the extension period.

Reporting Groups

| | Description |
|---|---|
| Insulin Glargine (Extension Period) | Insulin glargine starting dose: 0.2 Unit per kilogram of body weight or 10 Units. Insulin titration (by 2 or 4 Units) every 3 days according to the median value of Fast Plasma Glucose of the last 3 days |

Measured Values

| | Insulin Glargine (Extension Period) |
|---|---|
| Number of Participants Analyzed | 160 |
| Hypoglycemia Occurence: Number of Patients With at Least One Episode of Symptomatic / Severe Symptomatic Hypoglycemia During the Extension Period<br>[units: participants] | |
| symptomatic hypoglycemia | 58 |
| severe symptomatic hypoglycemia | 0 |

## Reported Adverse Events

| | |
|---|---|
| Time Frame | Adverse events were collected throughout the study from the time the patient signed the informed consent until 7 days after the last dose of study treatment. |
| Additional Description | The population analyzed was the safety population defined for each of the 2 periods (comparative and extension) as the patients treated with at least one dose of the study treatment during the considered period. |

Reporting Groups

| | Description |
|---|---|
| Comparative Period: Insulin Glargine | Insulin glargine starting dose: 0.2 Unit per kilogram of body weight or 10 Units. Insulin titration (by 2 or 4 Units) every 3 days according to the median value of Fast Plasma Glucose of the last 3 days |
| Comparative Period: Liraglutide | Liraglutide dose: 0.6 mg/day during the first week, 1.2 mg/day during the second week and 1.8 mg/day until week 24 (comparative period) |
| Extension Period: Insulin Glargine | Following a treatment with liraglutide during the comparative period, those patients have received insulin glargine during the extension period.<br>Insulin glargine starting dose: 0.2 Unit per kilogram of body weight or 10 Units. Insulin titration (by 2 or 4 Units) every 3 days according to the median value of Fast Plasma Glucose of the last 3 days |

Serious Adverse Events

| | Comparative Period: Insulin Glargine | Comparative Period: Liraglutide | Extension Period: Insulin Glargine |
|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| Total | 11/484 (2.27%) | 15/481 (3.12%) | 5/160 (3.12%) |
| Cardiac disorders | | | |
| Atrioventricular block second degree [A] * | 1/484 (0.21%) | 0/481 (0%) | 0/160 (0%) |
| Cardiac arrest [A] * | 0/484 (0%) | 0/481 (0%) | 1/160 (0.63%) |
| Gastrointestinal disorders | | | |
| Faecaloma [A] * | 0/484 (0%) | 1/481 (0.21%) | 0/160 (0%) |
| Pancreatitis acute [A] * | 0/484 (0%) | 1/481 (0.21%) | 0/160 (0%) |
| Small intestinal obstruction [A] * | 1/484 (0.21%) | 0/481 (0%) | 0/160 (0%) |
| Vomiting [A] * | 1/484 (0.21%) | 0/481 (0%) | 0/160 (0%) |

| | Comparative Period: Insulin Glargine | Comparative Period: Liraglutide | Extension Period: Insulin Glargine |
|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| General disorders | | | |
| Chest pain [A] * | 0/484 (0%) | 0/481 (0%) | 1/160 (0.63%) |
| Pyrexia [A] * | 1/484 (0.21%) | 0/481 (0%) | 0/160 (0%) |
| Hepatobiliary disorders | | | |
| Cholecystitis [A] * | 0/484 (0%) | 1/481 (0.21%) | 0/160 (0%) |
| Infections and infestations | | | |
| Cellulitis [A] * | 0/484 (0%) | 1/481 (0.21%) | 0/160 (0%) |
| Cystitis [A] * | 0/484 (0%) | 1/481 (0.21%) | 0/160 (0%) |
| Diabetic gangrene [A] * | 1/484 (0.21%) | 0/481 (0%) | 0/160 (0%) |
| Endocarditis bacterial [A] * | 0/484 (0%) | 1/481 (0.21%) | 0/160 (0%) |
| Osteomyelitis [A] * | 0/484 (0%) | 1/481 (0.21%) | 0/160 (0%) |
| Pneumonia [A] * | 0/484 (0%) | 0/481 (0%) | 1/160 (0.63%) |
| Urinary tract infection [A] * | 1/484 (0.21%) | 0/481 (0%) | 0/160 (0%) |
| Investigations | | | |
| Blood glucose increased [A] * | 0/484 (0%) | 1/481 (0.21%) | 0/160 (0%) |
| Metabolism and nutrition disorders | | | |
| Dehydration [A] * | 1/484 (0.21%) | 0/481 (0%) | 0/160 (0%) |
| Musculoskeletal and connective tissue disorders | | | |
| Intervertebral disc protrusion [A] * | 0/484 (0%) | 0/481 (0%) | 1/160 (0.63%) |
| Rotator cuff syndrome [A] * | 1/484 (0.21%) | 0/481 (0%) | 0/160 (0%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer [A] * | 0/484 (0%) | 1/481 (0.21%) | 0/160 (0%) |

| | Comparative Period: Insulin Glargine | Comparative Period: Liraglutide | Extension Period: Insulin Glargine |
|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| Non-Hodgkin's lymphoma [A] * | 0/484 (0%) | 1/481 (0.21%) | 0/160 (0%) |
| Pancreatic carcinoma [A] * | 1/484 (0.21%) | 1/481 (0.21%) | 0/160 (0%) |
| Prostate cancer [A] * | 1/484 (0.21%) | 0/481 (0%) | 0/160 (0%) |
| Thyroid cancer [A] * | 1/484 (0.21%) | 0/481 (0%) | 0/160 (0%) |
| Nervous system disorders | | | |
| Carpal tunnel syndrome [A] * | 0/484 (0%) | 1/481 (0.21%) | 0/160 (0%) |
| Cerebrovascular accident [A] * | 1/484 (0.21%) | 2/481 (0.42%) | 0/160 (0%) |
| Headache [A] * | 0/484 (0%) | 1/481 (0.21%) | 0/160 (0%) |
| Ischaemic stroke [A] * | 1/484 (0.21%) | 0/481 (0%) | 0/160 (0%) |
| Presyncope [A] * | 0/484 (0%) | 1/481 (0.21%) | 0/160 (0%) |
| Psychiatric disorders | | | |
| Suicidal behaviour [A] * | 1/484 (0.21%) | 0/481 (0%) | 0/160 (0%) |
| Renal and urinary disorders | | | |
| Oliguria [A] * | 0/484 (0%) | 1/481 (0.21%) | 0/160 (0%) |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease [A] * | 0/484 (0%) | 1/481 (0.21%) | 0/160 (0%) |
| Pleurisy [A] * | 0/484 (0%) | 0/481 (0%) | 1/160 (0.63%) |

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA

Other Adverse Events

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

| | Comparative Period: Insulin Glargine | Comparative Period: Liraglutide | Extension Period: Insulin Glargine |
|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| Total | 92/484 (19.01%) | 239/481 (49.69%) | 22/160 (13.75%) |
| Gastrointestinal disorders | | | |
| Constipation [A] * | 6/484 (1.24%) | 26/481 (5.41%) | 0/160 (0%) |
| Diarrhoea [A] * | 18/484 (3.72%) | 62/481 (12.89%) | 5/160 (3.12%) |
| Dyspepsia [A] * | 4/484 (0.83%) | 25/481 (5.2%) | 1/160 (0.63%) |
| Nausea [A] * | 13/484 (2.69%) | 146/481 (30.35%) | 2/160 (1.25%) |
| Vomiting [A] * | 8/484 (1.65%) | 46/481 (9.56%) | 1/160 (0.63%) |
| Infections and infestations | | | |
| Nasopharyngitis [A] * | 38/484 (7.85%) | 35/481 (7.28%) | 12/160 (7.5%) |
| Metabolism and nutrition disorders | | | |
| Decreased appetite [A] * | 1/484 (0.21%) | 45/481 (9.36%) | 0/160 (0%) |
| Nervous system disorders | | | |
| Headache [A] * | 24/484 (4.96%) | 29/481 (6.03%) | 2/160 (1.25%) |

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA

## 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 abstract/manuscript for comment at least 20/45 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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