Clinical trial results:
A Phase II, 16-week, double-blind, placebo-controlled, parallel-group, randomised, multicentre trial to assess effect on glycaemic control of three doses of HM11260C in subjects with inadequately controlled type 2 diabetes receiving a stable dose of metformin

Summary

EudraCT number	2013-004250-13
Trial protocol	DE HU ES IT
Global end of trial date	30 April 2015

Results information

Result version number	v1 (current)
This version publication date	06 November 2016
First version publication date	06 November 2016

Trial information

Trial identification

Sponsor protocol code	HM-EXC-204

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02081118
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hanmi Pharmaceutical Co., Ltd.
Sponsor organisation address	14, Wiryeseong-daero, Songpa-gu, Seoul, Korea, Republic of, 05545
Public contact	Jahoon Kang, Executive Director of Clinical Research and Development, Hanmi Pharmaceutical Co. Ltd., +82 2-410-9041, jhkang@hanmi.co.kr
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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	01 October 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess and compare the efficacy of three doses of HM11260C (once monthly dosing) versus placebo on glycaemic control as assessed by the change in HbA1c over the 16 weeks from baseline in subjects with T2DM receiving a stable dose of metformin

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with ICH GCP ensuring that those involved with the conduct of the study abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy:

Metformin

Evidence for comparator: -

Actual start date of recruitment	18 February 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Germany: 21
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	United States: 165
Worldwide total number of subjects	209
EEA total number of subjects	42

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)	176
From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment from 18-Feb 2014 (First Patient In Screened) to 29th Oct 2014 (LPI Screened), Last patient last visit was 30-Apr-2015 - Regions- US, Europe (Hungary, Spain, Germany, Italy) and Asia (South Korea)

Pre-assignment

Screening details:

209 subjects were randomized. 4-week screening period, a 16-week treatment period, and a 6-week follow-up period. The screening visits took place between Study Days -28 and -5. Eligible subjects who met all of the inclusion criteria and none of the exclusion criteria returned to the clinic on Day 1 for baseline, randomisation, and study drug use.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

HM11260C and placebo for HM11260C were provided in identically matched prefilled syringe and packaged identically.

Arms

Are arms mutually exclusive?	Yes
Arm title	HM11260C (8 mg)

Arm description:

subcutaneous (sc) HM11260C 4 mg once a week (QW) for 4 weeks, then 8 mg QW for 1 week, then 8 mg once a month (every 28 days) for 2 months

Arm type	Experimental
Investigational medicinal product name	Long-acting CA Exendin-4-HMC001 conjugate
Investigational medicinal product code	HM11260C
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.53 ml of HM11260C was self administered by subcutaneous injection within 60 minutes before the meal using pre-filled syringe.

Arm title	HM11260C (12 mg)

Arm description:

subcutaneous (sc) HM11260C 4 mg once a week (QW) for 4 weeks, then 8 mg QW for 1 week, then 12 mg once a month (every 28 days) for 2 months

Arm type	Experimental
Investigational medicinal product name	Long-acting CA Exendin-4-HMC001 conjugate
Investigational medicinal product code	HM11260C
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.53 ml of HM11260C was self administered by subcutaneous injection within 60 minutes before the meal using pre-filled syringe.

Arm title	HM11260C (16 mg)

Arm description:

subcutaneous (sc) HM11260C 4 mg once a week (QW) for 4 weeks, then 8 mg QW for 1 week, then 16 mg once a month (every 28 days) for 2 months

Arm type	Experimental
Investigational medicinal product name	Long-acting CA Exendin-4-HMC001 conjugate
Investigational medicinal product code	HM11260C
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.53 ml of HM11260C was self administered by subcutaneous injection within 60 minutes before the meal using pre-filled syringe.

Arm title	Placebo

Arm description:

subcutaneous (sc) placebo identical in appearance and volume to HM11260C once a week (QW) for 5 weeks, then placebo once a month (every 28 days) for 2 months

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.53 ml of Placebo was self administered by subcutaneous injection within 60 minutes before the meal using pre-filled syringe.

