Clinical trial results:
Albiglutide versus Placebo in insulin-treated Subjects with new-onset type 1 diabetes mellitus

Summary

EudraCT number	2014-001825-33
Trial protocol	DE IT GB
Global end of trial date	18 October 2017

Results information

Result version number	v1
This version publication date	28 October 2018
First version publication date	28 October 2018

Trial information

Trial identification

Sponsor protocol code	110933

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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	27 April 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 October 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine the effect of albiglutide therapy versus placebo on endogenous insulin secretion over 52 weeks when added to standard of care in subjects with new onset type 1 diabetes mellitus (NOT1DM)

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 October 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	France: 6
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Spain: 29
Country: Number of subjects enrolled	United Kingdom: 14
Worldwide total number of subjects	67
EEA total number of subjects	67

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)	67
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a multicenter study conducted at 29 sites in Europe (Spain 10, United Kingdom (UK) 9, Germany 4, France 3 and Italy 3). A total of 67 participants with New-onset type 1 diabetes mellitus (NOT1DM) were randomized.

Pre-assignment

Screening details:

Study was terminated early as part of the decision to withdraw albiglutide for commercial reasons. Study stopped after 67 participants were randomized instead of 68 as per protocol. Impact of early termination was minimal and did not affect the interpretation of results.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Matching placebo was administered once weekly for 52 weeks by sc injection in the abdomen, thigh or upper arm region in addition to insulin.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo was administered once weekly by SC injection in the abdomen, thigh or upper arm region in addition to insulin

Arm title	Albiglutide

Arm description:

Albiglutide 30 mg was administered once weekly for 52 weeks by sc injection in the abdomen, thigh or upper arm region along with insulin (Dose increased to 50 mg once weekly at Week 6 if the 30 mg weekly dose was tolerated).

Arm type	Experimental
Investigational medicinal product name	Albiglutide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Albiglutide 30 mg was administered once weekly by SC injection in the abdomen, thigh or upper arm region in addition to insulin (Dose increased to 50 mg once weekly at Week 6 if the 30 mg weekly dose was tolerated)

Number of subjects in period 1	Placebo	Albiglutide
Started	17	50
Completed	11	40
Not completed	6	10
Consent withdrawn by subject	2	5
Physician decision	-	2
Adverse event, non-fatal	3	-
Lost to follow-up	1	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Matching placebo was administered once weekly for 52 weeks by sc injection in the abdomen, thigh or upper arm region in addition to insulin.	
Reporting group title	Albiglutide
Reporting group description:	
Albiglutide 30 mg was administered once weekly for 52 weeks by sc injection in the abdomen, thigh or upper arm region along with insulin (Dose increased to 50 mg once weekly at Week 6 if the 30 mg weekly dose was tolerated).	

Reporting group values	Placebo	Albiglutide	Total
Number of subjects	17	50	67
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	22.8	22.7	
standard deviation	± 3.83	± 3.72	-
Gender categorical			
Units: Subjects			
Female	7	21	28
Male	10	29	39
Race/Ethnicity, Customized			
Units: Subjects			
Black or African American	0	1	1
White	17	49	66
Multi Racial	0	0	0

Subject analysis sets	
Subject analysis set title	defend-1 placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Historical placebo data from the DEFEND-1 (NCT00678886) study was used as prior knowledge.	

Reporting group values	defend-1 placebo		
Number of subjects	53		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	22.7		
standard deviation	± 4.00		

Gender categorical Units: Subjects			
Female	20		
Male	33		
Race/Ethnicity, Customized Units: Subjects			
Black or African American	2		
White	49		
Multi Racial	2		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Matching placebo was administered once weekly for 52 weeks by sc injection in the abdomen, thigh or upper arm region in addition to insulin.	
Reporting group title	Albiglutide
Reporting group description:	
Albiglutide 30 mg was administered once weekly for 52 weeks by sc injection in the abdomen, thigh or upper arm region along with insulin (Dose increased to 50 mg once weekly at Week 6 if the 30 mg weekly dose was tolerated).	
Subject analysis set title	defend-1 placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Historical placebo data from the DEFEND-1 (NCT00678886) study was used as prior knowledge.	

Primary: Mean change from Baseline in stimulated (from mixed meal tolerance test [MMTT]) 2-hour plasma C-peptide area under the curve (AUC) at Week 52

End point title	Mean change from Baseline in stimulated (from mixed meal tolerance test [MMTT]) 2-hour plasma C-peptide area under the curve (AUC) at Week 52
End point description:	
Participants had a balanced diet consistent with dietitian's advice and made no major changes in exercise regimens. On the evening before the MMTT, participants had a full meal and then fasted from 9 post meridiem (pm) until the MMTT was completed. Plasma glucose was measured prior to the test using a finger-stick test and MMTT was performed only if it was in range > 3.9 millimoles per liter (mmol/L) [70 mg/deciliter (dL)] and <= 11.1 mmol/L (200 mg/dL). Baseline was defined as the last non-missing value with an assessment date on or before the first day of study medication. Change from Baseline was calculated by subtracting the Baseline value from the Week 52 value. Intent-to-treat Population comprised of all randomly assigned participants who received at least 1 dose of study medication and who had at least 1 post-Baseline assessment of primary endpoint. Only those participants with available data at the specified time points were analyzed.	
End point type	Primary
End point timeframe:	
Baseline and Week 52	

End point values	Placebo	Albiglutide	defend-1 placebo	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11[1]	40[2]	53[3]	
Units: Nanomoles per liter				
arithmetic mean (standard deviation)				
Nanomoles per liter	-0.16 (± 0.366)	-0.13 (± 0.244)	-0.27 (± 0.314)	

Notes:

[1] - Intent to treat (ITT) Population.

[2] - ITT Population.

[3] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Analysis was performed using a Bayesian model incorporating historical placebo data using a robust mixture prior. Values above are 95% credible intervals. Probability of treatment difference (Albiglutide – Placebo) >= 0.2 nmol/L = 0.097. Fifty one participants from current study and 53 participants from the DEFEND-1 study were included in the analysis.

Comparison groups	Albiglutide v Placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.24

Secondary: Mean change from Baseline in stimulated (from MMTT) 2 hour plasma C-peptide AUC at Week 16, 28 and Week 64

End point title	Mean change from Baseline in stimulated (from MMTT) 2 hour plasma C-peptide AUC at Week 16, 28 and Week 64

End point description:

Participants had a balanced diet consistent with dietitian’s advice and made no major changes in exercise regimens. On the evening before the MMTT, participants had a full meal and then fasted from 9 pm until the MMTT was completed. Water, black coffee or tea without sugar or artificial sweeteners was allowed. Plasma glucose was measured prior to the test using a finger-stick test and MMTT was performed only if it was in range > 3.9 mmol/L (70 mg/dL) and <= 11.1 mmol/L (200 mg/dL). Baseline was defined as the last non-missing value with an assessment date on or before the first day of study medication. Change from Baseline was calculated by subtracting Baseline value from the specified time point value. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and Weeks 16, 28 and 64

End point values	Placebo	Albiglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[4]	46[5]		
Units: Nanomoles per liter				
arithmetic mean (standard deviation)				
Week 16, n=15,44	0.00 (± 0.216)	0.07 (± 0.234)		
Week 28, n=13,41	-0.14 (± 0.177)	0.01 (± 0.225)		
Week 64, n=11,36	-0.22 (± 0.277)	-0.22 (± 0.246)		

Notes:

[4] - ITT Population.

[5] - ITT Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum stimulated plasma C-peptide (MMTT) at Baseline, Week 16, 28, 52 and 64

End point title	Maximum stimulated plasma C-peptide (MMTT) at Baseline, Week 16, 28, 52 and 64

End point description:

Maximum stimulated plasma C-peptide was the highest value at any time point during the 2 hour MMTT after the participant has ingested the mixed meal at Baseline, Week 16, Week 28, Week 52 and Week 64. Blood samples were taken to assess levels of C-peptide at: 10 minutes before Time 0 (-10 minutes), immediately before the participant starts drinking the nutritional drink (Time 0) and 15, 30, 60, 90, and 120 minutes after Time 0. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and Weeks 16, 28, 52 and 64

End point values	Placebo	Albiglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[6]	46[7]		
Units: Nanomoles per liter				
arithmetic mean (standard deviation)				
Baseline, n=15,46	0.86 (± 0.382)	0.82 (± 0.448)		
Week 16, n=15,45	0.84 (± 0.481)	1.02 (± 0.558)		
Week 28,n=13,42	0.68 (± 0.442)	0.91 (± 0.594)		
Week 52,n=11,41	0.63 (± 0.516)	0.69 (± 0.479)		
Week 64, n=11,37	0.58 (± 0.453)	0.48 (± 0.363)		

Notes:

[6] - ITT Population

[7] - ITT Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in plasma glucagon AUC (from MMTT) at Week 16, 28, 52 and 64

End point title	Mean change from Baseline in plasma glucagon AUC (from MMTT) at Week 16, 28, 52 and 64

End point description:

Blood samples were taken to assess levels of glucagon at: 10 minutes before Time 0 (-10 minutes), immediately before the participant started drinking the nutritional drink (Time 0) and 15, 30, 60, 90, and 120 minutes after Time 0. Mean change from Baseline in plasma glucagon AUC (from MMTT) at Week 16, 28, 52 and 64 was reported. Baseline was defined as the last non-missing value with an assessment date on or before the first day of study medication. Change from Baseline was calculated by subtracting Baseline value from the specified time point value. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and Weeks 16, 28, 52 and 64

End point values	Placebo	Albiglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[8]	46[9]		
Units: Nanograms per liter				
arithmetic mean (standard deviation)				
Week 16,n=15,45	-2.28 (± 11.221)	-1.10 (± 4.496)		
Week 28,n=13,43	-2.97 (± 11.574)	3.91 (± 22.197)		
Week 52,n=11,40	-0.31 (± 15.989)	4.66 (± 13.628)		
Week 64,n=11,37	3.19 (± 18.279)	8.82 (± 17.650)		

Notes:

[8] - ITT Population.

[9] - ITT Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of responders at Baseline, Weeks 4, 8, 16, 28, 40, 52 and 64

End point title	Percentage of responders at Baseline, Weeks 4, 8, 16, 28, 40, 52 and 64

End point description:

Responders were defined as participants achieving glycosylated hemoglobin A1c (HbA1c) <= 7.0 percent and mean daily insulin use < 0.5 units per kilograms (kg) per day. Percentages are based on the number of participants with available HbA1c and insulin use data in each treatment group at that visit. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 16, 28, 40, 52 and 64

End point values	Placebo	Albiglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[10]	46[11]		
Units: Percentage of participants				
number (not applicable)				
Baseline, n=15, 46	26.7	37.0		
Week 4,n=14,42	71.4	78.6		
Week 8,n=14,46	85.7	67.4		
Week 16,n=15,45	86.7	73.3		
Week 28,n=12,42	75.0	73.8		
Week 40,n=13,40	76.9	62.5		
Week 52,n=12,41	41.7	48.8		
Week 64,n=11,38	36.4	34.2		

Notes:

[10] - ITT Population.

[11] - ITT Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving partial remission status (insulin dose-adjusted hemoglobin A1c (IDAA1C)<= 9.0) at Baseline, Week 4, 8, 16, 28, 40, 52 and 64

End point title	Percentage of participants achieving partial remission status (insulin dose-adjusted hemoglobin A1c (IDAA1C)<= 9.0) at Baseline, Week 4, 8, 16, 28, 40, 52 and 64

End point description:

Participant achieving partial remission status was defined as a participant with IDAA1C <=9.0 . Percentages were based on the number of participants with available IDAA1c data in each treatment group at that visit. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 16, 28, 40, 52 and 64

End point values	Placebo	Albiglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[12]	46[13]		
Units: Percentage of participants				
number (not applicable)				
Baseline, n= 15, 46	73.3	60.9		
Week 4,n=14,42	92.9	88.1		
Week 8,n=14,46	92.9	87.0		
Week 16,n=15,45	86.7	86.7		
Week 28,n=12,42	75.0	85.7		
Week 40,n=13,40	84.6	82.5		
Week 52,n=12,41	58.3	70.7		
Week 64,n=11,38	54.5	55.3		

Notes:

[12] - ITT Population.

[13] - ITT Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in percent HbA1c at Week 52

End point title	Change from Baseline in percent HbA1c at Week 52

End point description:

Change from Baseline in percent HbA1c was reported. Baseline was defined as the last non-missing

value with an assessment date on or before the first day of study medication. Change from Baseline was calculated by subtracting Baseline value the Week 52 value. Only those participants with available data at the specified time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo	Albiglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[14]	43[15]		
Units: Percentage of HbA1c				
arithmetic mean (standard deviation)				
Percentage of HbA1c	-0.73 (± 1.033)	-0.59 (± 1.649)		

Notes:

[14] - ITT Population.

