

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

The word "LEAN" is written in a large, blue, serif font. The letters have a slight 3D effect with a dark blue shadow beneath them.

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Adverse Event Tables for EudraCT reporting

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1 Adverse Event Details for EudraCT

1.1 Number of patients with adverse events by CTCAE v4 Category

Table 1.1: Table of number of patients with Cardiac disorder adverse events

	Liraglutide (N=26)	Placebo (N=26)	Overall (N=52)
Cardiac disorders	3 (12%)	3 (12%)	6 (12%)
Cardiac chest pain	1 (4%)	0 (0%)	1 (2%)
Conduction disorder	0 (0%)	1 (4%)	1 (2%)
Sinus tachycardia	1 (4%)	0 (0%)	1 (2%)
ECG left bundle brach block	1 (4%)	0 (0%)	1 (2%)
ECG ischemic changes	0 (0%)	1 (4%)	1 (2%)
Intermittent palpitations	0 (0%)	1 (4%)	1 (2%)

Table 1.2: Table of number of patients with Ear and labyrinth disorder adverse events

	Liraglutide (N=26)	Placebo (N=26)	Overall (N=52)
Ear and labyrinth disorders	1 (4%)	0 (0%)	1 (2%)
Ear pain	1 (4%)	0 (0%)	1 (2%)

Table 1.3: Table of number of patients with Endocrine disorder adverse events

	Liraglutide (N=26)	Placebo (N=26)	Overall (N=52)
Endocrine disorders	1 (4%)	1 (4%)	2 (4%)
Hypothyroidism	1 (4%)	0 (0%)	1 (2%)
Poor glycaemic control	0 (0%)	1 (4%)	1 (2%)

Table 1.4: Table of number of patients with Eye disorder adverse events

	Liraglutide (N=26)	Placebo (N=26)	Overall (N=52)
Eye disorders	1 (4%)	5 (19%)	6 (12%)
Blurred vision	1 (4%)	1 (4%)	2 (4%)
Cataract	0 (0%)	1 (4%)	1 (2%)
Conjunctival haemorrhage	0 (0%)	2 (8%)	2 (4%)
Twitching eye	0 (0%)	1 (4%)	1 (2%)

Table 1.5: Table of number of patients with Gastrointestinal disorder adverse events

	Liraglutide (N=26)	Placebo (N=26)	Overall (N=52)
Gastrointestinal disorders	21 (81%)	17 (65%)	38 (73%)
Abdominal pain	8 (31%)	7 (27%)	15 (29%)
Bloating	4 (15%)	0 (0%)	4 (8%)
Colitis	0 (0%)	1 (4%)	1 (2%)
Constipation	7 (27%)	0 (0%)	7 (13%)
Diarrhea	10 (38%)	5 (19%)	15 (29%)
Dry mouth	0 (0%)	2 (8%)	2 (4%)
Dyspepsia	4 (15%)	1 (4%)	5 (10%)
Dysphagia	1 (4%)	0 (0%)	1 (2%)
Flatulence	4 (15%)	0 (0%)	4 (8%)
Hemorrhoids	1 (4%)	0 (0%)	1 (2%)
Nausea	12 (46%)	10 (38%)	22 (42%)
Gum Hypertrophy	0 (0%)	1 (4%)	1 (2%)
Halitosis	2 (8%)	0 (0%)	2 (4%)
Malena	0 (0%)	1 (4%)	1 (2%)
Vomiting	5 (19%)	3 (12%)	8 (15%)

Table 1.6: Table of number of patients with General disorders and administration site conditions

	Liraglutide (N=26)	Placebo (N=26)	Overall (N=52)
General disorders and administration site conditions	13 (50%)	17 (65%)	30 (58%)
Chills	4 (15%)	0 (0%)	4 (8%)
Edema limbs	2 (8%)	3 (12%)	5 (10%)
Fatigue	4 (15%)	5 (19%)	9 (17%)
Flu like symptoms	3 (12%)	6 (23%)	9 (17%)
Injection site reaction	9 (35%)	10 (38%)	19 (37%)
Irritability	0 (0%)	1 (4%)	1 (2%)
Malaise	0 (0%)	1 (4%)	1 (2%)
Pain	2 (8%)	4 (15%)	6 (12%)
Tasted trial medication	1 (4%)	0 (0%)	1 (2%)

Table 1.7: Table of number of patients with Infections and infestations

	Liraglutide (N=26)	Placebo (N=26)	Overall (N=52)
Infections and infestations	3 (12%)	9 (35%)	12 (23%)
Chest infection	0 (0%)	5 (19%)	5 (10%)
Urinary tract infection	0 (0%)	4 (15%)	4 (8%)
Eye infection	0 (0%)	1 (4%)	1 (2%)
Mucosal infection	0 (0%)	1 (4%)	1 (2%)
Sinusitis	2 (8%)	0 (0%)	2 (4%)
Tuberculosis	1 (4%)	0 (0%)	1 (2%)
Tooth infection	1 (4%)	0 (0%)	1 (2%)
Vaginal infection	0 (0%)	1 (4%)	1 (2%)

Table 1.8: Table of number of patients with Injury, poisoning and procedural complications

	Liraglutide (N=26)	Placebo (N=26)	Overall (N=52)
Injury, poisoning and procedural complications	1 (4%)	1 (4%)	2 (4%)
Burn	1 (4%)	0 (0%)	1 (2%)
Vascular access complication	0 (0%)	1 (4%)	1 (2%)
Trauma	0 (0%)	1 (4%)	1 (2%)

Table 1.9: Table of number of patients with Investigation adverse events

	Liraglutide (N=26)	Placebo (N=26)	Overall (N=52)
Investigations	5 (19%)	11 (42%)	16 (31%)
Increased alanine aminotransferase	1 (4%)	2 (8%)	3 (6%)
Increased aspartate aminotransferase	1 (4%)	3 (12%)	4 (8%)
Increased bilirubin	1 (4%)	2 (8%)	3 (6%)
High cholesterol	0 (0%)	1 (4%)	1 (2%)
Increased γ -glutamyl transferase	0 (0%)	3 (12%)	3 (6%)
Increased triglycerides	0 (0%)	2 (8%)	2 (4%)
Decreased Lymphocyte count	1 (4%)	0 (0%)	1 (2%)
Increased Lymphocyte count	0 (0%)	1 (4%)	1 (2%)
Decreased platelets	0 (0%)	1 (4%)	1 (2%)
High calcitonin	0 (0%)	1 (4%)	1 (2%)
Uncontrolled sweating	0 (0%)	1 (4%)	1 (2%)
Increased amylase	2 (8%)	0 (0%)	2 (4%)
Increased weight	1 (4%)	0 (0%)	1 (2%)
Decreased weight	1 (4%)	0 (0%)	1 (2%)

Table 1.10: Table of number of patients with Metabolism and nutrition disorder adverse events

	Liraglutide (N=26)	Placebo (N=26)	Overall (N=52)
Metabolism and nutrition disorders	11 (42%)	6 (23%)	17 (33%)
Anorexia	8 (31%)	2 (8%)	10 (19%)
Dehydration	1 (4%)	0 (0%)	1 (2%)
Hypoglycaemia	1 (4%)	1 (4%)	2 (4%)
Hyperglycaemia	1 (4%)	2 (8%)	3 (6%)
Increased Appetite	2 (8%)	1 (4%)	3 (6%)

Table 1.11: Table of number of patients with Musculoskeletal and connective tissue disorder adverse events

	Liraglutide (N=26)	Placebo (N=26)	Overall (N=52)
Musculoskeletal and connective tissue disorders	8 (31%)	14 (54%)	22 (42%)
Arthralgia	1 (4%)	4 (15%)	5 (10%)
Arthritis	1 (4%)	0 (0%)	1 (2%)
Back pain	3 (12%)	7 (27%)	10 (19%)
Bone pain	1 (4%)	0 (0%)	1 (2%)
Chest wall pain	0 (0%)	1 (4%)	1 (2%)
Muscle weakness	1 (4%)	1 (4%)	2 (4%)
Joint range of motion decreased	0 (0%)	1 (4%)	1 (2%)
Myalgia	0 (0%)	1 (4%)	1 (2%)
Cramp	0 (0%)	3 (12%)	3 (6%)
Pain in heel	0 (0%)	2 (8%)	2 (4%)
Fibromyalgia	0 (0%)	1 (4%)	1 (2%)
Trapped nerve	1 (4%)	0 (0%)	1 (2%)
Stiffness in joints	0 (0%)	2 (8%)	2 (4%)
Trigger finger	0 (0%)	1 (4%)	1 (2%)
Pain in extremity	2 (8%)	0 (0%)	2 (4%)

Table 1.12: Table of number of patients with Nervous system disorder adverse events

	Liraglutide (N=26)	Placebo (N=26)	Overall (N=52)
Nervous system disorders	14 (54%)	11 (42%)	25 (48%)
Dizziness	6 (23%)	7 (27%)	13 (25%)
Headache	9 (35%)	7 (27%)	16 (31%)
Neuralgia	1 (4%)	0 (0%)	1 (2%)
Drop in concentration	1 (4%)	1 (4%)	2 (4%)
Pins and Needles	2 (8%)	0 (0%)	2 (4%)
Sciatica	0 (0%)	1 (4%)	1 (2%)
Fainting or lightheaded	2 (8%)	0 (0%)	2 (4%)
Floating sensation	1 (4%)	0 (0%)	1 (2%)
Peripheral sensory neuropathy	0 (0%)	1 (4%)	1 (2%)

Table 1.13: Table of number of patients with Psychiatric disorder adverse events

	Liraglutide (N=26)	Placebo (N=26)	Overall (N=52)
Psychiatric disorders	6 (23%)	7 (27%)	13 (25%)
Anxiety	2 (8%)	1 (4%)	3 (6%)
Depression	2 (8%)	6 (23%)	8 (15%)
Insomnia	2 (8%)	1 (4%)	3 (6%)

Table 1.14: Table of number of patients with Renal and urinary disorder adverse events

	Liraglutide (N=26)	Placebo (N=26)	Overall (N=52)
Renal and urinary disorders	2 (8%)	3 (12%)	5 (10%)
Cystitis noninfective	0 (0%)	1 (4%)	1 (2%)
Hematuria	1 (4%)	0 (0%)	1 (2%)
Urinary frequency	0 (0%)	1 (4%)	1 (2%)
Urinary retention	0 (0%)	1 (4%)	1 (2%)

Table 1.15: Table of number of patients with Reproductive system and breast disorder adverse events

	Liraglutide (N=26)	Placebo (N=26)	Overall (N=52)
Reproductive system and breast disorders	0 (0%)	2 (8%)	2 (4%)
Breast pain	0 (0%)	1 (4%)	1 (2%)
Prolapsed uterus	0 (0%)	1 (4%)	1 (2%)

Table 1.16: Table of number of patients with Respiratory, thoracic and mediastinal disorder adverse events

	Liraglutide (N=26)	Placebo (N=26)	Overall (N=52)
Respiratory, thoracic and mediastinal disorders	3 (12%)	6 (23%)	9 (17%)
Bronchospasm	0 (0%)	2 (8%)	2 (4%)
Cough	2 (8%)	3 (12%)	5 (10%)
Dyspnea	2 (8%)	1 (4%)	3 (6%)
Nasal congestion	0 (0%)	1 (4%)	1 (2%)
Pain in lung	0 (0%)	1 (4%)	1 (2%)

Table 1.17: Table of number of patients with Skin and subcutaneous tissue disorder adverse events

	Liraglutide (N=26)	Placebo (N=26)	Overall (N=52)
Skin and subcutaneous tissue disorders	7 (27%)	3 (12%)	10 (19%)
Dry skin	0 (0%)	1 (4%)	1 (2%)
Erythema multiforme	1 (4%)	0 (0%)	1 (2%)
Lipoma at injection site	1 (4%)	0 (0%)	1 (2%)
Bruising not at injection site	1 (4%)	0 (0%)	1 (2%)
Insect bites	0 (0%)	1 (4%)	1 (2%)
Pruritus	2 (8%)	0 (0%)	2 (4%)
Sore hands	1 (4%)	0 (0%)	1 (2%)
Rash or Urticaria	0 (0%)	2 (8%)	2 (4%)
Palmar-plantar erythrodysesthesia syndrome	1 (4%)	0 (0%)	1 (2%)

Table 1.18: Table of number of patients with Surgical and medical procedures

	Liraglutide (N=26)	Placebo (N=26)	Overall (N=52)
Surgical and medical procedures	0 (0%)	1 (4%)	1 (2%)
Mole removed	0 (0%)	1 (4%)	1 (2%)

Table 1.19: Table of number of patients with Vascular disorder adverse events

	Liraglutide (N=26)	Placebo (N=26)	Overall (N=52)
Vascular disorders	1 (4%)	0 (0%)	1 (2%)
Hot flushes	1 (4%)	0 (0%)	1 (2%)

1.2 Number of incidences of adverse events

There were a total of 419 reported adverse events over the course of the trial, the details of which are provided in this section.

Table 1.20: Table of count of Cardiac disorder adverse events

	Liraglutide	Placebo	Overall
Cardiac disorders	4	3	7
Cardiac chest pain	2	0	2
Conduction disorder	0	1	1
Sinus tachycardia	1	0	1
ECG left bundle brach block	1	0	1
ECG ischemic changes	0	1	1
Intermittent palpitations	0	1	1

Table 1.21: Table of count of Ear and labyrinth disorder adverse events

	Liraglutide	Placebo	Overall
Ear and labyrinth disorders	1	0	1
Ear pain	1	0	1

Table 1.22: Table of count of Endocrine disorder adverse events

	Liraglutide	Placebo	Overall
Endocrine disorders	1	1	2
Hypothyroidism	1	0	1
Poor glycaemic control	0	1	1

Table 1.23: Table of count of Eye disorder adverse events

	Liraglutide	Placebo	Overall
Eye disorders	1	5	6
Blurred vision	1	1	2
Cataract	0	1	1
Conjunctival haemorrhage	0	2	2
Twitching eye	0	1	1

Table 1.24: Table of count of Gastrointestinal disorder adverse events

	Liraglutide	Placebo	Overall
Gastrointestinal disorders	79	42	121
Abdominal pain	12	10	22
Bloating	6	0	6
Colitis	0	1	1
Constipation	11	0	11
Diarrhea	15	8	23
Dry mouth	0	3	3
Dyspepsia	6	1	7
Dysphagia	1	0	1
Flatulence	5	0	5
Hemorrhoids	1	0	1
Nausea	15	12	27
Gum Hypertrophy	0	1	1
Halitosis	2	0	2
Malena	0	1	1
Vomiting	5	5	10

Table 1.25: Table of count of General disorders and administration site conditions

	Liraglutide	Placebo	Overall
General disorders and administration site conditions	30	32	62
Chills	4	0	4
Edema limbs	2	3	5
Fatigue	8	5	13
Flu like symptoms	3	7	10
Injection site reaction	10	10	20
Irritability	0	1	1
Malaise	0	1	1
Pain	2	5	7
Tasted trial medication	1	0	1

Table 1.26: Table of count of Infections and infestations

	Liraglutide	Placebo	Overall
Infections and infestations	4	14	18
Chest infection	0	7	7
Urinary tract infection	0	4	4
Eye infection	0	1	1
Mucosal infection	0	1	1
Sinusitis	2	0	2
Tuberculosis	1	0	1
Tooth infection	1	0	1
Vaginal infection	0	1	1

Table 1.27: Table of count of Injury, poisoning and procedural complications

	Liraglutide	Placebo	Overall
Injury, poisoning and procedural complications	1	2	3
Burn	1	0	1
Vascular access complication	0	1	1
Trauma	0	1	1

Table 1.28: Table of count of Investigation adverse events

Investigations	Liraglutide 10	Placebo 26	Overall 36
Increased alanine aminotransferase	1	3	4
Increased aspartate aminotransferase	2	6	8
Increased bilirubin	2	6	8
High cholesterol	0	1	1
Increased γ -glutamyl transferase	0	3	3
Increased triglycerides	0	2	2
Decreased Lymphocyte count	1	0	1
Increased Lymphocyte count	0	1	1
Decreased platelets	0	2	2
High calcitonin	0	1	1
Uncontrolled sweating	0	1	1
Increased amylase	2	0	2
Increased weight	1	0	1
Decreased weight	1	0	1

Table 1.29: Table of count of Metabolism and nutrition disorder adverse events

Metabolism and nutrition disorders	Liraglutide 13	Placebo 8	Overall 21
Anorexia	8	2	10
Dehydration	1	0	1
Hypoglycaemia	1	2	3
Hyperglycaemia	1	3	4
Increased Appetite	2	1	3

Table 1.30: Table of count of Musculoskeletal and connective tissue disorder adverse events

Musculoskeletal and connective tissue disorders	Liraglutide 11	Placebo 30	Overall 41
Arthralgia	2	7	9
Arthritis	1	0	1
Back pain	3	10	13
Bone pain	1	0	1
Chest wall pain	0	1	1
Muscle weakness	1	1	2
Joint range of motion decreased	0	1	1
Myalgia	0	1	1
Cramp	0	3	3
Pain in heel	0	2	2
Fibromyalgia	0	1	1
Trapped nerve	1	0	1
Stiffness in joints	0	2	2
Trigger finger	0	1	1
Pain in extremity	2	0	2

Table 1.31: Table of count of Nervous system disorder adverse events

	Liraglutide	Placebo	Overall
Nervous system disorders	31	21	52
Dizziness	8	10	18
Headache	15	8	23
Neuralgia	1	0	1
Drop in concentration	1	1	2
Pins and Needles	3	0	3
Sciatica	0	1	1
Fainting or lightheaded	2	0	2
Floating sensation	1	0	1
Peripheral sensory neuropathy	0	1	1

Table 1.32: Table of count of Psychiatric disorder adverse events

	Liraglutide	Placebo	Overall
Psychiatric disorders	7	8	15
Anxiety	2	1	3
Depression	3	6	9
Insomnia	2	1	3

Table 1.33: Table of count of Renal and urinary disorder adverse events

	Liraglutide	Placebo	Overall
Renal and urinary disorders	2	3	5
Cystitis noninfective	0	1	1
Hematuria	1	0	1
Urinary frequency	0	1	1
Urinary retention	0	1	1

Table 1.34: Table of count of Reproductive system and breast disorder adverse events

	Liraglutide	Placebo	Overall
Reproductive system and breast disorders	0	2	2
Breast pain	0	1	1
Prolapsed uterus	0	1	1

Table 1.35: Table of count of Respiratory, thoracic and mediastinal disorder adverse events

	Liraglutide	Placebo	Overall
Respiratory, thoracic and mediastinal disorders	4	9	13
Bronchospasm	0	3	3
Cough	2	3	5
Dyspnea	2	1	3
Nasal congestion	0	1	1
Pain in lung	0	1	1

Table 1.36: Table of count of Skin and subcutaneous tissue disorder adverse events

	Liraglutide	Placebo	Overall
Skin and subcutaneous tissue disorders	8	4	12
Dry skin	0	1	1
Erythema multiforme	1	0	1
Lipoma at injection site	1	0	1
Bruising not at injection site	1	0	1
Insect bites	0	1	1
Pruritus	3	0	3
Sore hands	1	0	1
Rash or Urticaria	0	2	2
Palmar-plantar erythrodysesthesia syndrome	1	0	1

Table 1.37: Table of count of Surgical and medical procedures

	Liraglutide	Placebo	Overall
Surgical and medical procedures	0	1	1
Mole removed	0	1	1

Table 1.38: Table of count of Vascular disorder adverse events

	Liraglutide	Placebo	Overall
Vascular disorders	1	0	1
Hot flushes	1	0	1