



## Clinical trial results:

### GLP-1 Receptor Agonist interVentlon for poor responders afTer bariAtric Surgery: The GRAVITAS trial

#### Summary

EudraCT number	2014-003923-23
Trial protocol	GB
Global end of trial date	08 August 2018

#### Results information

Result version number	v1 (current)
This version publication date	02 February 2020
First version publication date	02 February 2020

#### Trial information

##### Trial identification

Sponsor protocol code	1.1
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##### Additional study identifiers

ISRCTN number	ISRCTN13643081
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1159-1756

Notes:

#### Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	South Kensington Campus, London, United Kingdom, SW7 2AZ
Public contact	ALEXANDER MIRAS, IMPERIAL COLLEGE LONDON, +44 07958377674, a.miras@imperial.ac.uk
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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 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 August 2018
Global end of trial reached?	Yes
Global end of trial date	08 August 2018
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Will liraglutide improve diabetes in patients who have not responded as well to surgery for obesity and diabetes?

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 March 2015
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	United Kingdom: 80
Worldwide total number of subjects	80
EEA total number of subjects	80

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)	70
From 65 to 84 years	10
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Participants were recruited from five hospitals in London, UK: Imperial College Healthcare National Health Service (NHS) Trust, Guy's and St Thomas' NHS Foundation Trust, University College London Hospitals NHS Foundation Trust, St George's University Hospitals NHS Trust, and Chelsea and Westminster Hospital NHS Foundation Trust

### Pre-assignment

Screening details:

Between Jan 29, 2016, and May 2, 2018, 80 participants were randomly assigned to receive liraglutide or placebo for 26 weeks, as an adjunct to a calorie deficit diet and increased physical activity.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Liraglutide

Arm description:

Participants received Liraglutide treatment

Arm type	Experimental
Investigational medicinal product name	Liraglutide
Investigational medicinal product code	
Other name	VICTOZA
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The starting dose was 0.6 mg per day, starting at week 3. The dose was increased by 0.6 mg per day each week as tolerated, up to a maximum total of 1.8 mg per day.

<b>Arm title</b>	Placebo
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Arm description:

Participants received placebo.

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

Dosage and administration details:

The starting dose was 0.6 mg per day, starting at week 3. The dose was increased by 0.6 mg per day each week, up to a maximum total of 1.8 mg per day.

<b>Number of subjects in period 1</b>	Liraglutide	Placebo
Started	53	27
Completed	48	23
Not completed	5	4
Adverse event, serious fatal	-	1
Consent withdrawn by subject	2	1
Physician decision	3	1
Adverse event, non-fatal	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Liraglutide
Reporting group description: Participants received Liraglutide treatment	
Reporting group title	Placebo
Reporting group description: Participants received placebo.	

Reporting group values	Liraglutide	Placebo	Total
Number of subjects	53	27	80
Age categorical Units: Subjects			
Adult (18-69)	53	27	80
Age continuous Units: years			
median	55	57	
inter-quartile range (Q1-Q3)	50 to 61	52 to 64	-
Gender categorical Units: Subjects			
Female	33	14	47
Male	20	13	33

## End points

### End points reporting groups

Reporting group title	Liraglutide
Reporting group description:	
Participants received Liraglutide treatment	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo.	
Subject analysis set title	Baseline
Subject analysis set type	Full analysis
Subject analysis set description:	
Baseline values for participants who completed the study	
Subject analysis set title	Treatment
Subject analysis set type	Full analysis
Subject analysis set description:	
Liraglutide vs placebo treatment tp participants who completed the study	

### Primary: Change in HbA1C

End point title	Change in HbA1C
End point description:	
Data are estimated mean differences and 95%CI.	
End point type	Primary
End point timeframe:	
baseline, 26 weeks	

End point values	Baseline	Treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	71	71		
Units: mmol/mol				
number (confidence interval 95%)	0.7 (0.48 to 0.91)	-13.3 (-19.7 to -7)		

### Statistical analyses

Statistical analysis title	Change in HbA1c
Comparison groups	Baseline v Treatment
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority <sup>[1]</sup>
P-value	= 0.0001
Method	Regression, Linear

Notes:

[1] - Multivariable linear regression

**Secondary: Changes from baseline in bodyweight**

End point title	Changes from baseline in bodyweight
End point description: Data are estimated mean differences and 95%CI.	
End point type	Secondary
End point timeframe: Baseline, 26 weeks	

<b>End point values</b>	Baseline	Treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	71	71		
Units: kg				
arithmetic mean (confidence interval 95%)	0.95 (0.89 to 1.0)	-4.23 (-6.81 to -1.64)		

**Statistical analyses**

<b>Statistical analysis title</b>	Bodyweight
Comparison groups	Baseline v Treatment
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0017
Method	Regression, Linear

**Secondary: Changes in systolic blood pressure**

End point title	Changes in systolic blood pressure
End point description: Data are estimated mean differences and 95%CI.	
End point type	Secondary
End point timeframe: Baseline, 26 weeks	

<b>End point values</b>	Baseline	Treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	71	71		
Units: mm Hg				
arithmetic mean (confidence interval 95%)	0.65 (0.47 to 0.84)	2.14 (-4.52 to 8.80)		

### Statistical analyses

<b>Statistical analysis title</b>	Systolic blood pressure
Comparison groups	Baseline v Treatment
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.52
Method	Regression, Linear

### Secondary: Changes in Diastolic blood pressure

End point title	Changes in Diastolic blood pressure
End point description:	Data are estimated mean differences and 95%CI.
End point type	Secondary
End point timeframe:	Baseline, 26 weeks

<b>End point values</b>	Baseline	Treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	71	71		
Units: mm Hg				
arithmetic mean (confidence interval 95%)	0.51 (0.33 to 0.7)	2.88 (-1.67 to 7.44)		

### Statistical analyses

<b>Statistical analysis title</b>	Diastolic blood pressure
Comparison groups	Baseline v Treatment
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21
Method	Regression, Linear

**Secondary: Changes in total cholesterol**

End point title	Changes in total cholesterol
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End point description:

Data are estimated mean differences and 95%CI.

End point type	Secondary
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End point timeframe:

Baseline, 26 weeks

End point values	Baseline	Treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	71	71		
Units: mmol/L				
arithmetic mean (confidence interval 95%)	0.58 (0.42 to 0.75)	-0.03 (-0.41 to 0.35)		

**Statistical analyses**

<b>Statistical analysis title</b>	Total cholesterol
Comparison groups	Baseline v Treatment
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.88
Method	Regression, Linear

**Secondary: Changes in triglycerides**

End point title	Changes in triglycerides
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End point description:

Data are estimated mean differences and 95%CI.

End point type	Secondary
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End point timeframe:

Baseline, 26 weeks

End point values	Baseline	Treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	71	71		
Units: mmol/L				
arithmetic mean (confidence interval 95%)	0.18 (0.1 to 0.25)	-0.26 (-0.56 to 0.04)		

### Statistical analyses

<b>Statistical analysis title</b>	Triglycerides
Comparison groups	Baseline v Treatment
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.089
Method	Regression, Linear

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

26 weeks

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	10
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### Reporting groups

Reporting group title	Liraglutide
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Reporting group description:

Participants received Liraglutide treatment

Reporting group title	Placebo
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Reporting group description:

Participants received placebo.

<b>Serious adverse events</b>	Liraglutide	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 53 (3.77%)	2 / 27 (7.41%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
Lymphoma			
subjects affected / exposed	1 / 53 (1.89%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
Cellulitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Progression in chronic kidney disease			
subjects affected / exposed	1 / 53 (1.89%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

<b>Non-serious adverse events</b>	Liraglutide	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 53 (49.06%)	18 / 27 (66.67%)	
Nervous system disorders			
Facial paralysis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Headache			
subjects affected / exposed	1 / 53 (1.89%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Injection site bruising			
subjects affected / exposed	1 / 53 (1.89%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	0 / 53 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	9 / 53 (16.98%)	4 / 27 (14.81%)	
occurrences (all)	9	4	
Diarrhoea			
subjects affected / exposed	1 / 53 (1.89%)	2 / 27 (7.41%)	
occurrences (all)	1	2	
Constipation			
subjects affected / exposed	4 / 53 (7.55%)	2 / 27 (7.41%)	
occurrences (all)	4	2	
Vomiting			

subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	1 / 27 (3.70%) 1	
Abdominal discomfort subjects affected / exposed occurrences (all)	2 / 53 (3.77%) 2	0 / 27 (0.00%) 0	
Gastroesophageal reflux disease subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1	0 / 27 (0.00%) 0	
<b>Infections and infestations</b>			
Respiratory tract infection subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1	2 / 27 (7.41%) 2	
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	1 / 27 (3.70%) 1	
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	1 / 27 (3.70%) 1	
<b>Metabolism and nutrition disorders</b>			
Decreased appetite subjects affected / exposed occurrences (all)	3 / 53 (5.66%) 3	1 / 27 (3.70%) 1	
Hypoglycaemia subjects affected / exposed occurrences (all)	2 / 53 (3.77%) 2	1 / 27 (3.70%) 1	
Peripheral oedema subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1	0 / 27 (0.00%) 0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 March 2016	Removal of the upper age limit for inclusion and expansion of the allowable diabetes drugs for inclusion.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31174993>