[15] - ITT Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent HbA1c over time (at Weeks 4, 8, 16, 28, 40, 52 and 64)

End point title	Percent HbA1c over time (at Weeks 4, 8, 16, 28, 40, 52 and 64)

End point description:

Blood samples were collected from participants for analysis of HbA1c at indicated time points and percentage of HbA1c has been calculated for Weeks 4, 8, 16, 28, 40, 52 and 64. Only those participants with data available at the specified time points were analyzed (represented by n=x in the category titles).

End point type	Secondary

End point timeframe:

Weeks 4, 8, 16, 28, 40, 52 and 64

End point values	Placebo	Albiglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[16]	46[17]		
Units: Percentage of HbA1c				
arithmetic mean (standard deviation)				
Week 4,n=15,43	6.29 (± 0.688)	6.10 (± 0.725)		
Week 8,n=15,46	5.91 (± 0.689)	5.82 (± 0.725)		
Week 16,n=15,46	5.97 (± 0.801)	5.78 (± 0.733)		
Week 28,n=13,43	6.03 (± 0.747)	6.00 (± 0.824)		
Week 40,n=13,42	6.22 (± 0.860)	6.20 (± 0.894)		
Week 52,n=12,43	6.56 (± 0.950)	6.58 (± 1.512)		
Week 64,n=12,40	7.12 (± 1.335)	6.92 (± 1.176)		

Notes:

[16] - ITT Population.

[17] - ITT Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in mean daily insulin use at Week 4, 8, 16, 28, 40, 52 and 64

End point title	Change from Baseline in mean daily insulin use at Week 4, 8, 16, 28, 40, 52 and 64

End point description:

The mean daily insulin use value was calculated, in units per kg per day (units/kg/day) as the sum of average prandial insulin doses and average of basal insulin doses for each participant recorded daily for the 3 days prior to the specified visits, divided by the participant's body weight in kg. Baseline was defined as the last non-missing value with an assessment date on or before the first day of study medication. Change from Baseline was calculated by subtracting Baseline value from the specified time point value. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 16, 28, 40, 52 and 64

End point values	Placebo	Albiglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[18]	46[19]		
Units: Units/kg/day				
arithmetic mean (standard deviation)				
Week 4,n=14,43	-0.02 (± 0.076)	-0.03 (± 0.093)		
Week 8,n=14,46	-0.04 (± 0.105)	-0.02 (± 0.123)		
Week 16,n=15,45	-0.05 (± 0.100)	-0.01 (± 0.148)		
Week 28,n=12,42	-0.01 (± 0.139)	0.03 (± 0.145)		
Week 40,n=13,40	-0.01 (± 0.151)	0.03 (± 0.145)		
Week 52,n=12,41	0.04 (± 0.119)	0.11 (± 0.215)		
Week 64,n=11,38	0.04 (± 0.140)	0.10 (± 0.187)		

Notes:

[18] - ITT Population

[19] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of events of participant-reported significant hypoglycemia,

occurring > Week 24 and <= Week 52

End point title	Number of events of participant-reported significant hypoglycemia, occurring > Week 24 and <= Week 52

End point description:

Significant hypoglycemia was defined as an event with plasma glucose level <= 3.9 mmol/L (<= 70 mg/dL) and/or requiring third party intervention. This corresponds to American Diabetes Association (ADA) category definitions of severe, documented symptomatic, and asymptotic hypoglycemia. The time period was defined as: > Week 24 to <= Week 52 = Day 169 to Day 364. Number of Events were defined as the total number of significant hypoglycemic events at each level of summarization. Number of events of hypoglycemia with confirmed self plasma glucose monitoring <=3.9 mmol/L and/or requiring third party intervention (i.e., severe, documented symptomatic and asymptomatic hypoglycemic events) occurring >Week 24 and <=Week 52 are presented. Only those participants with available data at specified time points were analyzed.

End point type	Secondary

End point timeframe:

Week 24 to 52

End point values	Placebo	Albiglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[20]	45[21]		
Units: Number of Hypoglycemic events				
Any Significant Hypoglycemia	472	1592		
Severe Hypoglycemia	0	0		
Documented Symptomatic Hypoglycemia	241	996		
Asymptomatic Hypoglycemia	231	596		

Notes:

[20] - ITT Population

[21] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time Spent with Plasma Glucose Level <= 3.9, > 3.9 to <= 10.0, and > 10.0 measured by 72 hour Continuous Glucose Monitoring (CGM) at Baseline, Week 28 and 52