Number of subjects in period 1[1]	HM11260C (8 mg)	HM11260C (12 mg)	HM11260C (16 mg)
Started	52	52	53
Completed	41	39	37
Not completed	11	13	16
Adverse event, non-fatal	6	6	8
Other	1	-	-
Pregnancy	-	1	-
Lost to follow-up	-	3	4
Protocol deviation	1	-	-
Withdrawal by subject	3	2	3
Noncompliance	-	1	1

Number of subjects in period 1[1]	Placebo
Started	50
Completed	41
Not completed	9
Adverse event, non-fatal	1

Other	-
Pregnancy	-
Lost to follow-up	3
Protocol deviation	1
Withdrawal by subject	3
Noncompliance	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 209 subjects were randomised at 45 investigative sites. Of these, 158 subjects were randomised to HM11260C overall and 51 to placebo. A total of 207 subjects received study drug (HM11260C or placebo) and were included in the Safety Set.

Baseline characteristics

Reporting groups	
Reporting group title	HM11260C (8 mg)
Reporting group description:	
subcutaneous (sc) HM11260C 4 mg once a week (QW) for 4 weeks, then 8 mg QW for 1 week, then 8 mg once a month (every 28 days) for 2 months	
Reporting group title	HM11260C (12 mg)
Reporting group description:	
subcutaneous (sc) HM11260C 4 mg once a week (QW) for 4 weeks, then 8 mg QW for 1 week, then 12 mg once a month (every 28 days) for 2 months	
Reporting group title	HM11260C (16 mg)
Reporting group description:	
subcutaneous (sc) HM11260C 4 mg once a week (QW) for 4 weeks, then 8 mg QW for 1 week, then 16 mg once a month (every 28 days) for 2 months	
Reporting group title	Placebo
Reporting group description:	
subcutaneous (sc) placebo identical in appearance and volume to HM11260C once a week (QW) for 5 weeks, then placebo once a month (every 28 days) for 2 months	

Reporting group values	HM11260C (8 mg)	HM11260C (12 mg)	HM11260C (16 mg)
Number of subjects	52	52	53
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	56.7	56	56.4
standard deviation	± 8.05	± 9.51	± 9.52
Gender categorical			
Units: Subjects			
Female	19	28	25
Male	33	24	28

Reporting group values	Placebo	Total	
Number of subjects	50	207	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	54.7		
standard deviation	± 9.94	-	
Gender categorical			
Units: Subjects			
Female	23	95	
Male	27	112	

End points

End points reporting groups

Reporting group title	HM11260C (8 mg)
Reporting group description:	
subcutaneous (sc) HM11260C 4 mg once a week (QW) for 4 weeks, then 8 mg QW for 1 week, then 8 mg once a month (every 28 days) for 2 months	
Reporting group title	HM11260C (12 mg)
Reporting group description:	
subcutaneous (sc) HM11260C 4 mg once a week (QW) for 4 weeks, then 8 mg QW for 1 week, then 12 mg once a month (every 28 days) for 2 months	
Reporting group title	HM11260C (16 mg)
Reporting group description:	
subcutaneous (sc) HM11260C 4 mg once a week (QW) for 4 weeks, then 8 mg QW for 1 week, then 16 mg once a month (every 28 days) for 2 months	
Reporting group title	Placebo
Reporting group description:	
subcutaneous (sc) placebo identical in appearance and volume to HM11260C once a week (QW) for 5 weeks, then placebo once a month (every 28 days) for 2 months	

Primary: Change from Baseline in HbA1c

End point title	Change from Baseline in HbA1c
End point description:	
Least squares (LS) means and standard errors at Week 17 were obtained from a mixed effect model with repeated measures (MMRM). Full Analysis Set (FAS) population: all participants who received study drug and had at least 1 efficacy or safety assessment recorded after dosing.	
End point type	Primary
End point timeframe:	
Week 17	

End point values	HM11260C (8 mg)	HM11260C (12 mg)	HM11260C (16 mg)	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	52	49
Units: Percentage of Hemoglobin				
least squares mean (standard error)	-0.98 (± 0.118)	-0.99 (± 0.119)	-1.11 (± 0.122)	-0.32 (± 0.119)

Statistical analyses

Statistical analysis title	Change from baseline in HbA1c for 8 mg vs placebo
Comparison groups	Placebo v HM11260C (8 mg)

Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean Difference
Point estimate	-0.66
Confidence interval	
level	95.1 %
sides	2-sided
lower limit	-0.99
upper limit	-0.33
Variability estimate	Standard error of the mean

Notes:

[1] - The threshold for significance is a p-value <=0.049. No adjustments were made for multiple comparisons of each treatment group to placebo.

Statistical analysis title	Change from baseline in HbA1c for 12 mg vs placebo
Comparison groups	Placebo v HM11260C (12 mg)
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.0001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean Difference
Point estimate	-0.67
Confidence interval	
level	95.1 %
sides	2-sided
lower limit	-1
upper limit	-0.34
Variability estimate	Standard error of the mean

Notes:

[2] - The threshold for significance is a p-value <=0.049. No adjustments were made for multiple comparisons of each treatment group to placebo.

Statistical analysis title	Change from baseline in HbA1c for 16 mg vs placebo
Comparison groups	HM11260C (16 mg) v Placebo
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean Difference
Point estimate	-0.79
Confidence interval	
level	95.1 %
sides	2-sided
lower limit	-1.13
upper limit	-0.45
Variability estimate	Standard error of the mean

Notes:

[3] - The threshold for significance is a p-value <=0.049. No adjustments were made for multiple comparisons of each treatment group to placebo.

Secondary: Subjects who had a HbA1c level of < 7%

End point title	Subjects who had a HbA1c level of < 7%

End point description:

Percentage of subjects with HbA1c < 7% by visit, treatment group. FAS population.

End point type	Secondary

End point timeframe:

Week 17

End point values	HM11260C (8 mg)	HM11260C (12 mg)	HM11260C (16 mg)	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	52	49
Units: Percentage				
number (not applicable)	50	50	46.2	30.6

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Fasting Plasma Glucose

End point title	Change from Baseline in Fasting Plasma Glucose

End point description:

Least squares (LS) means and standard errors at Week 17 were obtained from a mixed effect model with repeated measures (MMRM). FAS population.

End point type	Secondary

End point timeframe:

Week 17

End point values	HM11260C (8 mg)	HM11260C (12 mg)	HM11260C (16 mg)	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	52	49
Units: mmol/L				
least squares mean (standard error)	-0.78 (± 0.285)	-0.45 (± 0.291)	-0.79 (± 0.296)	-0.07 (± 0.282)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Body Weight

End point title	Change from Baseline in Body Weight

End point description:

Least squares (LS) means and standard errors at Week 17 were obtained from a mixed effect model with repeated measures (MMRM). FAS population.

End point type	Secondary

End point timeframe:

Week 17

End point values	HM11260C (8 mg)	HM11260C (12 mg)	HM11260C (16 mg)	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	52	49
Units: kilogram(s)				
least squares mean (standard error)	-2.11 (± 0.504)	-3.16 (± 0.505)	-2.7 (± 0.526)	-0.51 (± 0.503)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Other diabetes-related parameters (fasting insulin)

End point title	Change from Baseline in Other diabetes-related parameters (fasting insulin)

End point description:

Least squares (LS) means and standard errors at Week 17 were obtained from a mixed effect model with repeated measures (MMRM). FAS population.

End point type	Secondary

End point timeframe:

Week 17

End point values	HM11260C (8 mg)	HM11260C (12 mg)	HM11260C (16 mg)	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	52	49
Units: pmol/L				
least squares mean (standard error)	-14.77 (± 9.819)	1.28 (± 9.913)	1.86 (± 9.891)	-6.4 (± 9.336)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Other diabetes-related parameters (C-peptide)

End point title	Change from Baseline in Other diabetes-related parameters (C-peptide)

End point description:

Least squares (LS) means and standard errors at Week 17 were obtained from a mixed effect model with repeated measures (MMRM). FAS population.

End point type	Secondary

End point timeframe:

Week 17

End point values	HM11260C (8 mg)	HM11260C (12 mg)	HM11260C (16 mg)	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	52	49
Units: nmol/L				
least squares mean (standard error)	0.014 (± 0.023)	0.013 (± 0.023)	0.036 (± 0.023)	0.027 (± 0.021)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Other diabetes-related parameters (Glycated Albumin)

End point title	Change from Baseline in Other diabetes-related parameters (Glycated Albumin)

End point description:

Least squares (LS) means and standard errors at Week 17 were obtained from a mixed effect model with repeated measures (MMRM). FAS population.

End point type	Secondary

End point timeframe:

Week 17

End point values	HM11260C (8 mg)	HM11260C (12 mg)	HM11260C (16 mg)	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	52	49
Units: Percentage				
least squares mean (standard error)	-0.29 (± 0.051)	-0.29 (± 0.051)	-0.33 (± 0.053)	-0.1 (± 0.051)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in 7-Point Glucose Profile (Mean Daily Blood Glucose)

End point title	Change from Baseline in 7-Point Glucose Profile (Mean Daily Blood Glucose)

End point description:

Least squares (LS) means and standard errors at Week 17 were obtained from a mixed effect model with repeated measures (MMRM). FAS population.

End point type	Secondary

End point timeframe:

Visit 14 (Week 17)

End point values	HM11260C (8 mg)	HM11260C (12 mg)	HM11260C (16 mg)	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	52	49
Units: mmol/L				
least squares mean (standard error)	-1.071 (± 0.268)	-1.295 (± 0.269)	-1.363 (± 0.267)	-0.311 (± 0.255)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Serum Lipid Profile (Parameters LDL-C- HDL-C, TG)

End point title	Change from Serum Lipid Profile (Parameters LDL-C- HDL-C, TG)

End point description:

Least squares (LS) means and standard errors at Week 17 were obtained from a mixed effect model with repeated measures (MMRM). FAS population.

End point type	Secondary

End point timeframe:

Week 17

End point values	HM11260C (8 mg)	HM11260C (12 mg)	HM11260C (16 mg)	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	52	49
Units: mmol/L				
least squares mean (standard error)				
Parameter LDL-C	0.12 (± 0.106)	0 (± 0.107)	0.01 (± 0.109)	0.3 (± 0.102)
Parameter HDL-C	0.03 (± 0.022)	0.02 (± 0.022)	-0.02 (± 0.023)	0.04 (± 0.022)
Parameter TG	-0.441 (± 0.116)	-0.251 (± 0.108)	-0.086 (± 0.112)	-0.309 (± 0.11)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected beginning at screening and continuing through the final patient visit. SAEs, regardless of suspected causality, were recorded until at least 30 days after the subject had stopped study participation.

Adverse event reporting additional description:

Reported AEs were TEAEs that had a start date on or after the first dose of IP or, if the start date was before the date of the first dose of IP, increased in severity on or after the date of the first dose of IP. Treatment-emergent SAEs and TEAEs were reported for the Safety Set, consisting of all participants who received any study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	HM11260C (8mg)

Reporting group description:

Subjects received HM11260C as a subcutaneous injection in the abdomen via a pre-filled syringe. HM11260C 4mg was administered once a week for 4 weeks, HM11260C 8mg once a week for 1 week, and HM11260C 8mg once a month (every 28 days) thereafter.

Reporting group title	HM11260C (12mg)

Reporting group description:

Subjects received HM11260C as a subcutaneous injection in the abdomen via a pre-filled syringe. HM11260C 4mg was administered once a week for 4 weeks, HM11260C 8mg once a week for 1 week, and HM11260C 12mg once a month (every 28 days) thereafter.

Reporting group title	HM11260C (16mg)

Reporting group description:

Subjects received HM11260C as a subcutaneous injection in the abdomen via a pre-filled syringe. HM11260C 4mg was administered once a week for 4 weeks, HM11260C 8mg once a week for 1 week, and HM11260C 16mg once a month (every 28 days) thereafter.

Reporting group title	Placebo

Reporting group description:

Subjects received placebo as a subcutaneous injection in the abdomen via a pre-filled syringe. Placebo was administered once a week for 5 weeks, and once a month (every 28 days) thereafter.

Serious adverse events	HM11260C (8mg)	HM11260C (12mg)	HM11260C (16mg)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 52 (0.00%)	5 / 52 (9.62%)	3 / 53 (5.66%)
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 metastatic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 53 (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

Colon cancer stage II			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 53 (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
Meniscus injury			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fractured sacrum			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 53 (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
Sciatica			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal spasm			

subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 53 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 53 (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

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 50 (4.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma metastatic			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colon cancer stage II			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Meniscus injury			

subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fractured sacrum			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sciatica			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oesophageal spasm			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	HM11260C (8mg)	HM11260C (12mg)	HM11260C (16mg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 52 (82.69%)	43 / 52 (82.69%)	42 / 53 (79.25%)
Investigations			
Lipase increased			
subjects affected / exposed	7 / 52 (13.46%)	1 / 52 (1.92%)	5 / 53 (9.43%)
occurrences (all)	10	3	5
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 52 (3.85%)	3 / 52 (5.77%)	0 / 53 (0.00%)
occurrences (all)	2	3	0
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 52 (13.46%)	3 / 52 (5.77%)	7 / 53 (13.21%)
occurrences (all)	7	4	9
Dizziness			
subjects affected / exposed	5 / 52 (9.62%)	6 / 52 (11.54%)	4 / 53 (7.55%)
occurrences (all)	6	8	4
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 52 (1.92%)	3 / 52 (5.77%)	0 / 53 (0.00%)
occurrences (all)	1	3	0
General disorders and administration site conditions			
Injection site bruising			
subjects affected / exposed	3 / 52 (5.77%)	1 / 52 (1.92%)	0 / 53 (0.00%)
occurrences (all)	3	1	0
Pain			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	3 / 53 (5.66%)
occurrences (all)	0	1	3
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	14 / 52 (26.92%)	24 / 52 (46.15%)	23 / 53 (43.40%)
occurrences (all)	21	37	33
Vomiting			
subjects affected / exposed	8 / 52 (15.38%)	13 / 52 (25.00%)	17 / 53 (32.08%)
occurrences (all)	12	19	26
Diarrhoea			
subjects affected / exposed	9 / 52 (17.31%)	8 / 52 (15.38%)	11 / 53 (20.75%)
occurrences (all)	16	11	12
Gastrooesophageal reflux disease			
subjects affected / exposed	7 / 52 (13.46%)	3 / 52 (5.77%)	4 / 53 (7.55%)
occurrences (all)	7	3	6
Abdominal distension			
subjects affected / exposed	3 / 52 (5.77%)	5 / 52 (9.62%)	0 / 53 (0.00%)
occurrences (all)	3	5	0
Dyspepsia			
subjects affected / exposed	4 / 52 (7.69%)	2 / 52 (3.85%)	1 / 53 (1.89%)
occurrences (all)	4	3	1
Abdominal pain			
subjects affected / exposed	1 / 52 (1.92%)	3 / 52 (5.77%)	2 / 53 (3.77%)
occurrences (all)	1	4	2
Abdominal pain upper			
subjects affected / exposed	2 / 52 (3.85%)	3 / 52 (5.77%)	0 / 53 (0.00%)
occurrences (all)	2	4	0
Abdominal tenderness			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	3 / 53 (5.66%)
occurrences (all)	0	1	3
Constipation			
subjects affected / exposed	2 / 52 (3.85%)	6 / 52 (11.54%)	3 / 53 (5.66%)
occurrences (all)	2	9	4
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 52 (1.92%)	1 / 52 (1.92%)	3 / 53 (5.66%)
occurrences (all)	1	1	5
Pain in extremity			

subjects affected / exposed	0 / 52 (0.00%)	3 / 52 (5.77%)	0 / 53 (0.00%)
occurrences (all)	0	3	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 52 (7.69%)	2 / 52 (3.85%)	4 / 53 (7.55%)
occurrences (all)	4	2	4
Urinary tract infection			
subjects affected / exposed	4 / 52 (7.69%)	4 / 52 (7.69%)	1 / 53 (1.89%)
occurrences (all)	4	7	1
Rhinitis			
subjects affected / exposed	1 / 52 (1.92%)	3 / 52 (5.77%)	0 / 53 (0.00%)
occurrences (all)	1	3	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 52 (17.31%)	10 / 52 (19.23%)	6 / 53 (11.32%)
occurrences (all)	9	11	8

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 50 (64.00%)		
Investigations			
Lipase increased			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	5		
Dizziness			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			

Anaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Injection site bruising			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	4		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Abdominal distension			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	2		

Abdominal tenderness subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0 1 / 50 (2.00%) 1		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 0 / 50 (0.00%) 0 1 / 50 (2.00%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Rhinitis subjects affected / exposed occurrences (all)	 5 / 50 (10.00%) 5 2 / 50 (4.00%) 3 0 / 50 (0.00%) 0		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 1 / 50 (2.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 April 2014	Version 2.0 Global (except Germany) protocol amendment developed from and replacing protocol Version 01: Contraception inclusion criteria were updated and study procedures were modified.
18 June 2014	Version 3.0 Global (except Germany) protocol amendment developed from and replacing protocol Version 2.0 to change when to conduct the interim analysis.
05 November 2014	Version 4.0 Global (except Germany) protocol amendment developed from and replacing protocol Version 3.0 to change the interim analysis from a futility analysis to an analysis conducted for administrative purposes.
12 December 2014	Version 5.0 Global (except Germany) protocol amendment developed from and replacing protocol Version 4.0 to remove the glucagon assessments and analyses from the study as the glucagon assay performed during the study up to that time was not sensitive enough and did not give results within the normal range for glucagon.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Per protocol amendment #5 (v.4.0, 12-Dec-2014) glucagon assessments were removed as the assay was not sensitive enough and did not give results within the normal range for glucagon.

Notes: