

# CONFIDENTIAL

CRCTU Birmingham

A 48-WEEK PHASE II, RANDOMISED, DOUBLE BLINDED  
PLACEBO CONTROLLED, PARALLEL-GROUP,  
MULTI-CENTRE TRIAL ON LIRAGLUTIDE'S SAFETY,  
EFFICACY AND ACTION ON LIVER HISTOLOGY AND  
METABOLISM IN OVERWEIGHT PATIENTS WITH  
NON-ALCOHOLIC STEATOHEPATITIS, WITH OR WITHOUT  
TYPE II DIABETES

Liraglutide Efficacy and Action in Non-alcoholic  
steatohepatitis

# LEAN

Prepared by:  
Piers Gaunt

Senior Statistician

EudraCT number:  
CRCTU reference Number:  
ISRCTN number:  
Clinicaltrials.gov identifier:

2009-016761-29  
HE2013  
ISRCTN8577427  
NCT01237119

Data For Histology Measurements

## Contents

1	Histology Results by Treatment	1
1.1	NAS Components . . . . .	1
1.1.1	NAS . . . . .	1
1.1.2	NAS Component scores - Steatosis . . . . .	2
1.1.3	NAS Component scores - Lobular Inflammation . . . . .	3
1.1.4	NAS Component scores - Hepatocyte Ballooning . . . . .	4
1.1.5	Fibrosis . . . . .	5
2	Summary tables for Trial paper	7

1 Histology Results by Treatment

1.1 NAS Components

1.1.1 NAS

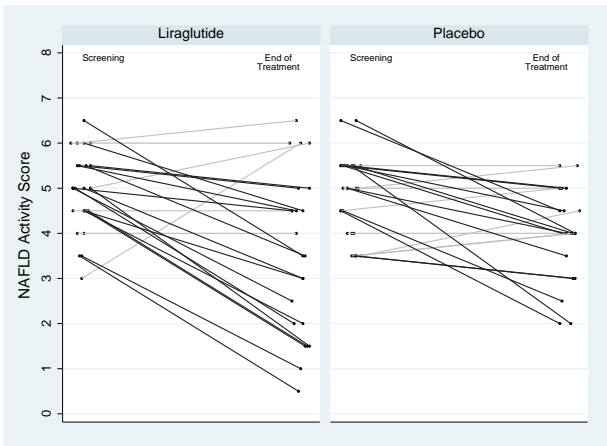
Table 1.1: Change in NAFLD Activity Score by treatment

	Liraglutide (N=26)	Placebo (N=26)	Overall (N=52)
Change in NAFLD Activity Score			
N	23	22	45
Mean (SD)	-1.3 (1.6)	-0.8 (1.2)	-1.1 (1.4)
Median	-1.5	-0.5	-1.0
IQR	-3.0, 0.0	-1.5, 0.0	-2.5, 0.0
Range	-3.5, 3.0	-3.5, 1.0	-3.5, 3.0

Table 1.2: Change in NAFLD Activity Score by Treatment

	Liraglutide (N=26)		Placebo (N=26)		Overall (N=52)	
Change in NAFLD Activity Score	N	%	N	%	N	%
Improvement	17	73.9%	14	63.6%	31	68.9%
No change	3	13%	3	13.6%	6	13.3%
Worsening	3	13%	5	22.7%	8	17.8%
.	3		4		7	
Total	23	100%	22	100%	45	100%

Figure 1.1: Graph of Change in NAFLD Activity Score



## 1.1.2 NAS Component scores - Steatosis

Table 1.3: Change in Steatosis by treatment

	<b>Liraglutide</b> (N=26)	<b>Placebo</b> (N=26)	<b>Overall</b> (N=52)
<b>Change in Steatosis score</b>			
N	23	22	45
Mean (SD)	-0.7 (0.8)	-0.4 (0.8)	-0.5 (0.8)
Median	-0.5	0.0	-0.5
IQR	-1.0, -0.5	-1.0, 0.0	-1.0, 0.0
Range	-2.0, 1.0	-2.0, 1.0	-2.0, 1.0

Table 1.4: Change in Steatosis by Treatment

Change in Steatosis Score	Liraglutide (N=26)		Placebo (N=26)		Overall (N=52)	
	N	%	N	%	N	%
Improvement	19	82.6%	10	45.5%	29	64.4%
No change	2	8.7%	8	36.4%	10	22.2%
Worsening	2	8.7%	4	18.2%	6	13.3%
.	3		4		7	
<b>Total</b>	23	100%	22	100%	45	100%

### 1.1.3 NAS Component scores - Lobular Inflammation

Table 1.5: Change in Lobular Inflammation by treatment

	<b>Liraglutide</b> (N=26)	<b>Placebo</b> (N=26)	<b>Overall</b> (N=52)
<b>Change in Lobular Inflammation score</b>			
N	23	22	45
Mean (SD)	-0.2 (0.6)	-0.2 (0.5)	-0.2 (0.5)
Median	0.0	-0.5	-0.5
IQR	-0.5, 0.0	-0.5, 0.0	-0.5, 0.0
Range	-1.5, 1.0	-1.0, 0.5	-1.5, 1.0

Table 1.6: Change in Lobular Inflammation by Treatment

	Liraglutide (N=26)		Placebo (N=26)		Overall (N=52)	
Change in Lobular Inflammation Score						
	N	%	N	%	N	%
Improvement	11	47.8%	12	54.5%	23	51.1%
No change	8	34.8%	5	22.7%	13	28.9%
Worsening	4	17.4%	5	22.7%	9	20%
.	3		4		7	
<b>Total</b>	23	100%	22	100%	45	100%

## 1.1.4 NAS Component scores - Hepatocyte Ballooning

Table 1.7: Change in Hepatocyte Ballooning by treatment

	<b>Liraglutide</b> (N=26)	<b>Placebo</b> (N=26)	<b>Overall</b> (N=52)
<b>Change in Hepatocyte Ballooning score</b>			
N	23	22	45
Mean (SD)	-0.5 (0.7)	-0.2 (0.6)	-0.4 (0.6)
Median	-0.5	0.0	0.0
IQR	-1.0, 0.0	-0.5, 0.0	-1.0, 0.0
Range	-1.5, 1.0	-1.5, 1.0	-1.5, 1.0

Table 1.8: Change in Hepatocyte Ballooning by Treatment

	Liraglutide (N=26)		Placebo (N=26)		Overall (N=52)	
Change in Hepatocyte Ballooning Score	N	%	N	%	N	%
Improvement	14	60.9%	7	31.8%	21	46.7%
No change	6	26.1%	14	63.6%	20	44.4%
Worsening	3	13%	1	4.5%	4	8.9%
.	3		4		7	
<b>Total</b>	23	100%	22	100%	45	100%

## 1.1.5 Fibrosis

Table 1.9: Change in Kleiner Fibrosis by treatment

	<b>Liraglutide</b> (N=26)	<b>Placebo</b> (N=26)	<b>Overall</b> (N=52)
<b>Change in Kleiner Fibrosis</b>			
N	23	22	45
Mean (SD)	-0.2 (0.8)	0.2 (1.0)	0.0 (0.9)
Median	0.0	0.0	0.0
IQR	-1.0, 0.0	0.0, 1.0	0.0, 0.0
Range	-2.0, 2.0	-2.0, 2.0	-2.0, 2.0

T-test p=0.178

Table 1.10: Change in Kleiner Fibrosis by Treatment

Change in Kleiner Fibrosis Score	Liraglutide (N=26)		Placebo (N=26)		Overall (N=52)	
	N	%	N	%	N	%
Improvement	6	26.1%	3	13.6%	9	20%
No change	15	65.2%	11	50%	26	57.8%
Worsening	2	8.7%	8	36.4%	10	22.2%
.	3		4		7	
<b>Total</b>	23	100%	22	100%	45	100%

Table 1.11: Change in 6-point Ishak Fibrosis by treatment

	<b>Liraglutide</b> (N=26)	<b>Placebo</b> (N=26)	<b>Overall</b> (N=52)
<b>Change in 6-point Ishak Fibrosis score</b>			
N	23	22	45
Mean (SD)	-0.2 (1.2)	0.1 (0.8)	-0.1 (1.1)
Median	-0.5	0.0	0.0
IQR	-1.0, 0.0	0.0, 0.5	-1.0, 0.0
Range	-2.5, 3.0	-2.0, 2.0	-2.5, 3.0

Table 1.12: Change in 6-point Ishak Fibrosis by Treatment

	Liraglutide (N=26)		Placebo (N=26)		Overall (N=52)	
Change in 6-point Ishak Fibrosis Score	N	%	N	%	N	%
Improvement	12	52.2%	5	22.7%	17	37.8%
No change	7	30.4%	11	50%	18	40%
Worsening	4	17.4%	6	27.3%	10	22.2%
.	3		4		7	
<b>Total</b>	23	100%	22	100%	45	100%



## 2 Summary tables for Trial paper

Table 2.1: Baseline Histology by treatment

	<b>Liraglutide</b> (N=26)	<b>Placebo</b> (N=26)	<b>Overall</b> (N=52)
<b>Kleiner Fibrosis Score</b>			
Mean (SD)	2.3 (0.9)	2.3 (1.3)	2.3 (1.1)
<b>6-point Ishak Fibrosis</b>			
Mean (SD)	2.5 (1.5)	2.8 (1.7)	2.6 (1.5)
<b>NAS</b>			
Mean (SD)	4.9 (0.9)	4.8 (0.9)	4.9 (0.9)
<b>Steatosis</b>			
Mean (SD)	2.1 (0.7)	1.9 (0.7)	2.0 (0.7)
<b>Lobular Inflammation</b>			
Mean (SD)	1.4 (0.3)	1.4 (0.4)	1.4 (0.4)
<b>Hepatocyte Ballooning</b>			
Mean (SD)	1.5 (0.5)	1.5 (0.4)	1.5 (0.5)
<b>Portal Inflammation (Ishak 1995)</b>			
Mean (SD)	1.0 (0.6)	1.0 (0.5)	1.0 (0.6)
<b>Interface Hepatitis (Ishak 1995)</b>			
Mean (SD)	0.6 (0.5)	0.6 (0.5)	0.6 (0.5)
<b>Ductular Reaction</b>			
Mean (SD)	0.9 (0.5)	0.9 (0.7)	0.9 (0.6)
<b>Number of Complete Portal Tracts</b>			
Mean (SD)	18.5 (7.1)	16.2 (5.3)	17.4 (6.3)
<b>Length of Biopsy (mm)</b>			
Mean (SD)	21.0 (7.6)	19.7 (5.7)	20.3 (6.7)

Table 2.2: Histology Results by treatment

	<b>Liraglutide</b> (N=26)	<b>Placebo</b> (N=26)	<b>Overall</b> (N=52)
<b>Change in NAFLD Activity Score</b>			
Mean (SD)	-1.3 (1.6)	-0.8 (1.2)	-1.1 (1.4)
<b>Change in Steatosis score</b>			
Mean (SD)	-0.7 (0.8)	-0.4 (0.8)	-0.5 (0.8)
<b>Change in Lobular Inflammation score</b>			
Mean (SD)	-0.2 (0.6)	-0.2 (0.5)	-0.2 (0.5)
<b>Change in Hepatocyte Ballooning score</b>			
Mean (SD)	-0.5 (0.7)	-0.2 (0.6)	-0.4 (0.6)
<b>Change in Portal Inflammation (Ishak 1995) score</b>			
Mean (SD)	0.1 (0.6)	0.1 (0.5)	0.1 (0.5)
<b>Change in Interface Hepatitis (Ishak 1995) score</b>			
Mean (SD)	0.0 (0.5)	-0.0 (0.5)	-0.0 (0.5)
<b>Change in Ductular Reaction score</b>			
Mean (SD)	-0.0 (0.5)	-0.0 (0.5)	-0.0 (0.5)
<b>Change in Kleiner Fibrosis</b>			
Mean (SD)	-0.2 (0.8)	0.2 (1.0)	0.0 (0.9)
<b>Change in 6-point Ishak Fibrosis score</b>			
Mean (SD)	-0.2 (1.2)	0.1 (0.8)	-0.1 (1.1)

Table 2.3: Histology Results by Treatment

	Liraglutide (N=26)		Placebo (N=26)	
NAFLD Activity Score				
Patients with Improvement	17	73.9%	14	63.6%
Patients worsen or no change	6	26.1%	8	36.4%
.	3		4	
Total	23	100%	22	100%
Steatosis				
Patients with Improvement	19	82.6%	10	45.5%
Patients worsen or no change	4	17.4%	12	54.5%
.	3		4	
Total	23	100%	22	100%
Lobular Inflammation				
Patients with Improvement	11	47.8%	12	54.5%
Patients worsen or no change	12	52.2%	10	45.5%
.	3		4	
Total	23	100%	22	100%
Hepatocyte Ballooning				
Patients with Improvement	14	60.9%	7	31.8%
Patients worsen or no change	9	39.1%	15	68.2%
.	3		4	
Total	23	100%	22	100%
Portal Inflammation (Ishak 1995)				
Patients with Improvement	4	17.4%	6	27.3%
Patients worsen or no change	19	82.6%	16	72.7%
.	3		4	
Total	23	100%	22	100%
Interface Hepatitis (Ishak 1995)				
Patients with Improvement	6	26.1%	7	31.8%
Patients worsen or no change	17	73.9%	15	68.2%
.	3		4	
Total	23	100%	22	100%
Ductular Reaction				
Patients with Improvement	8	34.8%	9	40.9%
Patients worsen or no change	15	65.2%	13	59.1%
.	3		4	
Total	23	100%	22	100%

Table 2.4: Histology Results by Treatment

	Liraglutide		Placebo	
Kleiner Fibrosis				
Patients with Improvement	6	26.1%	3	13.6%
Patients worsen or no change	17	73.9%	19	86.4%
.	3		4	
6-point Ishak Fibrosis				
Patients with Improvement	12	52.2%	5	22.7%
Patients worsen or no change	11	47.8%	17	77.3%
.	3		4	
Number of patients with biopsy at end of treatment visit				
no	3	11.5%	4	15.4%
yes	23	88.5%	22	84.6%