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 (± 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) (± 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) (± 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 Male	281 301		
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 sitaglitin 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 sitaglitin 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 sitaglitin 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 sitaglitin 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 sitaglitin 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 sitaglitin 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-

	defined HbA1c Targets (HbA1c ≤ 6.5%)

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 ≤ 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 sitaglitin 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 ≤ 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 sitaglitin 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 ≤ 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 sitaglitin 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 sitaglitin 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 sitaglitin 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 sitaglitin 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 sitaglitin 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 sitaglitin 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 sitaglitin 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 sitaglitin 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 sitaglitin 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 sitaglitin 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 sitaglitin 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 sitaglitin 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 sitaglitin 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 (± 0.12)	1.66 (± 0.12)	1.88 (± 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 sitaglitin 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 sitaglitin 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 sitaglitin 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 (± 0.82)	5.93 (± 0.81)	6.2 (± 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 sitaglitin 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 sitaglitin 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 sitaglitin 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