End point title	Time Spent with Plasma Glucose Level <= 3.9, > 3.9 to <= 10.0, and > 10.0 measured by 72 hour Continuous Glucose Monitoring (CGM) at Baseline, Week 28 and 52

End point description:

Three days before the visit, the participants made an additional visit to the study site to have the CGM fitted/inserted. It was worn for 3 consecutive days and was removed at the scheduled study visit. Whilst wearing the CGM, participants continued to monitor their plasma glucose at least 4 times a day and on one of the days, conducted 7-point glucose profile (Before breakfast, 2 hours after breakfast, Before lunch, 2 hours after lunch, Before dinner, 2 hours after dinner, At bedtime). Time spent with a plasma glucose <=3.9 millimoles per liter (mmol/L), between >3.9 and 10.0 mmol/L, and >10.0 mmol/L, respectively as performed by 72-hour CGM at Baseline, Week 28 and Week 52 was reported. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and Weeks 28 and 52

End point values	Placebo	Albiglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[22]	46[23]		
Units: hours per day				
arithmetic mean (standard deviation)				
<= 3.9 mmol/L, Baseline,n=14,42	0.80 (± 1.251)	0.98 (± 1.400)		
<= 3.9 mmol/L, Week 28,n=12,36	1.72 (± 1.248)	1.38 (± 1.808)		
<= 3.9 mmol/L, Week 52,n=10,31	1.60 (± 2.142)	1.36 (± 2.405)		
> 3.9 to <= 10.0 mmol/L,Baseline,n=14,42	20.14 (± 3.675)	19.11 (± 3.732)		
> 3.9 to <= 10.0 mmol/L,Week 28,n=12,36	18.93 (± 3.452)	18.83 (± 4.009)		
> 3.9 to <= 10.0 mmol/L,Week 52,n=10,31	17.98 (± 4.491)	18.19 (± 4.772)		
> 10.0 mmol/L, Baseline,n=14,42	3.06 (± 3.560)	3.90 (± 3.727)		
> 10.0 mmol/L,Week 28,n=12,36	3.35 (± 3.115)	3.79 (± 3.782)		
> 10.0 mmol/L,Week 52,n=10,31	4.42 (± 4.597)	4.45 (± 4.781)		

Notes:

[22] - ITT Population.

[23] - ITT Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Hypoglycemic Excursions for each participant from 7-Point Glucose Profile at Baseline, Week 28 and 52

End point title	Number of Hypoglycemic Excursions for each participant from 7-Point Glucose Profile at Baseline, Week 28 and 52

End point description:

A hypoglycemic excursion was defined as an occurrence where the plasma glucose level was <=3.9 mmol/L (<=70 mg/dL). At each visit, only evaluable participants, defined as those with >= 4 non-missing glucose values or >= 1 hypoglycemic excursions were included. Number of Hypoglycemic Excursions for each participant from 7-Point Glucose Profile (Before breakfast, 2 hours after breakfast, Before lunch, 2 hours after lunch, Before dinner, 2 hours after dinner, At bedtime) were reported. Baseline was defined as the last non-missing value with an assessment date on or before the first day of study medication. Only evaluable participants, as defined above were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and Weeks 28 and 52

End point values	Placebo	Albiglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[24]	46[25]		
Units: Hypoglycemic excursions				
arithmetic mean (standard deviation)				
Bseline,n=15,42	0.40 (± 0.632)	0.36 (± 0.656)		

Week 28,n=13,40	0.31 (± 0.630)	0.28 (± 0.554)		
Week 52,n=12,40	0.25 (± 0.452)	0.40 (± 0.672)		

Notes:

[24] - ITT Population.

[25] - ITT Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Greatest magnitude of Hypoglycemic Excursions for each participant from 7-Point Glucose Profile at Baseline, Week 28 and 52

End point title	Greatest magnitude of Hypoglycemic Excursions for each participant from 7-Point Glucose Profile at Baseline, Week 28 and 52

End point description:

A hypoglycemic excursion was defined as an occurrence where the plasma glucose level was <=3.9 mmol/L (<= 70 mg/dL). At each visit, only evaluable participants, defined as those with >= 4 non-missing glucose values or >= 1 hypoglycemic excursions were included. Greatest hypoglycemic excursion was calculated as 3.9 mmol/L minus the lowest recorded glucose level during the 7-point glucose profile (Before breakfast, 2 hours after breakfast, Before lunch, 2 hours after lunch, Before dinner, 2 hours after dinner, At bedtime). If a participant had data recorded at that visit, but did not have a value <= 3.9 mmol/L, their greatest hypoglycemic excursion were 0 mmol/L for that visit. Baseline was defined as the last non-missing value with an assessment date on or before the first day of study medication. Only evaluable participants, as defined above were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and Weeks 28 and 52

End point values	Placebo	Albiglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[26]	46[27]		
Units: mmol/L				
arithmetic mean (standard deviation)				
Baseline,n=15,42	0.24 (± 0.470)	0.22 (± 0.597)		
Week 28,n=13,40	0.18 (± 0.359)	0.08 (± 0.231)		
Week 52,n=12,40	0.22 (± 0.484)	0.17 (± 0.393)		

Notes:

[26] - ITT Population.

[27] - ITT Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Hyperglycemic Excursions for each participant from 7-Point Glucose Profile at Baseline, Week 28 and 52

End point title	Number of Hyperglycemic Excursions for each participant from 7-Point Glucose Profile at Baseline, Week 28 and 52

End point description:

A hyperglycemic excursion was defined as an occurrence where the plasma glucose level was > 10.0

mmol/L (> 180 mg/dL). At each visit, only evaluable participants, defined as those with >= 4 non-missing glucose values or >= 1 hyperglycemic excursions were included. Number of Hyperglycemic Excursions for each participant from 7-Point Glucose Profile (Before breakfast, 2 hours after breakfast, Before lunch, 2 hours after lunch, Before dinner, 2 hours after dinner, At bedtime) were reported. Baseline was defined as the last non-missing value with an assessment date on or before the first day of study medication. Only evaluable participants, as defined above were analyzed (represented by n=X in the category titles)

End point type	Secondary

End point timeframe:

Baseline and Weeks 28 and 52

End point values	Placebo	Albiglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[28]	46[29]		
Units: Hyperglycemic excursions				
arithmetic mean (standard deviation)				
Baseline,n=15,43	0.80 (± 1.014)	1.53 (± 1.502)		
Week 28,n=13,40	1.23 (± 1.301)	0.73 (± 0.933)		
Week 52,n=12,40	1.17 (± 1.115)	1.30 (± 1.522)		

Notes:

[28] - ITT Population.

[29] - ITT Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Greatest magnitude of Hyperglycemic Excursions for each participant from 7-Point Glucose Profile at Baseline, Week 28 and 52

End point title	Greatest magnitude of Hyperglycemic Excursions for each participant from 7-Point Glucose Profile at Baseline, Week 28 and 52

End point description:

A hyperglycemic excursion is defined as an occurrence where the plasma glucose level > 10.0 mmol/L (> 180 mg/dL). At each visit, only evaluable participants, defined as those with >= 4 non-missing glucose values or >= 1 hyperglycemic excursions were included. Greatest hyperglycemic excursion was calculated as the largest recorded glucose level during the 7-point glucose profile (before breakfast, 2 hours after breakfast, before lunch, 2 hours after lunch, before dinner, 2 hours after dinner) minus 10.0 mmol/L. If a participant had data recorded at that visit, but did not have a value >10.0 mmol/L, their greatest hyperglycemic excursion would be 0 mmol/L for that visit. Baseline was defined as the last non-missing value with an assessment date on or before the first day of study medication. Only evaluable participants, as defined above were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and Weeks 28 and 52

End point values	Placebo	Albiglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[30]	46[31]		
Units: mmol/L				
arithmetic mean (standard deviation)				
Baseline,n=15,43	0.94 (± 1.805)	2.72 (± 3.466)		
Week 28,n=13,40	2.05 (± 2.154)	1.52 (± 2.493)		
Week 52,n=12,40	2.19 (± 2.823)	2.42 (± 3.042)		

Notes:

[30] - ITT Population.

[31] - ITT Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in body weight (kilograms) at Week 52

End point title	Change from Baseline in body weight (kilograms) at Week 52

End point description:

Change from Baseline in body weight of participants was reported. Baseline was defined as the last non-missing value with an assessment date on or before the first day of study medication. Change from Baseline was calculated by subtracting Baseline value the Week 52 value. Only those participants with available data at the specified time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo	Albiglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	43		
Units: Kilograms				
arithmetic mean (standard deviation)				
Kilograms	0.26 (± 2.738)	0.77 (± 3.504)		

Statistical analyses

No statistical analyses for this end point

Secondary: Weight over time (at Weeks 2, 4, 6, 8, 16, 28, 40, 52 and 64)

End point title	Weight over time (at Weeks 2, 4, 6, 8, 16, 28, 40, 52 and 64)

End point description:

Body weight was measured in kilograms for participants at indicated time points. Only those participants with data available at the specified time points were analyzed (represented by n=x in the category titles).

End point type	Secondary

End point timeframe:

Weeks 2, 4, 6, 8, 16, 28, 40, 52 and 64

End point values	Placebo	Albiglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[32]	46[33]		
Units: kilograms				
arithmetic mean (standard deviation)				
Week 2,n=15, 43	70.16 (± 14.087)	66.16 (± 11.944)		
Week 4,n=15, 44	69.87 (± 14.409)	66.39 (± 11.952)		
Week 6,n=15, 46	69.83 (± 14.013)	65.65 (± 12.559)		
Week 8,n=15, 46	70.08 (± 14.121)	65.32 (± 12.825)		
Week 16,n=15, 46	69.40 (± 15.191)	65.41 (± 12.824)		
Week 28,n=13, 43	66.08 (± 11.767)	65.32 (± 13.252)		
Week 40,n=13, 42	66.08 (± 11.266)	66.20 (± 13.146)		
Week 52,n=12, 43	66.86 (± 12.401)	66.80 (± 12.696)		
Week 64,n=12, 40	68.29 (± 11.511)	68.13 (± 12.649)		

Notes:

[32] - ITT Population

[33] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Population estimates of Pharmacokinetic (PK) parameters: apparent clearance [CL/F]

End point title	Population estimates of Pharmacokinetic (PK) parameters: apparent clearance [CL/F][34]

End point description:

PK of Albiglutide was evaluated in participants using CL/F using PK samples collected on Weeks 4, 6, 8, 16. CL/F was evaluated by population PK methods and mean and standard error from the final model has been tabulated. Estimates have been presented from the final model centered to mean bodyweights of 67 kilograms, and electronic glomerular filtration rate (eGFR) of 123 milliliters per minute. PK population comprised of participants in Safety Population for whom a PK sample was obtained and analyzed. Only participants who received albiglutide were included in PK Population.

End point type	Secondary

End point timeframe:

48 hours after the most recent dose at Week 4, 6, 8 and 16

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was performed only for arm: Albiglutide

End point values	Albiglutide			
Subject group type	Reporting group			
Number of subjects analysed	49[35]			
Units: Milliliters per hour				
arithmetic mean (standard error)				
Milliliters per hour	45.1 (± 2.56)			

Notes:

[35] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Population estimates of PK parameters: apparent volume of distribution [V/F]

End point title	Population estimates of PK parameters: apparent volume of distribution [V/F][36]

End point description:

PK of Albiglutide was evaluated in participants using V/F using PK samples collected on Weeks 4, 6, 8, 16. V/F was evaluated by population PK methods and mean and standard error from the final model has been tabulated. Estimates have been presented from the final model centered to mean body weights of 67 kilograms, and eGFR of 123 milliliters per minute.

End point type	Secondary

End point timeframe:

48 hours after the most recent dose at Week 4, 6, 8 and 16

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was performed only for arm: Albiglutide

End point values	Albiglutide			
Subject group type	Reporting group			
Number of subjects analysed	49[37]			
Units: Milliliters				
arithmetic mean (standard error)				
Milliliters	4830 (± 677)			

Notes:

[37] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Population estimates of PK parameters: first-order absorption rate constant [Ka]

End point title	Population estimates of PK parameters: first-order absorption rate constant [Ka][38]

End point description:

PK of Albiglutide was evaluated in participants using Ka using PK samples collected on Weeks 4, 6, 8, 16. Ka was evaluated by population PK methods and mean and standard error from the final model has been tabulated. Estimates have been presented from the final model centered to mean body weights of 67 kilograms, and eGFR of 123 milliliters per minute.

End point type	Secondary

End point timeframe:

48 hours after the most recent dose at Week 4, 6, 8 and 16

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This analysis was performed only for arm: Albiglutide

End point values	Albiglutide			
Subject group type	Reporting group			
Number of subjects analysed	49[39]			
Units: Per hour				
arithmetic mean (standard error)				
1/hour	0.0122 (± 0.0022)			

Notes:

[39] - PK Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-therapy AEs and SAEs were collected from start of study treatment up to 52-weeks

Adverse event reporting additional description:

AEs and SAEs were summarized in Safety Population. Safety Population comprised of all participants who received at least one dose of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Albiglutide

Reporting group description:

Albiglutide 30 mg was administered once weekly for 52 weeks by sc injection in the abdomen, thigh or upper arm region along with insulin (Dose increased to 50 mg once weekly at Week 6 if the 30 mg weekly dose was tolerated).

Reporting group title	Placebo

Reporting group description:

Matching placebo was administered once weekly for 52 weeks by sc injection in the abdomen, thigh or upper arm region in addition to insulin.

Serious adverse events	Albiglutide	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 50 (2.00%)	2 / 17 (11.76%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	1 / 50 (2.00%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 50 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			

subjects affected / exposed	0 / 50 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Albiglutide	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 50 (74.00%)	13 / 17 (76.47%)	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 50 (8.00%)	5 / 17 (29.41%)	
occurrences (all)	12	22	
Carpal tunnel syndrome			
subjects affected / exposed	0 / 50 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	0 / 50 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Hypoaesthesia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Somnolence			
subjects affected / exposed	0 / 50 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 50 (2.00%)	2 / 17 (11.76%)	
occurrences (all)	2	2	
Injection site erythema			
subjects affected / exposed	3 / 50 (6.00%)	0 / 17 (0.00%)	
occurrences (all)	18	0	
Malaise			
subjects affected / exposed	3 / 50 (6.00%)	0 / 17 (0.00%)	
occurrences (all)	8	0	
Pyrexia			

subjects affected / exposed	1 / 50 (2.00%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 50 (6.00%)	1 / 17 (5.88%)	
occurrences (all)	3	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	19 / 50 (38.00%)	5 / 17 (29.41%)	
occurrences (all)	41	7	
Diarrhoea			
subjects affected / exposed	13 / 50 (26.00%)	2 / 17 (11.76%)	
occurrences (all)	32	2	
Vomiting			
subjects affected / exposed	10 / 50 (20.00%)	4 / 17 (23.53%)	
occurrences (all)	23	7	
Abdominal distension			
subjects affected / exposed	7 / 50 (14.00%)	0 / 17 (0.00%)	
occurrences (all)	9	0	
Abdominal pain			
subjects affected / exposed	7 / 50 (14.00%)	0 / 17 (0.00%)	
occurrences (all)	22	0	
Abdominal pain upper			
subjects affected / exposed	4 / 50 (8.00%)	3 / 17 (17.65%)	
occurrences (all)	8	6	
Dyspepsia			
subjects affected / exposed	3 / 50 (6.00%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Flatulence			
subjects affected / exposed	2 / 50 (4.00%)	1 / 17 (5.88%)	
occurrences (all)	4	1	
Gastrointestinal pain			
subjects affected / exposed	1 / 50 (2.00%)	1 / 17 (5.88%)	
occurrences (all)	1	5	
Reproductive system and breast disorders			

Dysmenorrhoea			
subjects affected / exposed	0 / 50 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	3 / 50 (6.00%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Cough			
subjects affected / exposed	0 / 50 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Wheezing			
subjects affected / exposed	0 / 50 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 50 (2.00%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Lipodystrophy acquired			
subjects affected / exposed	0 / 50 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 50 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 50 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 50 (26.00%)	5 / 17 (29.41%)	
occurrences (all)	20	5	
Influenza			
subjects affected / exposed	4 / 50 (8.00%)	0 / 17 (0.00%)	
occurrences (all)	5	0	
Gastroenteritis			

subjects affected / exposed	3 / 50 (6.00%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Urinary tract infection			
subjects affected / exposed	2 / 50 (4.00%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Folliculitis			
subjects affected / exposed	0 / 50 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Sinusitis			
subjects affected / exposed	1 / 50 (2.00%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Bronchitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Candida infection			
subjects affected / exposed	0 / 50 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Laryngitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Paronychia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Tooth infection			
subjects affected / exposed	0 / 50 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Varicella			
subjects affected / exposed	0 / 50 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 50 (12.00%)	1 / 17 (5.88%)	
occurrences (all)	8	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 September 2014	Amendment No. 1: Clarification added to wording in the treatment compliance section regarding Week 2. Clarification added regarding the collection of daily insulin use prior to Baseline and correction of typographical errors was made.
24 September 2014	Amendment No. 2: Change to the acceptable contraceptive methods for United Kingdom (UK) sites only at the request of the Medicines & Healthcare products Regulatory Agency (MHRA).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported