



Clinical trial results:

A 24 week randomised, open label, 3 parallel-group comparison of once and twice daily biphasic insulin aspart (BIAsp) 30 plus sitagliptin and twice daily BIAsp 30, all in combination with metformin in insulin naïve type 2 diabetic subjects inadequately controlled on sitagliptin and metformin.

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2011-004930-33 |
| Trial protocol | GR PT |
| Global end of trial date | 18 October 2013 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 15 March 2016 |
| First version publication date | 26 July 2015 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | BIASP-3963 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01519674 |
| WHO universal trial number (UTN) | U1111-1125-0850 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novo Nordisk A/S |
| Sponsor organisation address | Novo Allé, Bagsvaerd, Denmark, 2880 |
| Public contact | Global Clinical Registry (GCR,1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com |
| Scientific contact | Global Clinical Registry (GCR,1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 28 May 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 18 October 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 October 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy in terms of glycaemic control of biphasic insulin aspart 30 (BIAsp 30) twice daily + sitagliptin + metformin, BIAsp 30 twice daily + metformin and BIAsp 30 once daily + sitagliptin + metformin in subjects with type 2 diabetes inadequately controlled on sitagliptin and metformin (\pm other oral anti-diabetic drugs (OADs))

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2008) and ICH Good Clinical Practice (1996).

Background therapy:

Subjects on pre-trial metformin (1000 mg/day) (\pm additional OAD treatment) continued their medication. Subjects on pre-trial sitagliptin (100 mg/day) either continued or discontinued their sitagliptin treatment depending on the treatment group the subjects were randomised to.

Evidence for comparator:

Not applicable.

| | |
|---|--------------|
| Actual start date of recruitment | 04 June 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 105 |
| Country: Number of subjects enrolled | Australia: 34 |
| Country: Number of subjects enrolled | Brazil: 73 |
| Country: Number of subjects enrolled | India: 162 |
| Country: Number of subjects enrolled | Malaysia: 26 |
| Country: Number of subjects enrolled | Korea, Republic of: 51 |
| Country: Number of subjects enrolled | Thailand: 22 |
| Country: Number of subjects enrolled | Turkey: 35 |
| Country: Number of subjects enrolled | Portugal: 22 |
| Country: Number of subjects enrolled | Greece: 52 |
| Worldwide total number of subjects | 582 |
| EEA total number of subjects | 74 |

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 484 |
| From 65 to 84 years | 98 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 60 sites in 10 countries as follows: Argentina (6); Australia (2); Brazil (4); Greece (5); India (17); Malaysia (3); Portugal (6); Republic of Korea (7); Thailand (5); Turkey (5)

Pre-assignment

Screening details:

Subjects on pre-trial metformin (1000 mg/day) (\pm additional OAD treatment) continued their medication. Subjects on pre-trial sitagliptin (100 mg/day) either continued or discontinued their sitagliptin treatment depending on the treatment group the subjects were randomised to.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

Not applicable

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | BID+Met |

Arm description:

Biphasic insulin aspart 30 (BIAsp 30) was injected twice daily, subcutaneously (under the skin) for 24 weeks. Subjects continued on their pre-trial metformin (1000 mg/day) treatment.

| | |
|--|---|
| Arm type | Active comparator |
| Investigational medicinal product name | NovoMix 30 FlexPen 100 U/mL suspension for injection in a prefilled pen (BIAsp-30). |
| Investigational medicinal product code | |
| Other name | INSULIN ASPART |
| Pharmaceutical forms | Suspension for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Biphasic insulin aspart 30 (BIAsp 30) was injected twice daily, 6 U before breakfast and 6 U before dinner (evening meal), subcutaneously (under the skin) for 24 weeks. Dosing of BIAsp 30 was adjusted individually according to the titration guideline and the subject's self-measured plasma glucose (SMPG) levels. Subjects continued on their pre-trial metformin (1000 mg/day) treatment.

| | |
|------------------|--------------|
| Arm title | BID+Sita+Met |
|------------------|--------------|

Arm description:

Biphasic insulin aspart 30 (BIAsp 30) was injected twice daily, subcutaneously under the skin) for 24 weeks. Subjects continued on their pre-trial metformin (1000 mg/day) and sitagliptin (100 mg/day) treatments.

| | |
|--|---|
| Arm type | Active comparator |
| Investigational medicinal product name | NovoMix 30 FlexPen 100 U/mL suspension for injection in a prefilled pen (BIAsp 30). |
| Investigational medicinal product code | |
| Other name | INSULIN ASPART |
| Pharmaceutical forms | Suspension for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Biphasic insulin aspart 30 (BIAsp 30) was injected twice daily, 6 U before breakfast and 6 U before dinner (evening meal), subcutaneously (under the skin) for 24 weeks. Dosing of BIAsp 30 was adjusted individually according to the titration guideline and the subject's self-measured plasma glucose (SMPG)

levels. Subjects continued on their pre-trial metformin (1000 mg/day) and sitagliptin (100 mg/day) treatments.

| | |
|---|---|
| Arm title | OD+Sita+Met |
| Arm description: Biphasic insulin aspart 30 (BIAsp 30) was injected once daily, subcutaneously (under the skin) for 24 weeks. Subjects continued on their pre-trial metformin (1000 mg/day) and sitagliptin (100 mg/day) treatments. | |
| Arm type | Active comparator |
| Investigational medicinal product name | NovoMix 30 FlexPen 100 U/mL suspension for injection in a prefilled pen (BIAsp 30). |
| Investigational medicinal product code | |
| Other name | INSULIN ASPART |
| Pharmaceutical forms | Suspension for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Biphasic insulin aspart 30 (BIAsp 30) was injected once daily, 12 U before dinner (evening meal), subcutaneously (under the skin) for 24 weeks. Dosing of BIAsp 30 was adjusted individually according to the titration guideline and the subject's self-measured plasma glucose (SMPG) levels. Subjects continued on their pre-trial metformin (1000 mg/day) and sitagliptin (100 mg/day) treatments.

| Number of subjects in period 1 | BID+Met | BID+Sita+Met | OD+Sita+Met |
|---------------------------------------|---------|--------------|-------------|
| Started | 194 | 195 | 193 |
| Completed | 173 | 182 | 181 |
| Not completed | 21 | 13 | 12 |
| Adverse event, non-fatal | 3 | 3 | - |
| Withdrawal criteria | 7 | 2 | 7 |
| Unclassified | 10 | 4 | 3 |
| Lack of efficacy | 1 | 1 | 1 |
| Protocol deviation | - | 3 | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | BID+Met |
|-----------------------|---------|

Reporting group description:

Biphasic insulin aspart 30 (BIAsp 30) was injected twice daily, subcutaneously (under the skin) for 24 weeks. Subjects continued on their pre-trial metformin (1000 mg/day) treatment.

| | |
|-----------------------|--------------|
| Reporting group title | BID+Sita+Met |
|-----------------------|--------------|

Reporting group description:

Biphasic insulin aspart 30 (BIAsp 30) was injected twice daily, subcutaneously under the skin) for 24 weeks. Subjects continued on their pre-trial metformin (1000 mg/day) and sitagliptin (100 mg/day) treatments.

| | |
|-----------------------|-------------|
| Reporting group title | OD+Sita+Met |
|-----------------------|-------------|

Reporting group description:

Biphasic insulin aspart 30 (BIAsp 30) was injected once daily, subcutaneously (under the skin) for 24 weeks. Subjects continued on their pre-trial metformin (1000 mg/day) and sitagliptin (100 mg/day) treatments.

| Reporting group values | BID+Met | BID+Sita+Met | OD+Sita+Met |
|------------------------|---------|--------------|-------------|
| Number of subjects | 194 | 195 | 193 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|----------------------------------|--------|--------|--------|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 54.8 | 56.3 | 55.7 |
| standard deviation | ± 9.5 | ± 10.2 | ± 10.4 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 83 | 101 | 97 |
| Male | 111 | 94 | 96 |
| Body weight | | | |
| Units: Kg | | | |
| arithmetic mean | 79.4 | 78.3 | 77.5 |
| standard deviation | ± 15.8 | ± 16.1 | ± 16.8 |
| Body Mass Index | | | |
| Units: kg/m2 | | | |
| arithmetic mean | 29.3 | 29.4 | 29.4 |
| standard deviation | ± 4.3 | ± 4.5 | ± 5 |
| Glycosylated haemoglobin (HbA1c) | | | |
| Units: Percentage (%) | | | |
| arithmetic mean | 8.4 | 8.4 | 8.4 |
| standard deviation | ± 0.8 | ± 0.8 | ± 0.8 |
| Fasting plasma glucose (FPG) | | | |
| Units: mmol/L | | | |
| arithmetic mean | 8.9 | 9.3 | 8.7 |
| standard deviation | ± 2.2 | ± 2.8 | ± 2.7 |

| Reporting group values | Total | | |
|------------------------|-------|--|--|
| Number of subjects | 582 | | |

| | | | |
|--|-----|--|--|
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 281 | | |
| Male | 301 | | |
| Body weight Units: Kg arithmetic mean standard deviation | - | | |
| Body Mass Index Units: kg/m2 arithmetic mean standard deviation | - | | |
| Glycosylated haemoglobin (HbA1c) Units: Percentage (%) arithmetic mean standard deviation | - | | |
| Fasting plasma glucose (FPG) Units: mmol/L arithmetic mean standard deviation | - | | |

End points

End points reporting groups

| | |
|---|--------------|
| Reporting group title | BID+Met |
| Reporting group description: Biphasic insulin aspart 30 (BIAsp 30) was injected twice daily, subcutaneously (under the skin) for 24 weeks. Subjects continued on their pre-trial metformin (1000 mg/day) treatment. | |
| Reporting group title | BID+Sita+Met |
| Reporting group description: Biphasic insulin aspart 30 (BIAsp 30) was injected twice daily, subcutaneously under the skin) for 24 weeks. Subjects continued on their pre-trial metformin (1000 mg/day) and sitagliptin (100 mg/day) treatments. | |
| Reporting group title | OD+Sita+Met |
| Reporting group description: Biphasic insulin aspart 30 (BIAsp 30) was injected once daily, subcutaneously (under the skin) for 24 weeks. Subjects continued on their pre-trial metformin (1000 mg/day) and sitagliptin (100 mg/day) treatments. | |

Primary: Change From Baseline in HbA1c (Glycosylated Haemoglobin)

| | |
|---|--|
| End point title | Change From Baseline in HbA1c (Glycosylated Haemoglobin) |
| End point description: Mean change from baseline in HbA1c after 24 weeks of treatment. | |
| End point type | Primary |
| End point timeframe: Week 0 to Week 24 | |

| End point values | BID+Met | BID+Sita+Met | OD+Sita+Met | |
|---|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 183 | 189 | 187 | |
| Units: percentage of glycosylated haemoglobin | | | | |
| least squares mean (standard error) | -1.27 (± 0.07) | -1.51 (± 0.07) | -1.15 (± 0.07) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis 1 - BID + Met versus BID + Sita + Met |
| Statistical analysis description: Analysis method: The endpoint was analysed by means of a normal linear regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliptin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline HbA1c as independent variables. LOCF was applied. From this model, the treatment difference 'BID+Met' vs 'BID+Sita+Met' was estimated. | |
| Comparison groups | BID+Met v BID+Sita+Met |

| | |
|---|----------------------|
| Number of subjects included in analysis | 372 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| P-value | = 0.011 |
| Method | Regression, Linear |
| Parameter estimate | Treatment difference |
| Point estimate | 0.24 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.06 |
| upper limit | 0.43 |

Notes:

[1] - Test of no difference between the two treatments.

| | |
|-----------------------------------|---|
| Statistical analysis title | Analysis 2 - BID + Met versus OD + Sita + Met |
|-----------------------------------|---|

Statistical analysis description:

Method: The endpoint was analysed by means of a normal linear regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliptin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline HbA1c as independent variables. LOCF was applied. From this model, the treatment difference 'BID+Met' vs 'OD+Sita+Met' was estimated.

| | |
|---|-----------------------|
| Comparison groups | BID+Met v OD+Sita+Met |
| Number of subjects included in analysis | 370 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| P-value | = 0.231 |
| Method | Regression, Linear |
| Parameter estimate | Treatment difference |
| Point estimate | -0.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3 |
| upper limit | 0.07 |

Notes:

[2] - Test of no difference between the two treatments.

| | |
|-----------------------------------|--|
| Statistical analysis title | Analysis 3 - BID+Sita+Met versus OD + Sita + Met |
|-----------------------------------|--|

Statistical analysis description:

Method: The endpoint was analysed by means of a normal linear regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliptin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline HbA1c as independent variables. LOCF was applied. From this model, the treatment difference 'BID+Sita+Met' vs 'OD+Sita+Met' was estimated.

| | |
|---|----------------------------|
| Comparison groups | BID+Sita+Met v OD+Sita+Met |
| Number of subjects included in analysis | 376 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| P-value | < 0.001 |
| Method | Regression, Linear |
| Parameter estimate | Treatment difference |
| Point estimate | -0.36 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.54 |
| upper limit | -0.17 |

Notes:

[3] - Test of no difference between the two treatments.

Secondary: Responder for HbA1c, Proportion of Subjects Achieving Pre-defined HbA1c Targets (HbA1c < 7.0%)

| | |
|--|--|
| End point title | Responder for HbA1c, Proportion of Subjects Achieving Pre-defined HbA1c Targets (HbA1c < 7.0%) |
| End point description: Proportion of subjects achieving HbA1c below 7.0% after 24 weeks of treatment. Last observation carried forward (LOCF) has been applied. | |
| End point type | Secondary |
| End point timeframe: After 24 weeks of treatment | |

| End point values | BID+Met | BID+Sita+Met | OD+Sita+Met | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 194 | 195 | 193 | |
| Units: Percentage | | | | |
| number (not applicable) | 49.7 | 59.8 | 46.5 | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis 1 - BID + Met versus BID + Sita + Met |
| Statistical analysis description: The endpoint (achiever of HbA1c 7.0 % after 24 weeks of treatment [Y/N]) was analysed by means of a logistic regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliitin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline HbA1c as independent variables. LOCF was applied. From this model, the treatment odds ratio 'BID+Met' vs 'BID+Sita+Met' was estimated. | |
| Comparison groups | BID+Met v BID+Sita+Met |
| Number of subjects included in analysis | 389 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[4] |
| P-value | = 0.022 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.39 |
| upper limit | 0.93 |

Notes:

[4] - Test of no difference between the two treatments.

| Statistical analysis title | Analysis 2 - BID + Met versus OD + Sita + Met |
|---|---|
| Statistical analysis description: | |
| The endpoint (achiever of HbA1c < 7.0 % after 24 weeks of treatment [Y/N]) was analysed by means of a logistic regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliitin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline HbA1c as independent variables. LOCF was applied. From this model, the treatment odds ratio 'BID+Met' vs 'OD+Sita+Met' was estimated. | |
| Comparison groups | OD+Sita+Met v BID+Met |
| Number of subjects included in analysis | 387 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[5] |
| P-value | = 0.618 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 1.71 |

Notes:

[5] - Test of no difference between the two treatments.

| Statistical analysis title | Analysis 3 - BID+Sita+Met versus OD + Sita + Met |
|--|--|
| Statistical analysis description: | |
| The endpoint (achiever of HbA1c < 7.0 % after 24 weeks of treatment [Y/N]) was analysed by means of a logistic regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliitin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline HbA1c as independent variables. LOCF was applied. From this model, the treatment odds ratio 'BID+Sita+Met' vs 'OD+Sita+Met' was estimated. | |
| Comparison groups | BID+Sita+Met v OD+Sita+Met |
| Number of subjects included in analysis | 388 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[6] |
| P-value | = 0.005 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.2 |
| upper limit | 2.85 |

Notes:

[6] - Test of no difference between the two treatments.

Secondary: Responder for HbA1c, Proportion of Subjects Achieving Pre-defined HbA1c Targets (HbA1c ≤ 6.5%)

| | |
|-----------------|--|
| End point title | Responder for HbA1c, Proportion of Subjects Achieving Pre- |
|-----------------|--|

End point description:

Proportion of subjects achieving HbA1c equal to or below 6.5% after 24 weeks of treatment. Last observation carried forward (LOCF) has been applied.

End point type Secondary

End point timeframe:

After 24 weeks of treatment

| End point values | BID+Met | BID+Sita+Met | OD+Sita+Met | |
|-------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 183 | 189 | 187 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 30.6 | 40.7 | 25.1 | |

Statistical analyses

Statistical analysis title Analysis 1: BID+Met versus BID+Sita+Met

Statistical analysis description:

The endpoint (achiever of HbA1c \leq 6.5 % after 24 weeks of treatment [Y/N]) was analysed by means of a logistic regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliitin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline HbA1c as independent variables. LOCF was applied. From this model, the treatment odds ratio 'BID+Met' vs 'BID+Sita+Met' was estimated.

| | |
|---|------------------------|
| Comparison groups | BID+Met v BID+Sita+Met |
| Number of subjects included in analysis | 372 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[7] |
| P-value | = 0.02 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.59 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.38 |
| upper limit | 0.92 |

Notes:

[7] - Test of no difference between the two treatments.

Statistical analysis title Analysis 2: BID+Met versus OD+Sita+Met

Statistical analysis description:

The endpoint (achiever of HbA1c \leq 6.5 % after 24 weeks of treatment [Y/N]) was analysed by means of a logistic regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliitin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline HbA1c as independent variables. LOCF was applied. From this model, the treatment odds ratio 'BID+Met' vs 'OD+Sita+Met' was estimated.

| | |
|-------------------|-----------------------|
| Comparison groups | BID+Met v OD+Sita+Met |
|-------------------|-----------------------|

| | |
|---|----------------------|
| Number of subjects included in analysis | 370 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[8] |
| P-value | = 0.286 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 2.07 |

Notes:

[8] - Test of no difference between the two treatments.

| | |
|-----------------------------------|---|
| Statistical analysis title | Analysis 3: BID+Sita+Met versus OD+Sita+Met |
|-----------------------------------|---|

Statistical analysis description:

The endpoint (achiever of HbA1c \leq 6.5 % after 24 weeks of treatment [Y/N]) was analysed by means of a logistic regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliitin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline HbA1c as independent variables. LOCF was applied. From this model, the treatment odds ratio 'BID+Sita+Met' vs 'OD+Sita+Met' was estimated.

| | |
|---|----------------------------|
| Comparison groups | BID+Sita+Met v OD+Sita+Met |
| Number of subjects included in analysis | 376 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[9] |
| P-value | < 0.001 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.39 |
| upper limit | 3.47 |

Notes:

[9] - Test of no difference between the two treatments.

Secondary: Change From Baseline in Fasting Plasma Glucose (FPG)

| | |
|--|--|
| End point title | Change From Baseline in Fasting Plasma Glucose (FPG) |
| End point description: | |
| Mean change from baseline in fasting plasma glucose (FPG) after 24 weeks of treatment. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 0 to Week 24 | |

| End point values | BID+Met | BID+Sita+Met | OD+Sita+Met | |
|-------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 181 | 188 | 187 | |
| Units: mmol/L | | | | |
| least squares mean (standard error) | -1.9 (± 0.14) | -2.03 (± 0.14) | -1.96 (± 0.14) | |

Statistical analyses

| Statistical analysis title | Analysis 1: BID+Met versus BID+Sita+Met |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

The endpoint was analysed by means of a normal linear regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliitin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline FPG as independent variables. LOCF was applied. From this model, the treatment difference 'BID+Met' vs 'BID+Sita+Met' was estimated.

| | |
|---|------------------------|
| Comparison groups | BID+Met v BID+Sita+Met |
| Number of subjects included in analysis | 369 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[10] |
| P-value | = 0.52 |
| Method | Regression, Linear |
| Parameter estimate | Treatment difference |
| Point estimate | 0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.26 |
| upper limit | 0.52 |

Notes:

[10] - Test of no difference between the two treatments.

| Statistical analysis title | Analysis 2 - BID+Met versus OD+Sita+Met |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

The endpoint was analysed by means of a normal linear regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliitin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline FPG as independent variables. LOCF was applied. From this model, the treatment difference 'BID+Met' vs 'OD+Sita+Met' was estimated.

| | |
|---|-----------------------|
| Comparison groups | OD+Sita+Met v BID+Met |
| Number of subjects included in analysis | 368 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[11] |
| P-value | = 0.788 |
| Method | Regression, Linear |
| Parameter estimate | Treatment difference |
| Point estimate | 0.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.34 |
| upper limit | 0.45 |

Notes:

[11] - Test of no difference between the two treatments.

| | |
|--|--|
| Statistical analysis title | Analysis 3 - BID+Sita+Met versus OD+Sita+Met |
| Statistical analysis description: The endpoint was analysed by means of a normal linear regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliitin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline FPG as independent variables. LOCF was applied. From this model, the treatment difference 'BID+Sita+Met' vs 'OD+Sita+Met' was estimated. | |
| Comparison groups | BID+Sita+Met v OD+Sita+Met |
| Number of subjects included in analysis | 375 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[12] |
| P-value | = 0.708 |
| Method | Regression, Linear |
| Parameter estimate | Treatment difference |
| Point estimate | -0.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.46 |
| upper limit | 0.31 |

Notes:

[12] - Test of no difference between the two treatments.

Secondary: Prandial Plasma Glucose (PPG) Increments at Breakfast

| | |
|--|---|
| End point title | Prandial Plasma Glucose (PPG) Increments at Breakfast |
| End point description: Prandial plasma glucose increments at breakfast after 24 weeks of treatment. | |
| End point type | Secondary |
| End point timeframe: After 24 weeks of treatment | |

| | | | | |
|-------------------------------------|-----------------|-----------------|-----------------|--|
| End point values | BID+Met | BID+Sita+Met | OD+Sita+Met | |
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 184 | 187 | 184 | |
| Units: mmol/L | | | | |
| least squares mean (standard error) | 2.01 (± 0.19) | 1.73 (± 0.19) | 2.89 (± 0.19) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis 1 - BID + Met versus BID + Sita + Met |
| Statistical analysis description: The endpoint was analysed by means of a normal linear regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliitin and metformin] and no previous use of | |

such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline PG increment at breakfast as independent variables. LOCF was applied. From this model, the treatment difference 'BID+Met' vs 'BID+Sita+Met' was estimated.

| | |
|---|------------------------|
| Comparison groups | BID+Met v BID+Sita+Met |
| Number of subjects included in analysis | 371 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[13] |
| P-value | = 0.291 |
| Method | Regression, Linear |
| Parameter estimate | Treatment difference |
| Point estimate | 0.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.24 |
| upper limit | 0.81 |

Notes:

[13] - Test of no difference between the two treatments.

| | |
|-----------------------------------|---|
| Statistical analysis title | Analysis 2 - BID + Met versus OD + Sita + Met |
|-----------------------------------|---|

Statistical analysis description:

The endpoint was analysed by means of a normal linear regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliitin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline PG increment at breakfast as independent variables. LOCF was applied. From this model, the treatment difference 'BID+Met' vs 'OD+Sita+Met' was estimated.

| | |
|---|-----------------------|
| Comparison groups | BID+Met v OD+Sita+Met |
| Number of subjects included in analysis | 368 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[14] |
| P-value | = 0.001 |
| Method | Regression, Linear |
| Parameter estimate | Treatment difference |
| Point estimate | -0.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.41 |
| upper limit | -0.35 |

Notes:

[14] - Test of no difference between the two treatments.

| | |
|-----------------------------------|--|
| Statistical analysis title | Analysis 3-BID + Sita + Met versus OD + Sita + Met |
|-----------------------------------|--|

Statistical analysis description:

The endpoint was analysed by means of a normal linear regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliitin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline PG increment at breakfast as independent variables. LOCF was applied. From this model, the treatment difference 'BID+Sita+Met' vs 'OD+Sita+Met' was estimated.

| | |
|-------------------|----------------------------|
| Comparison groups | BID+Sita+Met v OD+Sita+Met |
|-------------------|----------------------------|

| | |
|---|-----------------------|
| Number of subjects included in analysis | 371 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[15] |
| P-value | < 0.001 |
| Method | Regression, Linear |
| Parameter estimate | Treatment difference |
| Point estimate | -1.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.69 |
| upper limit | -0.64 |

Notes:

[15] - Test of no difference between the two treatments.

Secondary: Prandial Plasma Glucose (PPG) Increments at Lunch

| | |
|------------------------|--|
| End point title | Prandial Plasma Glucose (PPG) Increments at Lunch |
| End point description: | Prandial plasma glucose increments at lunch after 24 weeks of treatment. |
| End point type | Secondary |
| End point timeframe: | After 24 weeks of treatment |

| End point values | BID+Met | BID+Sita+Met | OD+Sita+Met | |
|-------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 180 | 186 | 182 | |
| Units: mmol/L | | | | |
| least squares mean (standard error) | 3.05 (± 0.22) | 2.19 (± 0.21) | 2.52 (± 0.21) | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Analysis 1 - BID + Met versus BID + Sita + Met |
| Statistical analysis description: | The endpoint was analysed by means of a normal linear regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliitin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline PG increment at lunch as independent variables. LOCF was applied. From this model, the treatment difference 'BID+Met' vs 'BID+Sita+Met' was estimated. |
| Comparison groups | BID+Met v BID+Sita+Met |
| Number of subjects included in analysis | 366 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[16] |
| P-value | = 0.005 |
| Method | Regression, Linear |
| Parameter estimate | Treatment difference |
| Point estimate | 0.85 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.26 |
| upper limit | 1.45 |

Notes:

[16] - Test of no difference between the two treatments.

| | |
|-----------------------------------|---|
| Statistical analysis title | Analysis 2 - BID + Met versus OD + Sita + Met |
|-----------------------------------|---|

Statistical analysis description:

The endpoint was analysed by means of a normal linear regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliitin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline PG increment at lunch as independent variables. LOCF was applied. From this model, the treatment difference 'BID+Met' vs 'OD+Sita+Met' was estimated.

| | |
|---|-----------------------|
| Comparison groups | BID+Met v OD+Sita+Met |
| Number of subjects included in analysis | 362 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[17] |
| P-value | = 0.085 |
| Method | Regression, Linear |
| Parameter estimate | Treatment difference |
| Point estimate | 0.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.07 |
| upper limit | 1.12 |

Notes:

[17] - Test of no difference between the two treatments.

| | |
|-----------------------------------|--|
| Statistical analysis title | Analysis 3 - BID + Sita + Met vs OD + Sita + Met |
|-----------------------------------|--|

Statistical analysis description:

The endpoint was analysed by means of a normal linear regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliitin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline PG increment at lunch as independent variables. LOCF was applied. From this model, the treatment difference 'BID+Sita+Met' vs 'OD+Sita+Met' was estimated.

| | |
|---|----------------------------|
| Comparison groups | OD+Sita+Met v BID+Sita+Met |
| Number of subjects included in analysis | 368 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[18] |
| P-value | = 0.275 |
| Method | Regression, Linear |
| Parameter estimate | Treatment difference |
| Point estimate | -0.33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.92 |
| upper limit | 0.26 |

Notes:

[18] - Test of no difference between the two treatments.

Secondary: Prandial Plasma Glucose (PPG) Increments at Dinner.

| | |
|-----------------|---|
| End point title | Prandial Plasma Glucose (PPG) Increments at Dinner. |
|-----------------|---|

End point description:

Prandial plasma glucose increments at dinner after 24 weeks of treatment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

After 24 weeks of treatment

| End point values | BID+Met | BID+Sita+Met | OD+Sita+Met | |
|-------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 178 | 188 | 184 | |
| Units: mmol/L | | | | |
| least squares mean (standard error) | 0.89 (± 0.21) | 1.01 (± 0.2) | 0.17 (± 0.21) | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Analysis 1 - BID + Met versus BID + Sita + Met |
|----------------------------|--|

Statistical analysis description:

The endpoint was analysed by means of a normal linear regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliitin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline PG increment at dinner as independent variables. LOCF was applied. From this model, the treatment difference 'BID+Met' vs 'BID+Sita+Met' was estimated.

| | |
|-------------------|------------------------|
| Comparison groups | BID+Met v BID+Sita+Met |
|-------------------|------------------------|

| | |
|---|-----|
| Number of subjects included in analysis | 366 |
|---|-----|

| | |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

| | |
|---------------|-----------------------|
| Analysis type | other ^[19] |
|---------------|-----------------------|

| | |
|---------|---------|
| P-value | = 0.674 |
|---------|---------|

| | |
|--------|--------------------|
| Method | Regression, Linear |
|--------|--------------------|

| | |
|--------------------|----------------------|
| Parameter estimate | Treatment difference |
|--------------------|----------------------|

| | |
|----------------|-------|
| Point estimate | -0.12 |
|----------------|-------|

Confidence interval

| | |
|-------|------|
| level | 95 % |
|-------|------|

| | |
|-------|---------|
| sides | 2-sided |
|-------|---------|

| | |
|-------------|------|
| lower limit | -0.7 |
|-------------|------|

| | |
|-------------|------|
| upper limit | 0.45 |
|-------------|------|

Notes:

[19] - Test of no difference between the two treatments.

| | |
|----------------------------|---|
| Statistical analysis title | Analysis 2 - BID + Met versus OD + Sita + Met |
|----------------------------|---|

Statistical analysis description:

The endpoint was analysed by means of a normal linear regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliitin and metformin] and no previous use of

such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline PG increment at dinner as independent variables. LOCF was applied. From this model, the treatment difference 'BID+Met' vs 'OD+Sita+Met' was estimated.

| | |
|---|-----------------------|
| Comparison groups | OD+Sita+Met v BID+Met |
| Number of subjects included in analysis | 362 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[20] |
| P-value | = 0.015 |
| Method | Regression, Linear |
| Parameter estimate | Treatment difference |
| Point estimate | 0.72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.14 |
| upper limit | 1.3 |

Notes:

[20] - Test of no difference between the two treatments.

| | |
|-----------------------------------|--|
| Statistical analysis title | Analysis 3 -BID + Sita+ Met versus OD + Sita + Met |
|-----------------------------------|--|

Statistical analysis description:

The endpoint was analysed by means of a normal linear regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliptin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline PG increment at dinner as independent variables. LOCF was applied. From this model, the treatment difference 'BID+Sita+Met' vs 'OD+Sita+Met' was estimated.

| | |
|---|----------------------------|
| Comparison groups | BID+Sita+Met v OD+Sita+Met |
| Number of subjects included in analysis | 372 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[21] |
| P-value | = 0.004 |
| Method | Regression, Linear |
| Parameter estimate | Treatment difference |
| Point estimate | 0.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.27 |
| upper limit | 1.41 |

Notes:

[21] - Test of no difference between the two treatments.

Secondary: Prandial Plasma Glucose (PPG) Overall Mean Increment.

| | |
|-----------------|---|
| End point title | Prandial Plasma Glucose (PPG) Overall Mean Increment. |
|-----------------|---|

End point description:

The average over all three prandial plasma glucose increments (breakfast, lunch, dinner) after 24 weeks of treatment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

After 24 weeks of treatment

| End point values | BID+Met | BID+Sita+Met | OD+Sita+Met | |
|-------------------------------------|--------------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 184 | 188 | 185 | |
| Units: mmol/L | | | | |
| least squares mean (standard error) | 1.97 (\pm 0.12) | 1.66 (\pm 0.12) | 1.88 (\pm 0.12) | |

Statistical analyses

| Statistical analysis title | Analysis 1 - BID + Met versus BID + Sita + Met |
|-----------------------------------|--|
|-----------------------------------|--|

Statistical analysis description:

The endpoint was analysed by means of a normal linear regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliitin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline over all mean PPG increment as independent variables. LOCF was applied. From this model, the treatment difference 'BID+Met' vs 'BID+Sita+Met' was estimated.

| | |
|---|------------------------|
| Comparison groups | BID+Met v BID+Sita+Met |
| Number of subjects included in analysis | 372 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[22] |
| P-value | = 0.08 |
| Method | Regression, Linear |
| Parameter estimate | Treatment difference |
| Point estimate | 0.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.04 |
| upper limit | 0.65 |

Notes:

[22] - Test of no difference between the two treatments.

| Statistical analysis title | Analysis 2 - BID + Met versus OD + Sita + Met |
|-----------------------------------|---|
|-----------------------------------|---|

Statistical analysis description:

The endpoint was analysed by means of a normal linear regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliitin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline over all mean PPG increment as independent variables. LOCF was applied. From this model, the treatment difference 'BID+Met' vs 'OD+Sita+Met' was estimated.

| | |
|---|-----------------------|
| Comparison groups | BID+Met v OD+Sita+Met |
| Number of subjects included in analysis | 369 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[23] |
| P-value | = 0.613 |
| Method | Regression, Linear |
| Parameter estimate | Treatment difference |
| Point estimate | 0.09 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.26 |
| upper limit | 0.43 |

Notes:

[23] - Test of no difference between the two treatments.

| | |
|-----------------------------------|--|
| Statistical analysis title | Analysis 3-BID + Sita + Met versus OD + Sita + Met |
|-----------------------------------|--|

Statistical analysis description:

The endpoint was analysed by means of a normal linear regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliitin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline over all mean PPG increment as independent variables. LOCF was applied. From this model, the treatment difference 'BID+Sita+Met' vs 'OD+Sita+Met' was estimated.

| | |
|---|----------------------------|
| Comparison groups | BID+Sita+Met v OD+Sita+Met |
| Number of subjects included in analysis | 373 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[24] |
| P-value | = 0.213 |
| Method | Regression, Linear |
| Parameter estimate | Treatment difference |
| Point estimate | -0.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.56 |
| upper limit | 0.13 |

Notes:

[24] - Test of no difference between the two treatments.

Secondary: Adverse Events (AEs)

| | |
|-----------------|----------------------|
| End point title | Adverse Events (AEs) |
|-----------------|----------------------|

End point description:

Rate of AEs per 100 years of patient exposure. An AE was defined as treatment emergent if the event had onset date on or after the first day of exposure to randomised treatment and no later than the last day of randomised treatment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 0 to Week 24

| End point values | BID+Met | BID+Sita+Met | OD+Sita+Met | |
|---|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 192 | 193 | 190 | |
| Units: Events/100 years of patient exposure | | | | |
| number (not applicable) | 262.2 | 209.9 | 281.2 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Treatment Emergent Hypoglycaemic Episodes (Nocturnal and Day-time) Classified Both According to the American Diabetes Association (ADA) Definition and to an Additional Definition for Minor Episodes.

| | |
|-----------------|--|
| End point title | Number of Treatment Emergent Hypoglycaemic Episodes (Nocturnal and Day-time) Classified Both According to the American Diabetes Association (ADA) Definition and to an Additional Definition for Minor Episodes. |
|-----------------|--|

End point description:

Number of treatment emergent hypoglycaemic episodes. Treatment emergent hypoglycaemic episode: if the onset of the episode was on or after the first day of exposure to randomised treatment and no later than the last day of randomised treatment. Nocturnal: Time of onset between 00:01 and 05:59 a.m. (both included). Additional minor hypoglycaemic episode: symptomatic or asymptomatic hypoglycaemia with blood glucose (BG) values < 2.8 mmol/L (50 mg/dL) or plasma glucose (PG) < 3.1 mmol/L (56 mg/dL), and which was handled by the subject him/herself.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 0 to Week 24

| End point values | BID+Met | BID+Sita+Met | OD+Sita+Met | |
|------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 192 | 193 | 190 | |
| Units: Number of episodes | | | | |
| All events | 600 | 509 | 320 | |
| Diurnal | 515 | 440 | 249 | |
| Nocturnal | 68 | 54 | 63 | |
| Diurnal (additional minor) | 163 | 112 | 71 | |
| Nocturnal (additional minor) | 21 | 14 | 23 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient Reported Outcome by Use of the Treatment Related Impact Measure - Diabetes.

| | |
|-----------------|---|
| End point title | Change From Baseline in Patient Reported Outcome by Use of the Treatment Related Impact Measure - Diabetes. |
|-----------------|---|

End point description:

Change from baseline in 'total score' for Treatment Related Impact Measure - Diabetes (TRIM-D) after 24 wk of treatment. The TRIM-D 'total score' is reported on a 0 to 100 scale, where higher scores

indicate greater satisfaction.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 0 to Week 24 | |

| End point values | BID+Met | BID+Sita+Met | OD+Sita+Met | |
|-------------------------------------|--------------------|--------------------|-------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 178 | 184 | 183 | |
| Units: Scores | | | | |
| least squares mean (standard error) | 6.22 (\pm 0.82) | 5.93 (\pm 0.81) | 6.2 (\pm 0.81) | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Analysis 1 - BID + Met versus BID + Sita + Met |
|-----------------------------------|--|

Statistical analysis description:

The endpoint was analysed by means of a normal linear regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliitin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline TRIM-D 'total score' as independent variables. LOCF was applied. From this model, the treatment difference 'BID+Met' vs 'BID+Sita+Met' was estimated.

| | |
|---|------------------------|
| Comparison groups | BID+Met v BID+Sita+Met |
| Number of subjects included in analysis | 362 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[25] |
| P-value | = 0.8 |
| Method | Regression, Linear |
| Parameter estimate | Treatment difference |
| Point estimate | 0.29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.97 |
| upper limit | 2.56 |

Notes:

[25] - Test of no difference between the two treatments.

| | |
|-----------------------------------|---|
| Statistical analysis title | Analysis 2 - BID + Met versus OD + Sita + Met |
|-----------------------------------|---|

Statistical analysis description:

The endpoint was analysed by means of a normal linear regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliitin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline TRIM-D 'total score' as independent variables. LOCF was applied. From this model, the treatment difference 'BID+Met' vs 'OD+Sita+Met' was estimated.

| | |
|-------------------|-----------------------|
| Comparison groups | BID+Met v OD+Sita+Met |
|-------------------|-----------------------|

| | |
|---|-----------------------|
| Number of subjects included in analysis | 361 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[26] |
| P-value | = 0.989 |
| Method | Regression, Linear |
| Parameter estimate | Treatment difference |
| Point estimate | 0.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.26 |
| upper limit | 2.29 |

Notes:

[26] - Test of no difference between the two treatments.

| | |
|-----------------------------------|--|
| Statistical analysis title | Analysis 3-BID + Sita + Met versus OD + Sita + Met |
|-----------------------------------|--|

Statistical analysis description:

The endpoint was analysed by means of a normal linear regression model with treatment (3 levels), stratum (2 levels: Previous use of OAD [other than sitagliitin and metformin] and no previous use of such OADs), region (3 levels: EU, Korea, and International Operations [the rest]), and baseline TRIM-D 'total score' as independent variables. LOCF was applied. From this model, the treatment difference 'BID+Sita+Met' vs 'OD+Sita+Met' was estimated.

| | |
|---|-----------------------|
| Comparison groups | OD+Sita+Met v BID+Met |
| Number of subjects included in analysis | 361 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[27] |
| P-value | = 0.809 |
| Method | Regression, Linear |
| Parameter estimate | Treatment difference |
| Point estimate | -0.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.52 |
| upper limit | 1.97 |

Notes:

[27] - Test of no difference between the two treatments.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were captured the onset date on or after the first day of exposure to randomised treatment and no later than the last day of randomised treatment.

Adverse event reporting additional description:

Safety analysis set included all subjects receiving at least one dose of the investigational product.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | BID+Met |
|-----------------------|---------|

Reporting group description:

Biphasic insulin aspart 30 (BIAsp 30) was injected twice daily, 6 U before breakfast and 6 U before dinner (evening meal), subcutaneously (under the skin) for 24 weeks. Dosing of BIAsp 30 was adjusted individually according to the titration guideline and the subject's self-measured plasma glucose (SMPG) levels. Subjects continued on their pre-trial metformin (1000 mg/day) treatment.

| | |
|-----------------------|--------------|
| Reporting group title | BID+Sita+Met |
|-----------------------|--------------|

Reporting group description:

Biphasic insulin aspart 30 (BIAsp 30) was injected twice daily, 6 U before breakfast and 6 U before dinner (evening meal), subcutaneously (under the skin) for 24 weeks. Dosing of BIAsp 30 was adjusted individually according to the titration guideline and the subject's self-measured plasma glucose (SMPG) levels. Subjects continued on their pre-trial metformin (1000 mg/day) and sitagliptin (100 mg/day) treatments.

| | |
|-----------------------|-------------|
| Reporting group title | OD+Sita+Met |
|-----------------------|-------------|

Reporting group description:

Biphasic insulin aspart 30 (BIAsp 30) was injected once daily, 12 U before dinner (evening meal), subcutaneously (under the skin) for 24 weeks. Dosing of BIAsp 30 was adjusted individually according to the titration guideline and the subject's self-measured plasma glucose (SMPG) levels. Subjects continued on their pre-trial metformin (1000 mg/day) and sitagliptin (100 mg/day) treatments.

| Serious adverse events | BID+Met | BID+Sita+Met | OD+Sita+Met |
|---|-----------------|-----------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 192 (3.65%) | 5 / 193 (2.59%) | 4 / 190 (2.11%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 193 (0.52%) | 0 / 190 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thyroid cancer metastatic | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 192 (0.52%) | 0 / 193 (0.00%) | 0 / 190 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Burns second degree | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | 0 / 193 (0.00%) | 0 / 190 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | 0 / 193 (0.00%) | 0 / 190 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 0 / 193 (0.00%) | 1 / 190 (0.53%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemic unconsciousness | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 0 / 193 (0.00%) | 1 / 190 (0.53%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VIIth nerve paralysis | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 193 (0.52%) | 0 / 190 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | 0 / 193 (0.00%) | 0 / 190 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 192 (0.00%) | 0 / 193 (0.00%) | 1 / 190 (0.53%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | 0 / 193 (0.00%) | 0 / 190 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 193 (0.52%) | 0 / 190 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 0 / 193 (0.00%) | 1 / 190 (0.53%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Liver abscess | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | 0 / 193 (0.00%) | 0 / 190 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 0 / 193 (0.00%) | 1 / 190 (0.53%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | 1 / 193 (0.52%) | 0 / 190 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 192 (0.52%) | 1 / 193 (0.52%) | 1 / 190 (0.53%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | BID+Met | BID+Sita+Met | OD+Sita+Met |
|---|-------------------|-------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 30 / 192 (15.63%) | 25 / 193 (12.95%) | 32 / 190 (16.84%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 7 / 192 (3.65%) | 11 / 193 (5.70%) | 8 / 190 (4.21%) |
| occurrences (all) | 11 | 19 | 15 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 8 / 192 (4.17%) | 1 / 193 (0.52%) | 10 / 190 (5.26%) |
| occurrences (all) | 10 | 1 | 10 |
| Infections and infestations | | | |
| Influenza | | | |
| subjects affected / exposed | 11 / 192 (5.73%) | 5 / 193 (2.59%) | 10 / 190 (5.26%) |
| occurrences (all) | 14 | 6 | 12 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 9 / 192 (4.69%) | 11 / 193 (5.70%) | 8 / 190 (4.21%) |
| occurrences (all) | 9 | 12 | 9 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/25488587>