GLP-1 agonists as a target in Parkinson's disease

Dr Dilan Athauda MRCP BSc PhD

Consultant Neurologist and Senior Research Fellow

Dept. Clinical and Movement Neurosciences

UCL Institute of Neurology & The National Hospital for Neurology and Neurosurgery; The Francis Crick Institute

Conflicts of Interest

Co-investigator on Exenatide-PD3 and Exenatide-MSA Clinical trials

Funding:

- National Institutes of Health (NIHR)
- Medical Research Council (MRC)
- Parkinson's UK
- Cure Parkinson's Trust

GLP-1 agonists & Parkinson's – **Epidemiological data**

GLP-1 agonists & Parkinson's – **Epidemiological data**

- **People with T2DM who use GLP-1 targeting drugs have a reduced risk of developing Parkinson's**

GLP-1 agonists & Parkinson's – **Epidemiological data**

- **People with T2DM who use GLP-1 targeting drugs have a reduced risk of developing Parkinson's**

- Swedish National Inpatient Register (n=6,000)

- Health Improvement Network (THIN) database (n=100,000)

- U.S. Medicare data (n=90,000)

DPP4 inhibitors
OR = 0.23
(95% CI 0.07-0.74)


Movement Disorders
Official Journal of the International Parkinson and Movement Disorder Society

Letters: New Observations | Full Access

Reduced incidence of Parkinson's disease after dipeptidyl peptidase-4 inhibitors—A nationwide case-control study

Per Svenningsson MD, PhD, Karin Wirdefeldt MD, PhD, Li Yin PhD, Fang Fang PhD, Ioanna Markaki MD,

GLP-1 A
IRR 0.38
(95% CI 0.17–0.60)

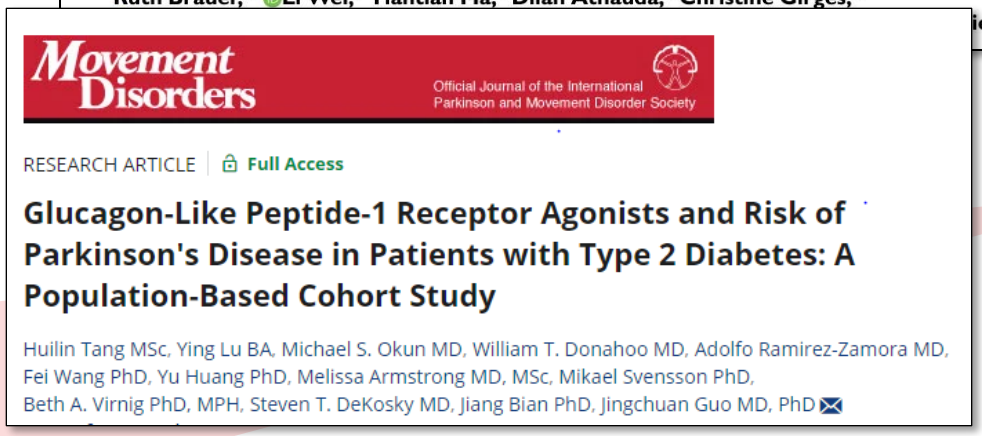

doi:10.1093/brain/awaa262 BRAIN 2020: Page 3067 of 3076 | 3067

BRAIN
A JOURNAL OF NEUROLOGY

Diabetes medications and risk of Parkinson's disease: a cohort study of patients with diabetes

Ruth Brauer,[1] Li Wei,[1] Tiantian Ma,[1] Dilan Athauda,[2] Christine Girges,[2]

GLP-1 A
HR 0.77
(95% CI 0.17–0.60)


Movement Disorders
Official Journal of the International Parkinson and Movement Disorder Society

RESEARCH ARTICLE | Full Access

Glucagon-Like Peptide-1 Receptor Agonists and Risk of Parkinson's Disease in Patients with Type 2 Diabetes: A Population-Based Cohort Study

Huilin Tang MSc, Ying Lu BA, Michael S. Okun MD, William T. Donahoo MD, Adolfo Ramirez-Zamora MD, Fei Wang PhD, Yu Huang PhD, Melissa Armstrong MD, MSc, Mikael Svensson PhD, Beth A. Virnig PhD, MPH, Steven T. DeKosky MD, Jiang Bian PhD, Jingchuan Guo MD, PhD

GLP-1 agonists & Parkinson's – **Exenatide-PD1 Trial (2013)**

Drug: Exenatide (*Byetta*)

GLP-1 agonists & Parkinson's – **Exenatide-PD1 Trial (2013)**

Drug: Exenatide (*Byetta*)

Pilot trial, n=44

Open label (placebo cost)

Exposure for 12 months

Final assessment 14 months

Primary outcome measure

- MDS UPDRS part 3 (OFF) at 14 months

Demographics

- Patients ~ 60yrs old
- Disease duration ~10 yrs
- Levodopa dose ~ 980mg daily

GLP-1 agonists & Parkinson's – **Exenatide-PD1 Trial (2013)**

Primary Outcome

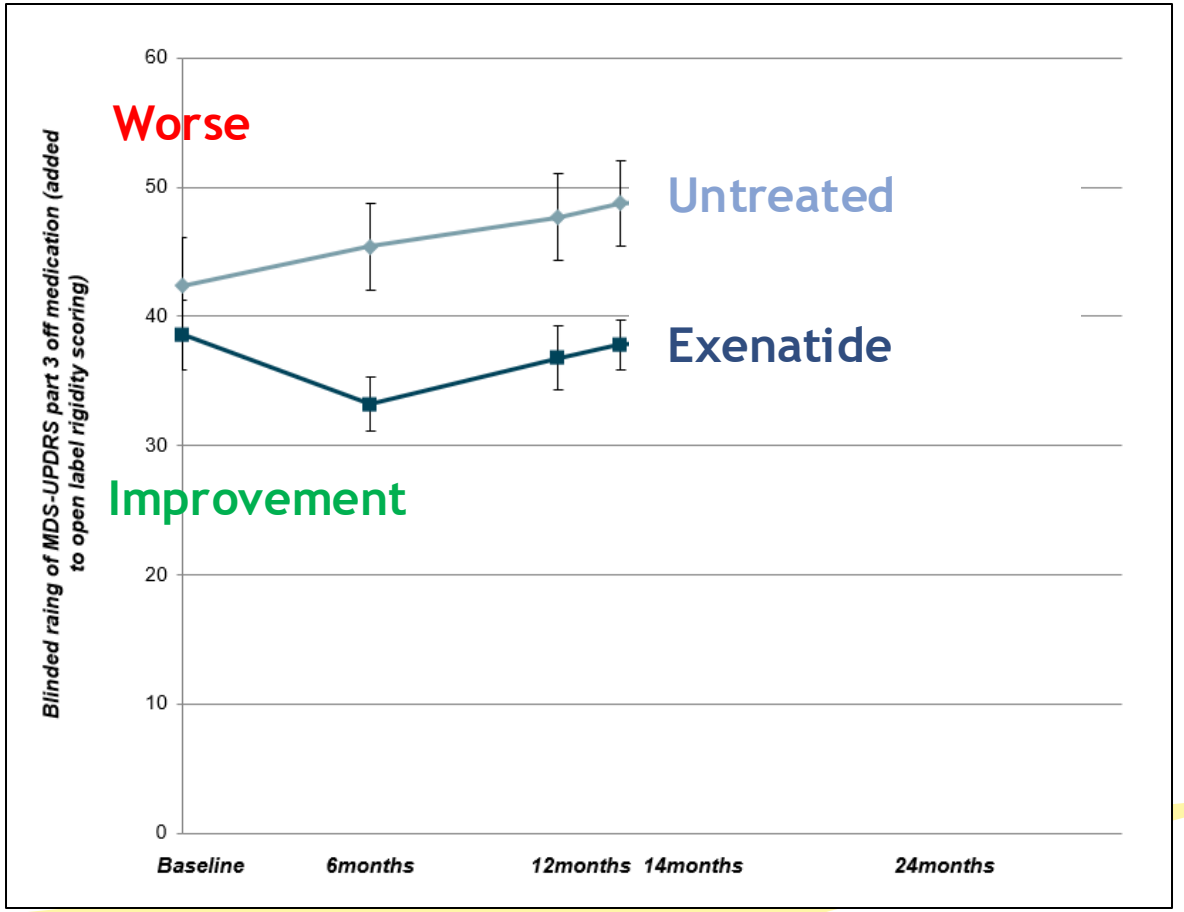
- MDS-UPDRS III OFF

GLP-1 agonists & Parkinson's – **Exenatide-PD1 Trial (2013)**

Primary Outcome

- MDS-UPDRS III OFF

	Baseline Mean (SD)	6 Months Mean (SD)	12 Months Mean (SD)	Difference Baseline to 12 months Mean (SE)	P value	14 Months Mean (SD)	Difference baseline to 14 months Mean (SE)	P value
Exenatide	31.0 (11.2)	25.2 (9.0)	28.3 (9.9)	-2.7 (1.7)	P=0.037	29.3 (8.5)	-1.7 (1.6)	P=0.04
Control	34.0 (16.1)	34.4 (15.0)	36.2 (15.4)	2.2 (1.5)		36.8 (15.2)	2.8 (1.4)	



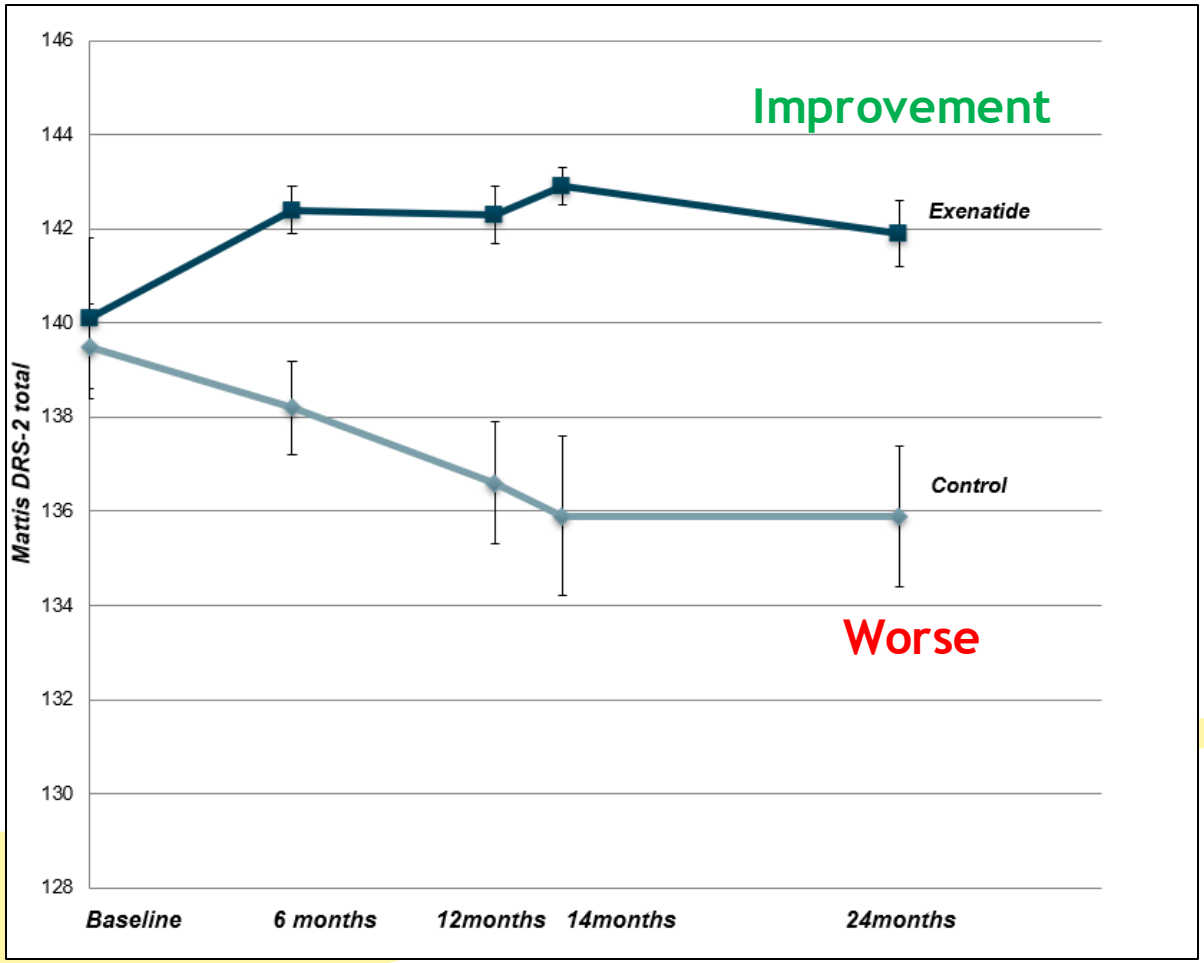
GLP-1 agonists & Parkinson's – **Exenatide-PD1 Trial (2013)**

Primary Outcome

- MDS-UPDRS III OFF

Secondary Outcomes

- MATTIS DRS-2



GLP-1 agonists & Parkinson's – **Exenatide-PD1 Trial (2013)**

Primary Outcome

- MDS-UPDRS III OFF

Secondary Outcomes

- MATTIS DRS-2
- Safety

	Adverse Events	n	Serious Adverse Events	n
Exenatide	Abdominal pain	6	Sciatica and epidural injection	1
	Back pain	5	Insomnia (polysomnography)	1
	Constipation	18	Possible transient ischaemic attack	2
	Diarrhoea	7		
	Increase dyskinesia	4		
	Increase off	4		
	Injection bruising	2		
	Hallucinations	2		
	Other pain	7		
	Loss of appetite	5		
	Nausea	13		
	Memory impairment	2		
	Urinary infection	2		
	Weight gain	3		
	Weight loss	19		
	Miscellaneous	36		

GLP-1 agonists & Parkinson's – **Exenatide-PD1 Trial (2013)**

Primary Outcome

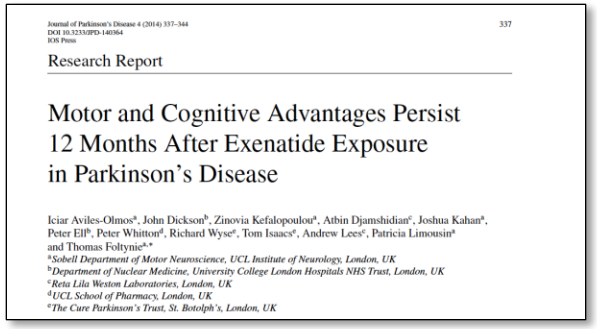
- MDS-UPDRS III OFF

Secondary Outcomes

- MATTIS DRS-2
- Safety

Exploratory Outcomes

- MDS-UPDRS OFF at 96 weeks

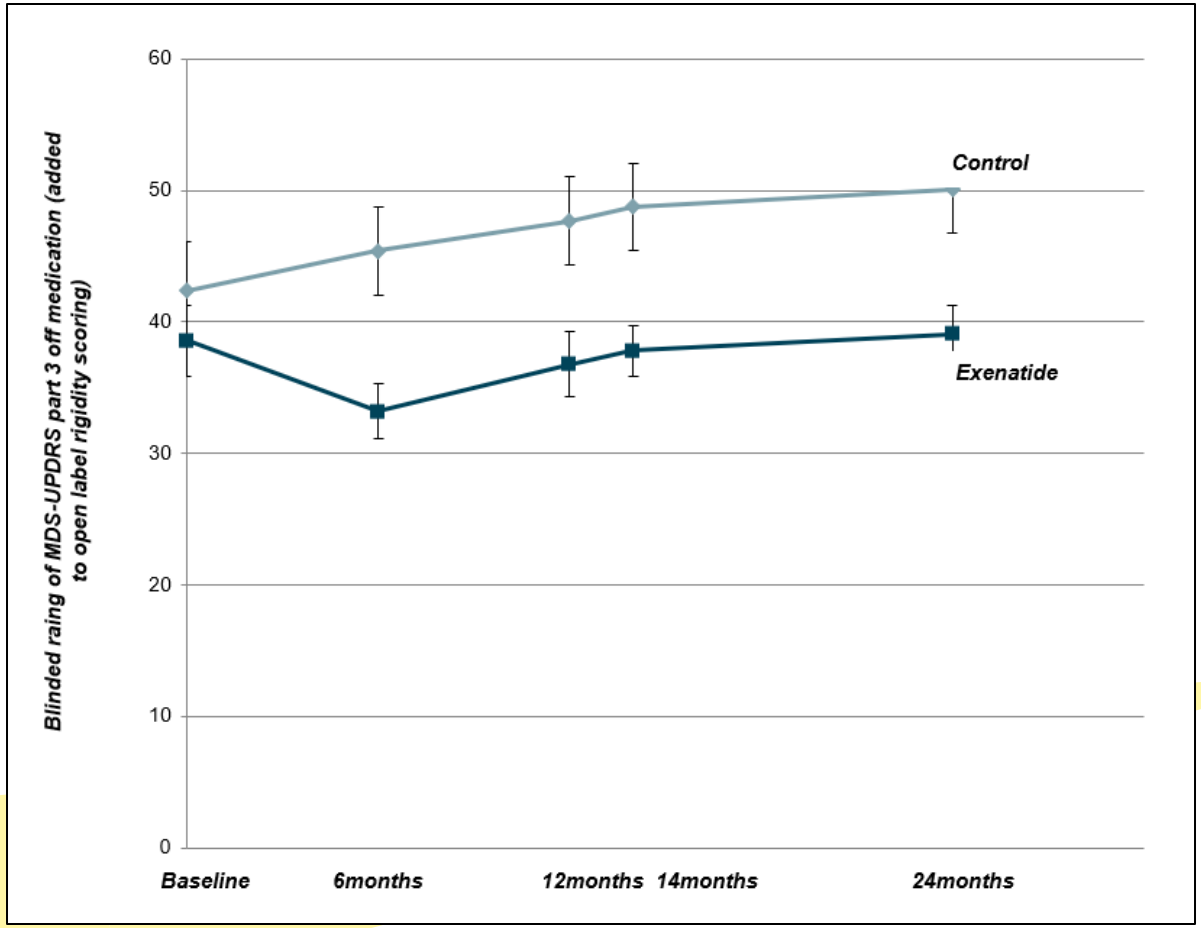


Journal of Parkinson's Disease 4 (2014) 337–344 337
DOI 10.3233/JPD-140364
IOS Press

Research Report

Motor and Cognitive Advantages Persist 12 Months After Exenatide Exposure in Parkinson's Disease

Iciar Aviles-Olmos[a], John Dickson[b], Zinovia Kefalopoulou[a], Atbin Djamshidian[c], Joshua Kahan[a], Peter Ell[b], Peter Whitton[d], Richard Wyse[a], Tom Isaacs[a], Andrew Lees[c], Patricia Limousin[a] and Thomas Foltynie[a,*]
[a]Sobell Department of Motor Neuroscience, UCL Institute of Neurology, London, UK
[b]Department of Nuclear Medicine, University College London Hospitals NHS Trust, London, UK
[c]Reta Lila Weston Laboratories, London, UK
[d]UCL School of Pharmacy, London, UK
[e]The Cure Parkinson's Trust, St. Botolph's, London, UK



GLP-1 agonists & Parkinson's – **Exenatide-PD2 Trial (2017)**

Drug: Exenatide (Bydureon Injection)

Articles

THE LANCET

Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial

Dilan Athauda, Kate Maclagan, Simon S Skene, Martha Bajwa-Joseph, Dawn Letchford, Kashfia Chowdhury, Steve Hibbert, Natalia Budnik, Luca Zampedri, John Dickson, Yazhou Li, Iciar Aviles-Olmos, Thomas T Warner, Patricia Limousin, Andrew J Lees, Nigel H Greig, Susan Tebbs, Thomas Foltynie

GLP-1 agonists & Parkinson's - **Exenatide-PD2 Trial (2017)**

Drug: Exenatide (Bydureon Injection)

- N=60
- Parallel group (placebo control)
- Exposure for 48 weeks

Demographics

- Patients ~ 59yrs old
- Disease duration ~6.5 yrs
- Levodopa dose ~ 780mg daily

Primary outcome measure

- MDS UPDRS part 3 at 60 weeks (OFF)

	Exenatide (n=31)	Placebo (n=29)
Age, years	61·6 (8·2)	57·8 (8·0)
Sex		
Female	9 (29%)	7 (24%)
Male	22 (71%)	22 (76%)
Age at diagnosis, years	55·9 (7·9)	52·2 (7·7)
Duration of diagnosis at baseline, years	6·4 (3·3)	6·4 (3·3)
Hoehn and Yahr stage		
1·0–2·0	29 (94%)	29 (100%)
2·5	2 (6%)	0 (0%)
MDS-UPDRS part 3 off medication	32·8 (9·7)	27·1 (10·3)
Levodopa equivalent dose, mg	773·9 (260·9)	825·7 (215·0)

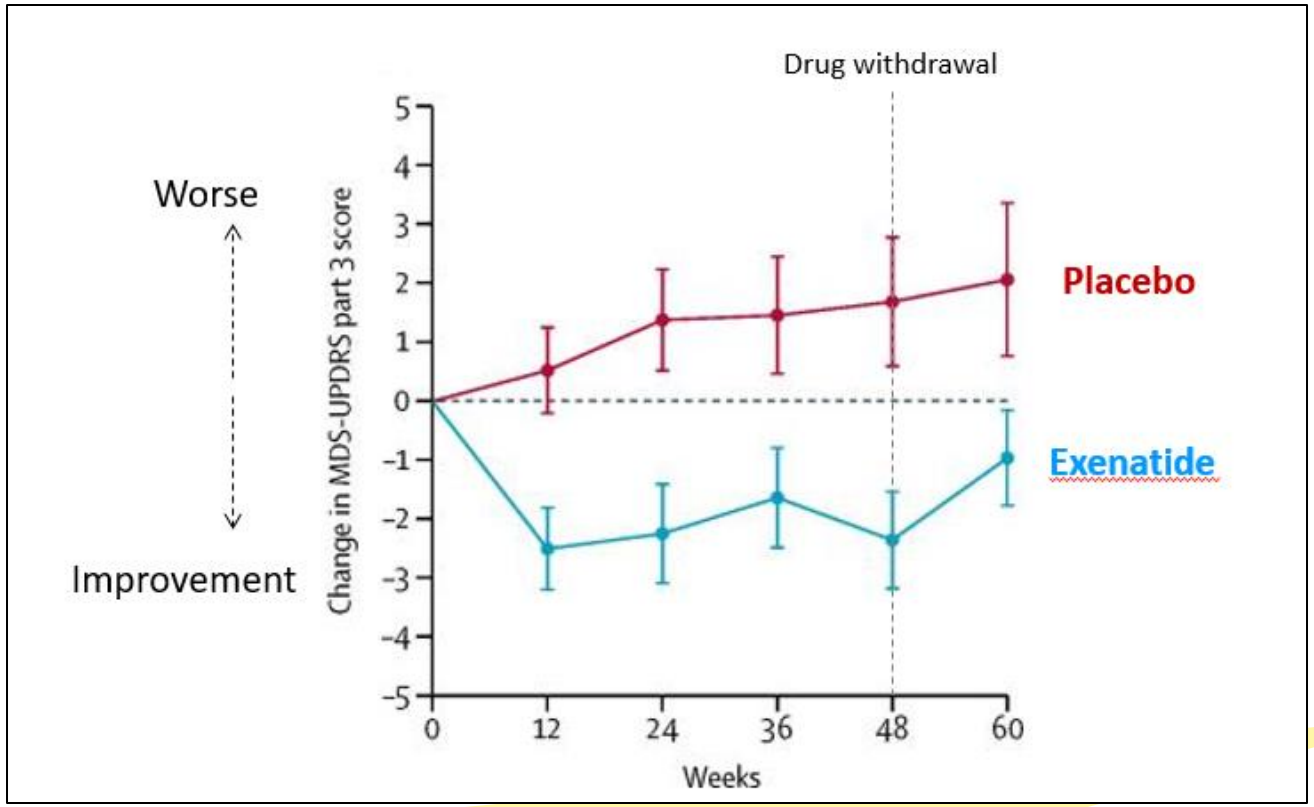
GLP-1 agonists & Parkinson's – **Exenatide-PD2 Trial (2017)**

THE FRANCIS CRICK INSTITUTE

Primary Outcome

- MDS-UPDRS at 60 weeks

	Baseline	12 weeks	24 weeks	36 weeks	48 weeks	Change, Baseline to 48 weeks	Adjusted difference, baseline to 48 weeks	60 weeks	Change, Baseline to 60 weeks	Adjusted difference, baseline to 60 weeks
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (95% CI)	Mean (95% CI) P value	Mean (SD)	Mean (95% CI)	Mean (95% CI) P value
OFF medication state										
MDS-UPDRS Part 3										
Exenatide	32.8 (9.7)	30.3 (10.9)	30.6 (10.8)	31.2 (11.3)	30.2 (11.1)	-2.3 (-4.1, -0.7)	-4.3 (-7.1, -1.6) **0.003**	31.9 (12.0)	-1.0 (-2.6, 0.7)	-3.5 (-6.7, -0.3) **0.032**
Placebo	27.1 (10.3)	27.6 (11.8)	28.5 (11.0)	28.6 (9.5)	28.8 (10.8)	1.7 (-0.6, 4.0)		29.2 (12.0)	2.1 (-0.6, 4.8)	



GLP-1 agonists & Parkinson's – **Exenatide-PD2 Trial (2017)**

THE FRANCIS CRICK INSTITUTE

Primary Outcome

- MDS-UPDRS at 60 weeks ✅

Secondary Outcomes ❌

- MDS-UPDRS I,II,IV; NMSS, PDQ-39

GLP-1 agonists & Parkinson's - **Exenatide-PD2 Trial (2017)**

Primary Outcome

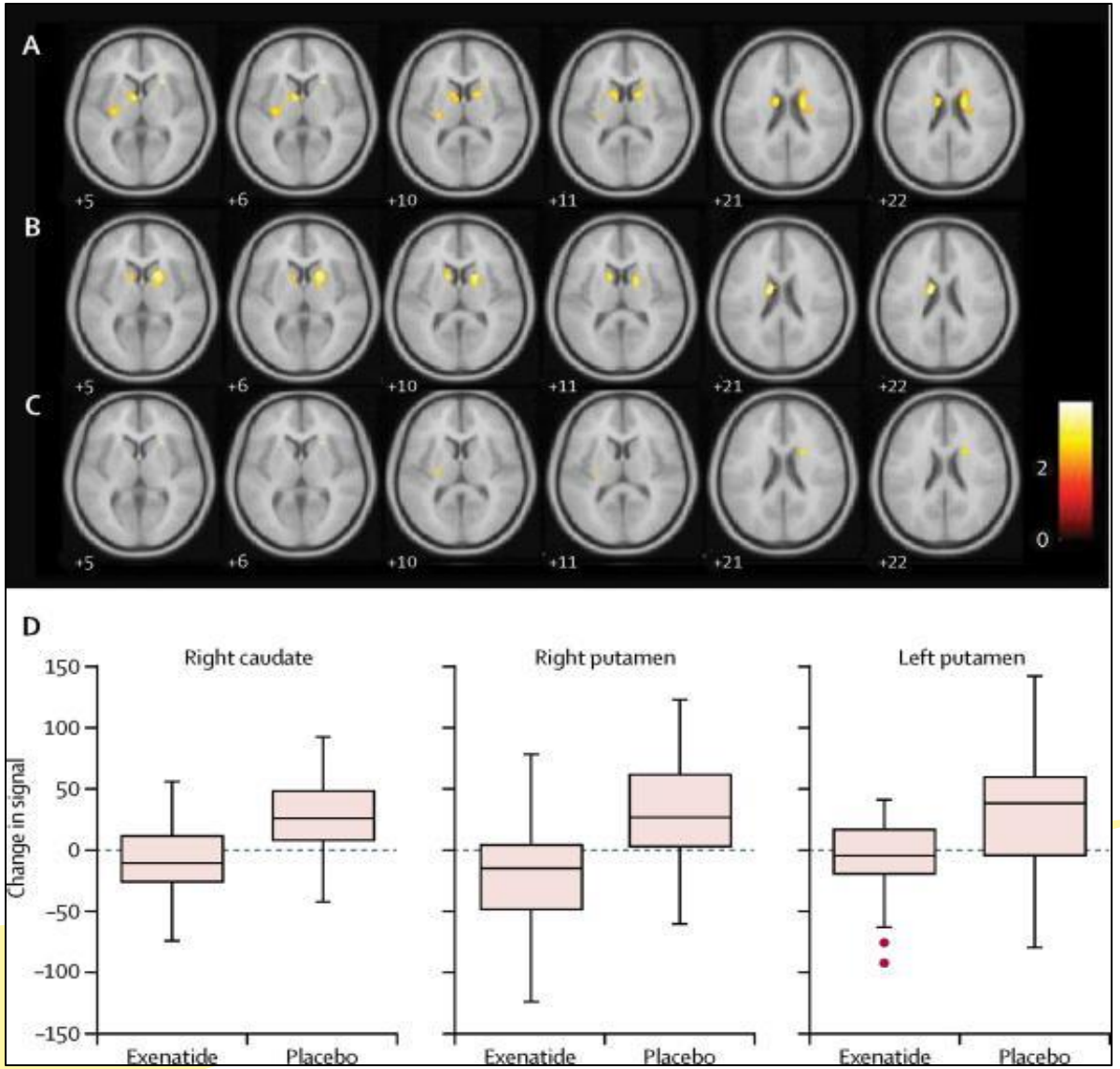
- MDS-UPDRS at 60 weeks

Secondary Outcomes

- MDS-UPDRS I,II,IV; NMSS, PDQ-39

Exploratory outcomes

- Reduced DA terminal loss at 60 weeks



GLP-1 agonists & Parkinson's – **Exenatide-PD2 Trial (2017)**

Primary Outcome

- MDS-UPDRS at 60 weeks

Secondary Outcomes

- MDS-UPDRS I,II,IV; NMSS, PDQ-39

Exploratory outcomes

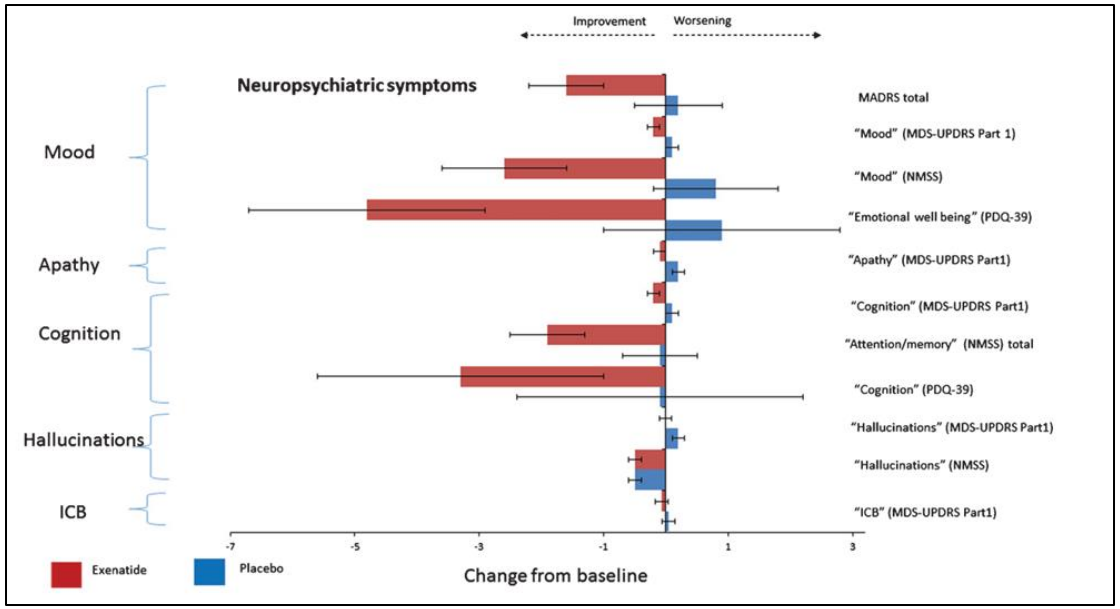
- Reduced DA terminal loss at 60 weeks
- Improved neuro-psychiatric symptoms

Journal of Parkinson's Disease 8 (2018) 247–258
DOI 10.3233/JPD-181329
IOS Press

Research Report

What Effects Might Exenatide have on Non-Motor Symptoms in Parkinson's Disease: A Post Hoc Analysis

Dilan Athauda[a], Kate Maclagan[b], Natalia Budnik[c], Luca Zampedri[c], Steve Hibbert[b], Simon S. Skene[b,d], Kashfia Chowdhury[b], Iciar Aviles-Olmos[a], Patricia Limousin[a] and Thomas Foltynie[a,*]



GLP-1 agonists & Parkinson's – **Exenatide-PD2 Trial (2017)**

Primary Outcome

- MDS-UPDRS at 60 weeks

Secondary Outcomes

- MDS-UPDRS I,II,IV; NMSS, PDQ-39

Exploratory outcomes

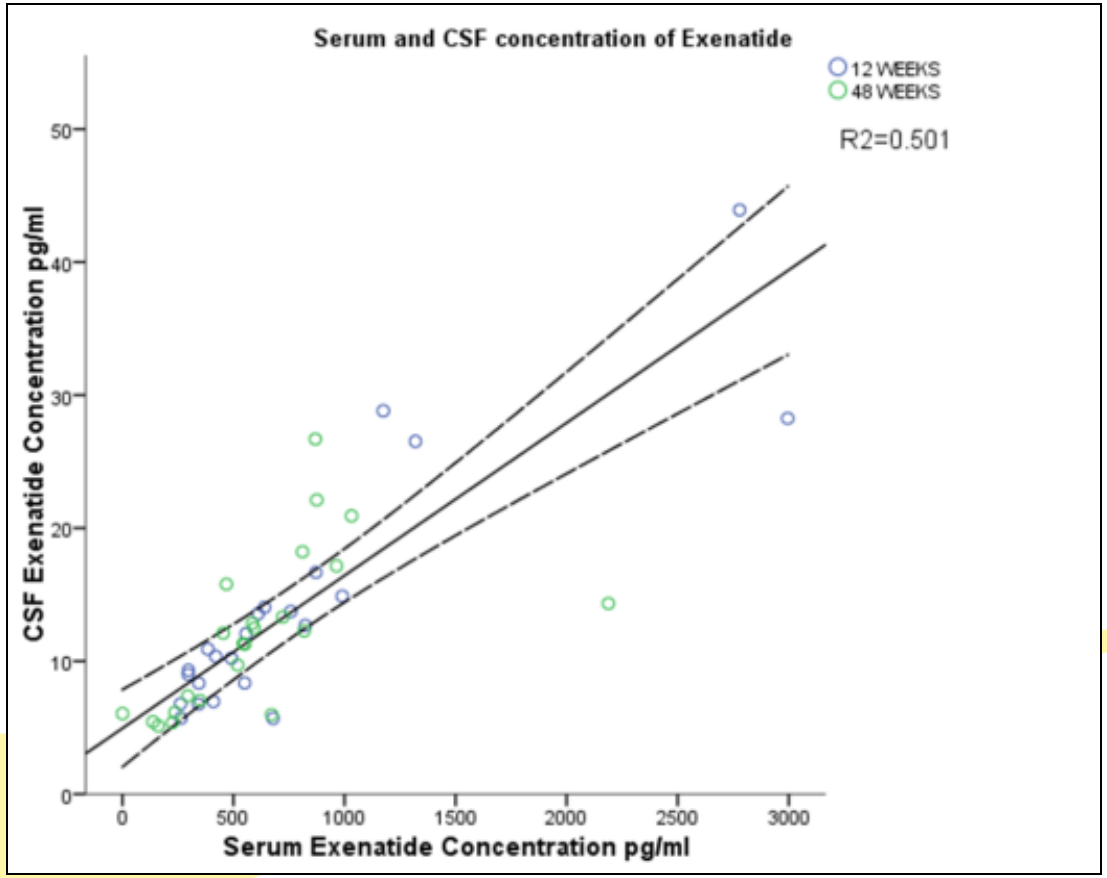
- Reduced DA terminal loss at 60 weeks
- Improved neuro-psychiatric symptoms
- Ex-4 penetrates BBB

Journal of Parkinson's Disease 8 (2018) 247–258
DOI 10.3233/JPD-181329
IOS Press

Research Report

What Effects Might Exenatide have on Non-Motor Symptoms in Parkinson's Disease: A Post Hoc Analysis

Dilan Athauda[a], Kate Maclagan[b], Natalia Budnik[c], Luca Zampedri[c], Steve Hibbert[b], Simon S. Skene[b,d], Kashfia Chowdhury[b], Iciar Aviles-Olmos[a], Patricia Limousin[a] and Thomas Foltynie[a,*]



GLP-1 agonists & Parkinson's - **Exenatide-PD2 Trial (2017)**

Primary Outcome

- MDS-UPDRS at 60 weeks

Secondary Outcomes

- MDS-UPDRS I,II,IV; NMSS, PDQ-39

Exploratory outcomes

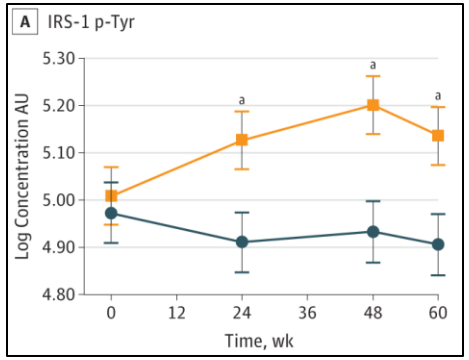
- Reduced DA terminal loss at 60 weeks
- Improved neuro-psychiatric symptoms
- Ex-4 penetrates BBB
- Ex-4 enhances brain insulin signalling

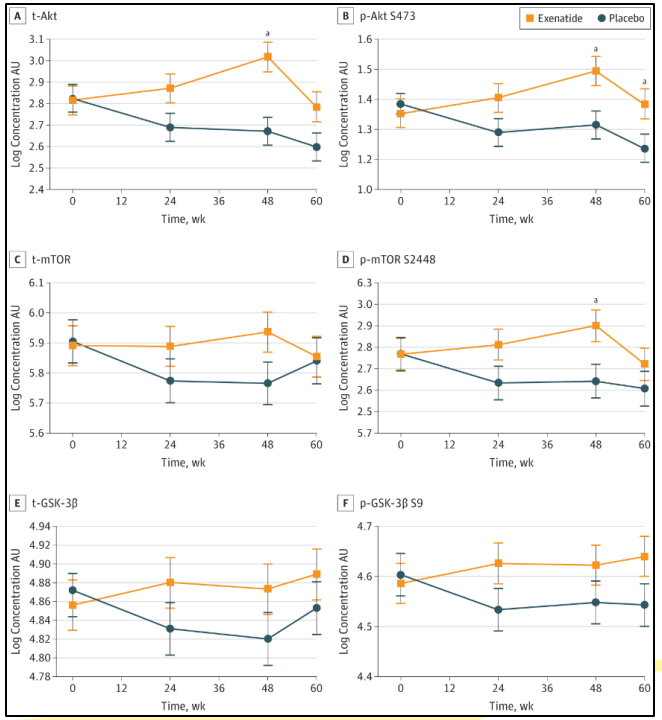
JAMA Neurology | Original Investigation

Utility of Neuronal-Derived Exosomes to Examine Molecular Mechanisms That Affect Motor Function in Patients With Parkinson Disease

A Secondary Analysis of the Exenatide-PD Trial

Dilan Athauda, MRCP, PhD; Seema Gulyani, PhD; Hanuma kumar Karnati, PhD; Yazhou Li, PhD; David Tweedie, PhD; Maja Mustapic, PhD; Sahil Chawla, BSc; Kashfia Chowdhury, MSc; Simon S. Skene, PhD; Nigel H. Greig, PhD; Dimitrios Kapogiannis, MD; Thomas Foltynie, MRCP, PhD





GLP-1 agonists & Parkinson's – **PT320 (2022)**

Drug: SR Exenatide

GLP-1 agonists & Parkinson's – **PT320 (2022)**

Drug: SR Exenatide

- RCT; N=99
- 3 groups (2.0mg / 2.5mg / placebo)
- Exposure for 48 weeks

Primary outcome measure

- MDS UPDRS III at 48 weeks

GLP-1 agonists & Parkinson's – **PT320 (2022)**

Drug: SR Exenatide

- RCT; N=99
- 3 groups (2.0mg / 2.5mg / placebo)
- Exposure for 48 weeks

Primary outcome measure

- MDS UPDRS III at 48 weeks

GLP-1 agonists & Parkinson's – **PT320 (2022)**

Drug: SR Exenatide

- RCT; N=99
- 3 groups (2.0mg / 2.5mg / placebo)
- Exposure for 48 weeks

Primary outcome measure

- MDS UPDRS III at 48 weeks

Secondary outcomes

- K-PDQ-39

GLP-1 agonists & Parkinson's – **PT320 (2022)**

Drug: SR Exenatide

- RCT; N=99
- 3 groups (2.0mg / 2.5mg / placebo)
- Exposure for 48 weeks

Primary outcome measure

- MDS UPDRS III at 48 weeks ✗

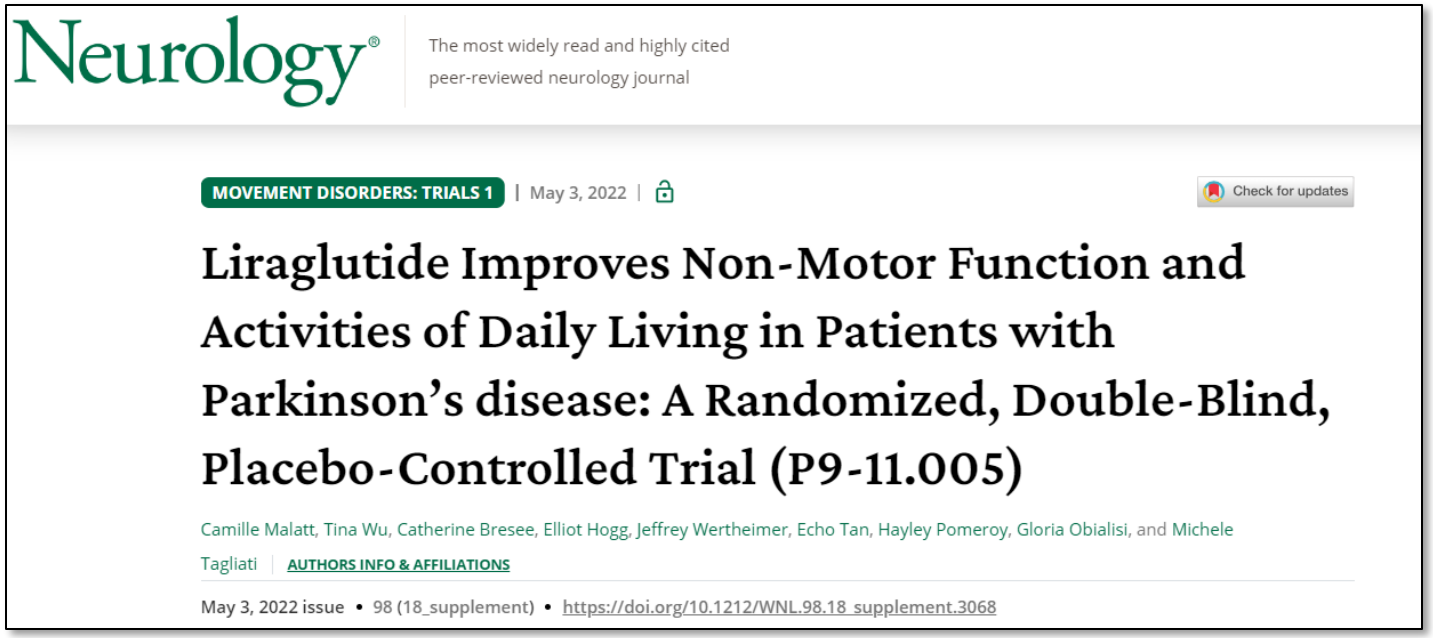
Secondary outcomes

- K-PDQ-39 ✓

"We believe PT320's insulin resistance-improving mechanism can be a fundamental treatment for degenerative brain diseases and will continue working on a treatment for Parkinson's disease,"

GLP-1 agonists & Parkinson's – **Liraglutide (2022)**

Drug: Liraglutide



Neurology®
The most widely read and highly cited peer-reviewed neurology journal

MOVEMENT DISORDERS: TRIALS 1 | May 3, 2022 |
Check for updates

Liraglutide Improves Non-Motor Function and Activities of Daily Living in Patients with Parkinson's disease: A Randomized, Double-Blind, Placebo-Controlled Trial (P9-11.005)

Camille Malatt, Tina Wu, Catherine Bresee, Elliot Hogg, Jeffrey Wertheimer, Echo Tan, Hayley Pomeroy, Gloria Obialisi, and Michele Tagliati | AUTHORS INFO & AFFILIATIONS

May 3, 2022 issue • 98 (18_supplement) • https://doi.org/10.1212/WNL.98.18_supplement.3068

GLP-1 agonists & Parkinson's – **Liraglutide (2022)**

Drug: Liraglutide

- RCT; N=63
- 2 groups (1.8mg / placebo)
- Exposure for 52 weeks

Primary outcome measure

- MDS UPDRS III at 52 weeks
- NMSS
- MATTIS-DRS2

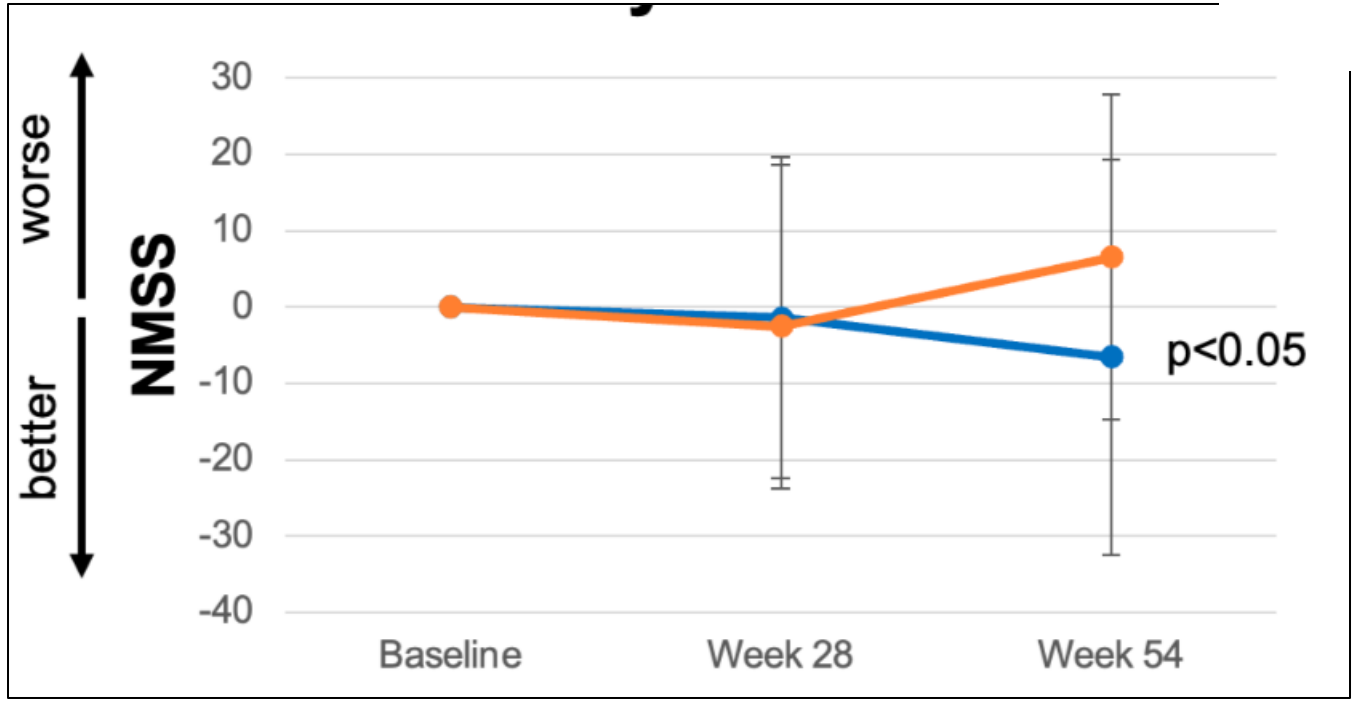
Secondary Outcomes

- MDS-UPDRS II

GLP-1 agonists & Parkinson's – **Liraglutide (2022)**

Drug: Liraglutide

- RCT; N=63
- 2 groups (1.8mg / placebo)
- Exposure for 52 weeks



Primary outcome measure

- MDS UPDRS III at 52 weeks ✗
- NMSS ✓
- MATTIS-DRS2 ✗

GLP-1 agonists & Parkinson's – **Liraglutide (2022)**

Drug: Liraglutide

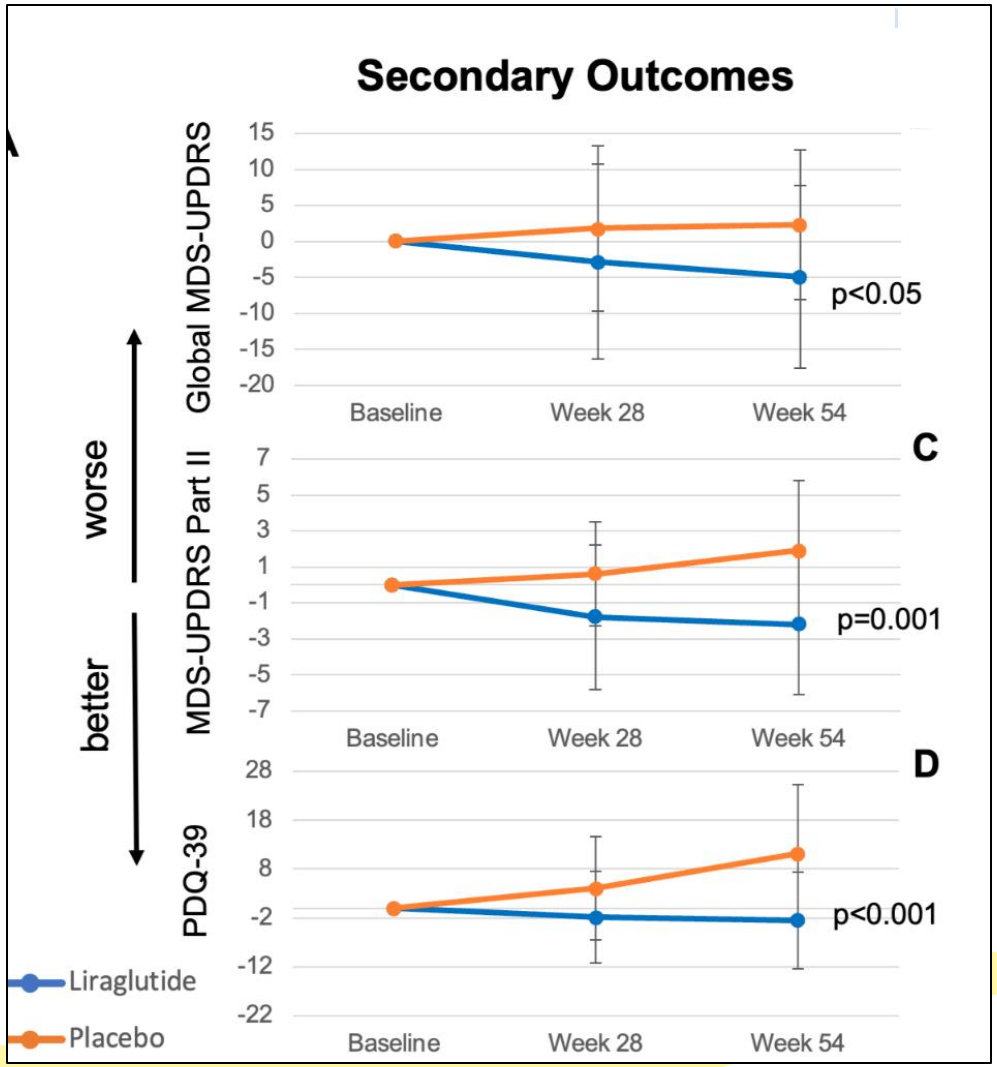
- RCT; N=63
- 2 groups (1.8mg / placebo)
- Exposure for 52 weeks

Primary outcome measure

- MDS UPDRS III at 52 weeks ✗
- NMSS ✓
- MATTIS-DRS2 ✗

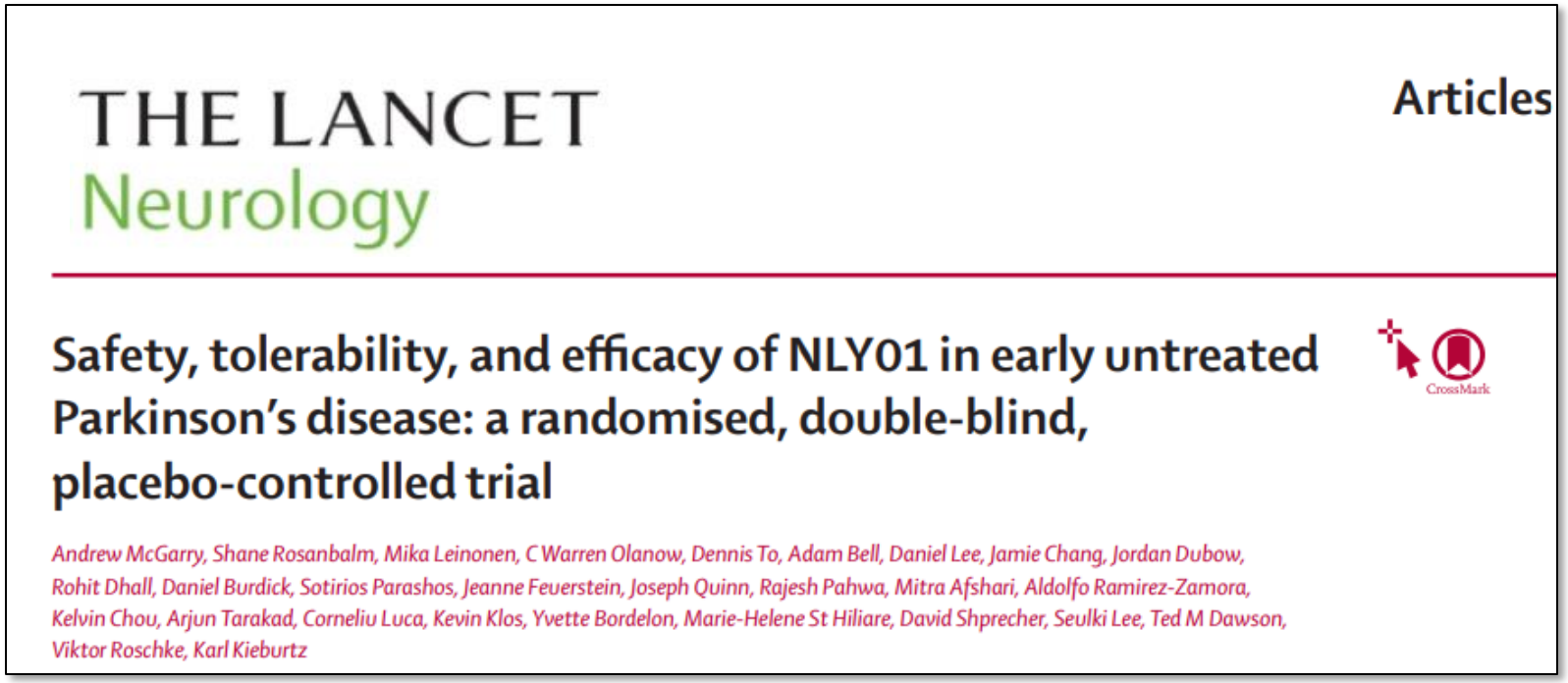
Secondary Outcomes

- MDS-UPDRS ✓
- MDS-UPDRS II ✓
- PDQ-39 ✓



GLP-1 agonists & Parkinson's – **NLY01 trial (2023)**

Drug: NLY01 (PEGylated form exendin-4)



THE LANCET
Neurology

Articles

Safety, tolerability, and efficacy of NLY01 in early untreated Parkinson's disease: a randomised, double-blind, placebo-controlled trial

Andrew McGarry, Shane Rosanbalm, Mika Leinonen, C Warren Olanow, Dennis To, Adam Bell, Daniel Lee, Jamie Chang, Jordan Dubow, Rohit Dhall, Daniel Burdick, Sotirios Parashos, Jeanne Feuerstein, Joseph Quinn, Rajesh Pahwa, Mitra Afshari, Aldolfo Ramirez-Zamora, Kelvin Chou, Arjun Tarakad, Corneliu Luca, Kevin Klos, Yvette Bordelon, Marie-Helene St Hiliare, David Shprecher, Seulki Lee, Ted M Dawson, Viktor Roschke, Karl Kieburtz

GLP-1 agonists & Parkinson's – **NLY01 trial (2023)**

Drug: NLY01 (PEGylated form exendin-4)

- RCT; N=225
- 3 groups (2.5mg / 5.0mg / placebo)
- Exposure for 36 weeks

Demographics

- Patients ~ 60yrs old
- Disease duration ~1.0 yrs
- Levodopa dose ~ 780mg daily

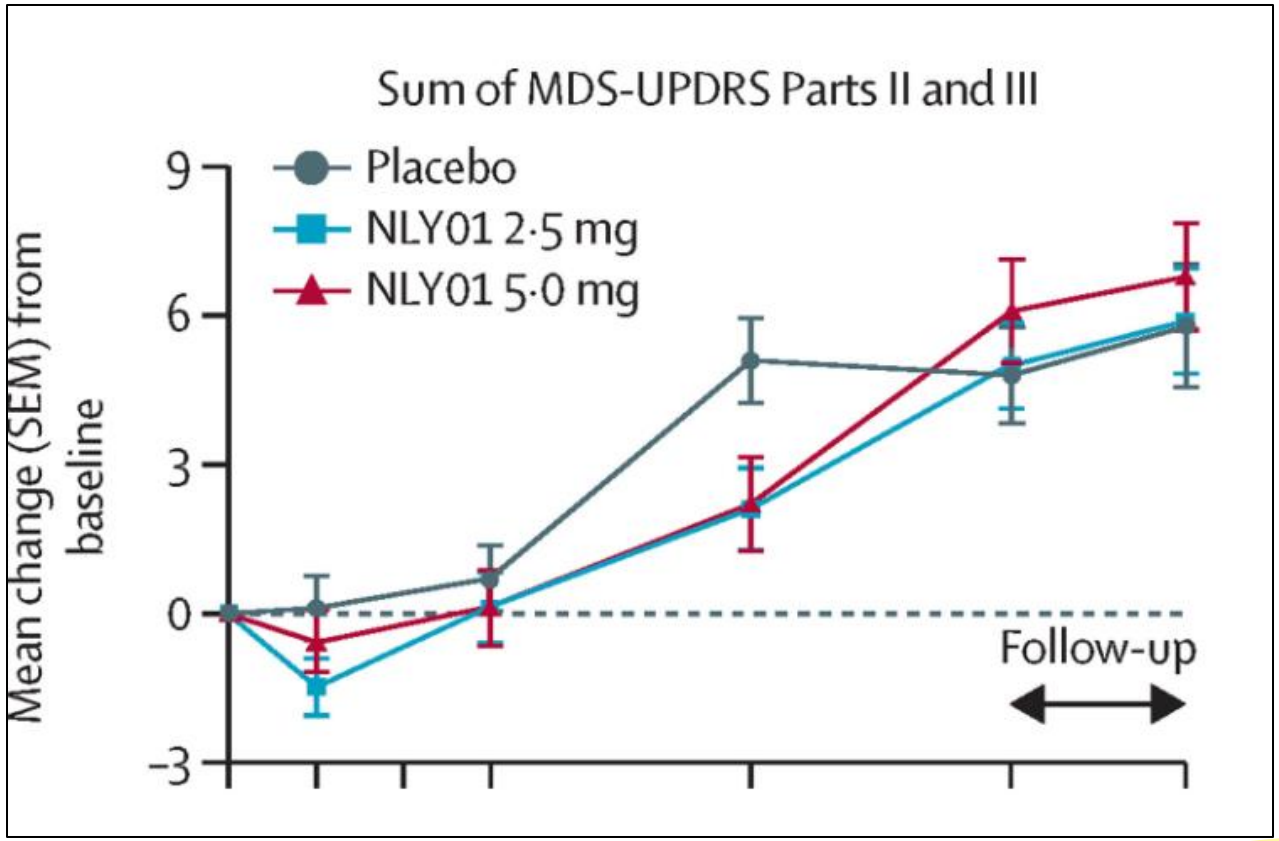
Primary outcome measure

- MDS UPDRS II & III at 36 weeks

GLP-1 agonists & Parkinson's – **NLY01 trial (2023)**

Primary Outcome

- MDS UPDRS II & III at 36 weeks



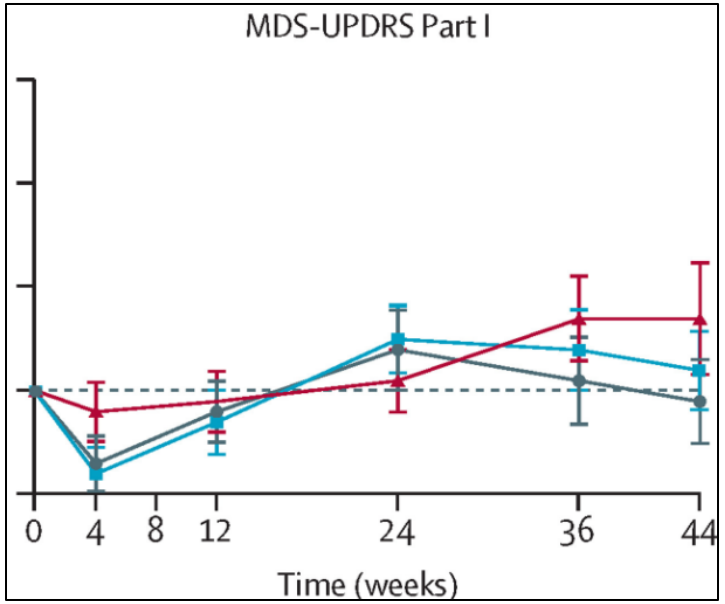
GLP-1 agonists & Parkinson's – **NLY01 trial (2023)**

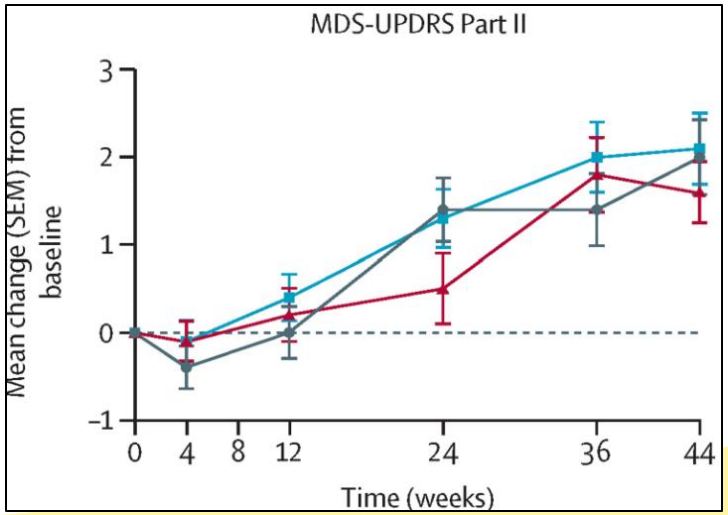
Primary Outcome

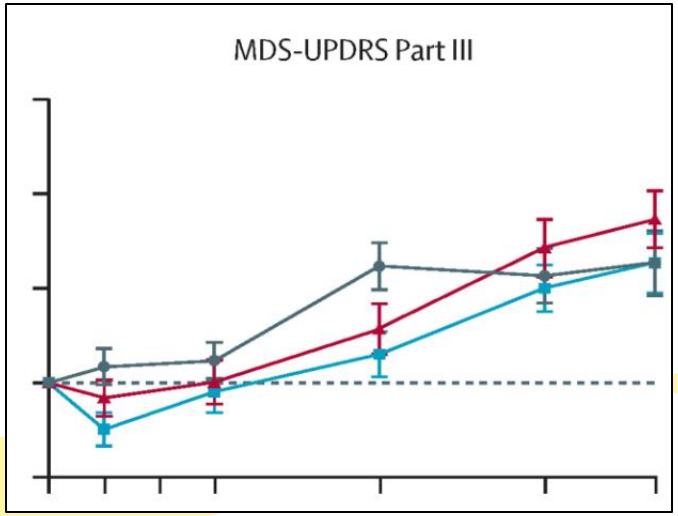
- MDS UPDRS II & III at 36 weeks

Secondary Outcomes

- MDS-UPDRS I, II, III







GLP-1 agonists & Parkinson's – **NLY01 trial (2023)**

Primary Outcome

- MDS UPDRS II & III at 36 weeks

Secondary Outcomes

- MDS-UPDRS I, II, III

Exploratory Outcomes

- Safety

	Placebo (n=84)	NLY01 2·5 mg (n=85)	NLY01 5·0 mg (n=85)
Any treatment-emergent adverse event	73 (87%)	71 (84%)	79 (93%)
Gastrointestinal disorders	30 (36%)	52 (61%)	64 (75%)
Nausea	16 (19%)	33 (39%)	49 (58%)
Constipation	6 (7%)	10 (12%)	14 (16%)
Vomiting	1 (1%)	4 (5%)	22 (26%)
Diarrhoea	7 (8%)	7 (8%)	11 (13%)
Dyspepsia	2 (2%)	8 (9%)	14 (16%)
Gastro-oesophageal reflux	2 (2%)	9 (11%)	13 (15%)
Abdominal discomfort	4 (5%)	5 (6%)	4 (5%)
Eructation	1 (1%)	4 (5%)	8 (9%)
Abdominal distention	1 (1%)	4 (5%)	5 (6%)
Nervous system disorders	34 (40%)	25 (29%)	39 (46%)
Headache	14 (17%)	14 (16%)	20 (24%)
Dizziness	7 (8%)	3 (3·5)	7 (8·2)
Worsening of parkinsonism	7 (8%)	3 (4%)	6 (7%)
General and administration site disorders	31 (37%)	32 (38%)	34 (40%)
Fatigue	11 (13%)	10 (12%)	12 (14%)
Injection site bruising	13 (15%)	9 (11%)	7 (8%)
Injection site erythema	1 (1%)	7 (8%)	8 (9%)
Infections	28 (33%)	14 (16%)	23 (27%)
COVID-19	11 (13%)	7 (8%)	13 (15%)
Urinary tract infection	6 (7%)	3 (4%)	2 (2%)
Musculoskeletal disorders	20 (24%)	19 (22%)	16 (19%)
Arthralgia	2 (2%)	5 (6%)	3 (4%)
Injury and procedural complications	16 (19%)	10 (12%)	10 (12%)
Skin and subcutaneous skin disorders	11 (13%)	9 (11%)	13 (15%)
Investigations	6 (7%)	11 (13%)	12 (14%)
Weight decreased	2 (2%)	5 (6%)	5 (6%)
Metabolism and nutrition disorders	7 (8%)	8 (9%)	13 (15%)
Decreased appetite	5 (6%)	7 (8%)	13 (15%)
Psychiatric disorders	7 (8%)	9 (11%)	12 (14%)
Anxiety	1 (1%)	3 (4%)	5 (6%)
Vascular disorders	5 (6%)	8 (9%)	7 (8%)
Renal and urinary disorders	9 (11%)	6 (7%)	4 (5%)
Respiratory and thoracic disorders	5 (6%)	2 (2%)	9 (11%)

Data are n (%). Treatment-emergent adverse events occurring with a frequency of 5% or greater in any group are shown.

Table 2: **Treatment-emergent adverse events**

GLP-1 agonists & Parkinson's – **NLY01 trial (2023)**

Primary Outcome

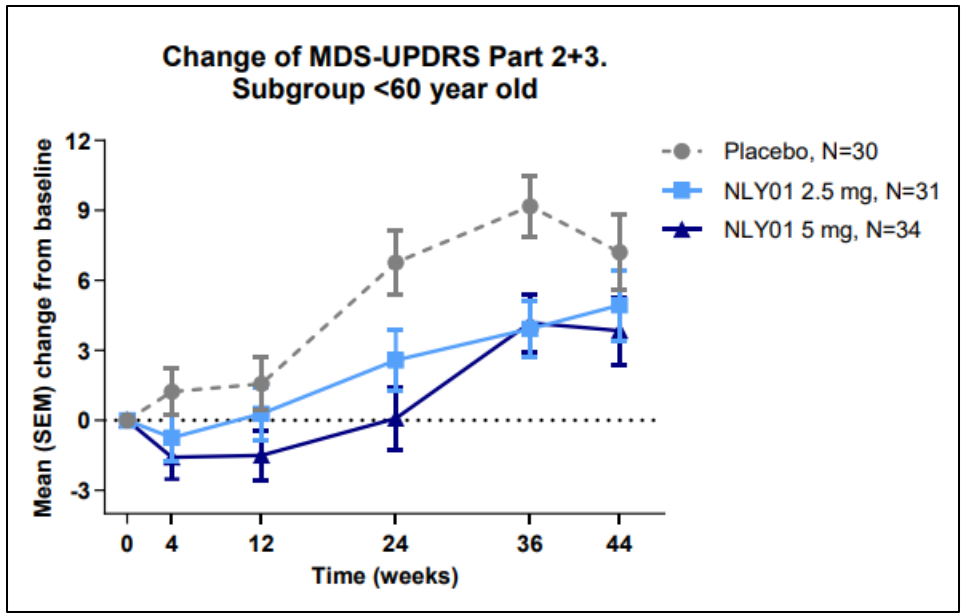
- MDS UPDRS II & III at 36 weeks

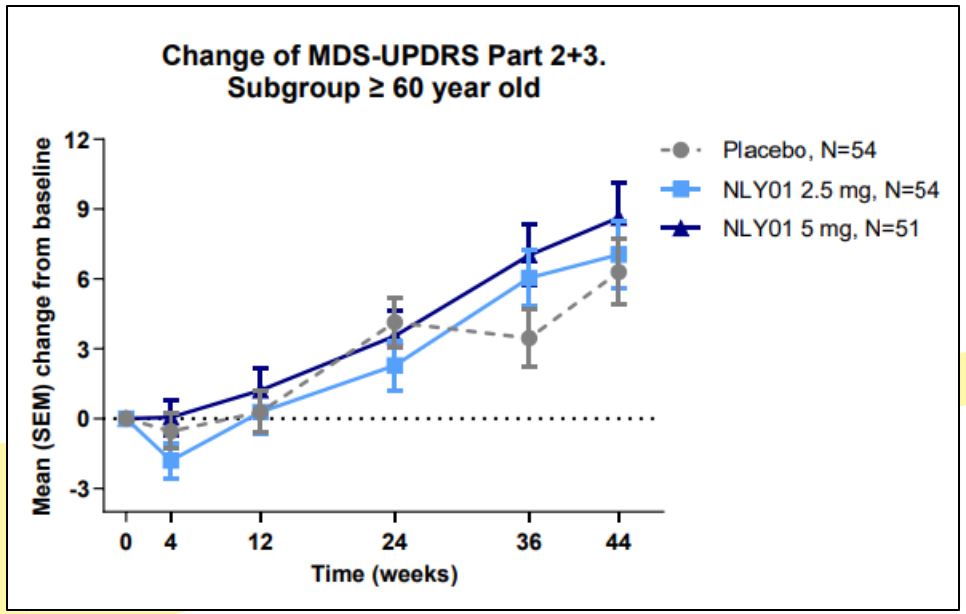
Secondary Outcomes

- MDS-UPDRS I, II, III

Exploratory Outcomes

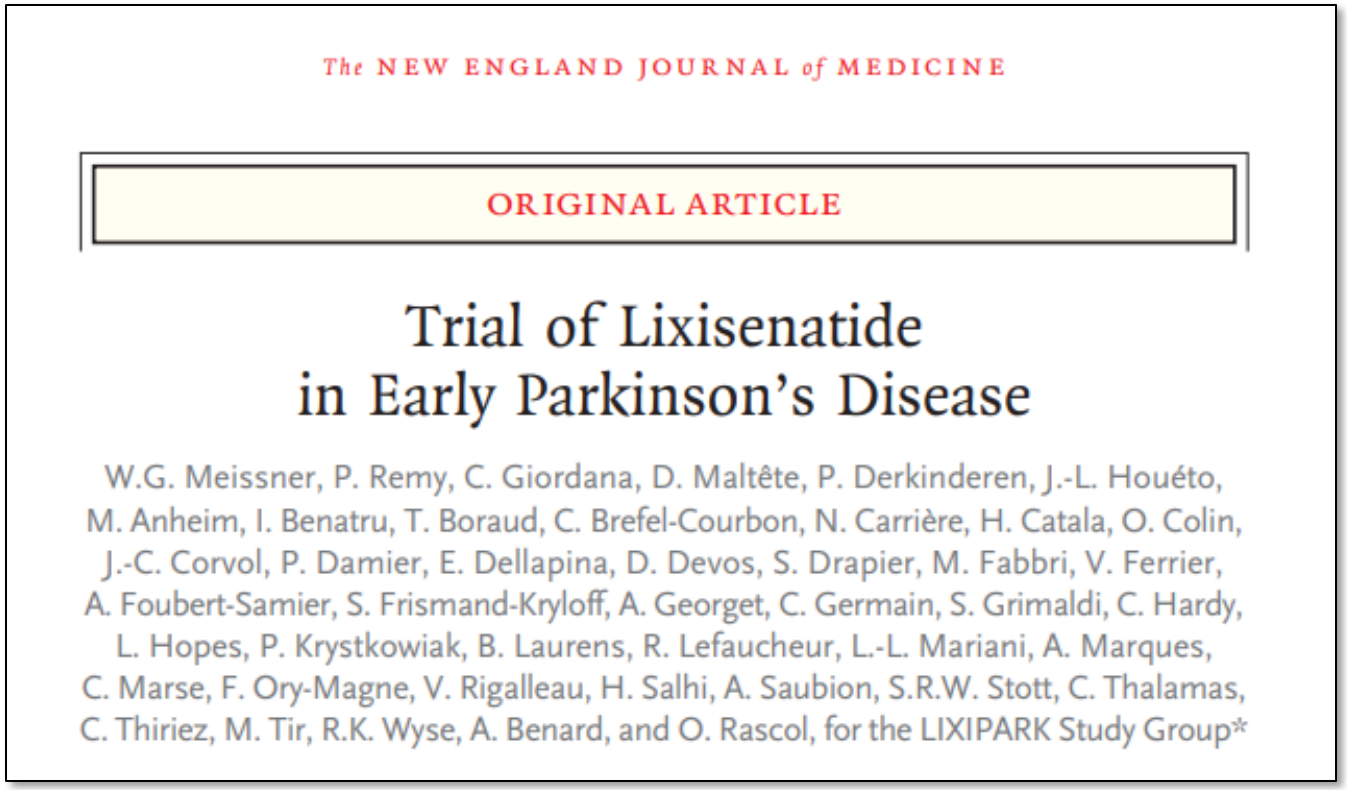
- Safety
- Patients <60yrs seemed to improve





GLP-1 agonists & Parkinson's – **LIXIPARK (2024)**

Drug: Lixisenatide



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Lixisenatide in Early Parkinson's Disease

W.G. Meissner, P. Remy, C. Giordana, D. Maltête, P. Derkinderen, J.-L. Houéto, M. Anheim, I. Benatru, T. Boraud, C. Brefel-Courbon, N. Carrière, H. Catala, O. Colin, J.-C. Corvol, P. Damier, E. Dellapina, D. Devos, S. Drapier, M. Fabbri, V. Ferrier, A. Foubert-Samier, S. Frismand-Kryloff, A. Georget, C. Germain, S. Grimaldi, C. Hardy, L. Hopes, P. Krystkowiak, B. Laurens, R. Lefaucheur, L.-L. Mariani, A. Marques, C. Marse, F. Ory-Magne, V. Rigalleau, H. Salhi, A. Saubion, S.R.W. Stott, C. Thalamas, C. Thiriez, M. Tir, R.K. Wyse, A. Benard, and O. Rascol, for the LIXIPARK Study Group*

GLP-1 agonists & Parkinson's – **LIXIPARK (2024)**

Drug: Lixisenatide

- RCT; N=156
- 2 groups (lixisenatide 20ug / placebo)
- Exposure for 12 months

Primary outcome measure

- MDS UPDRS III at 12 months

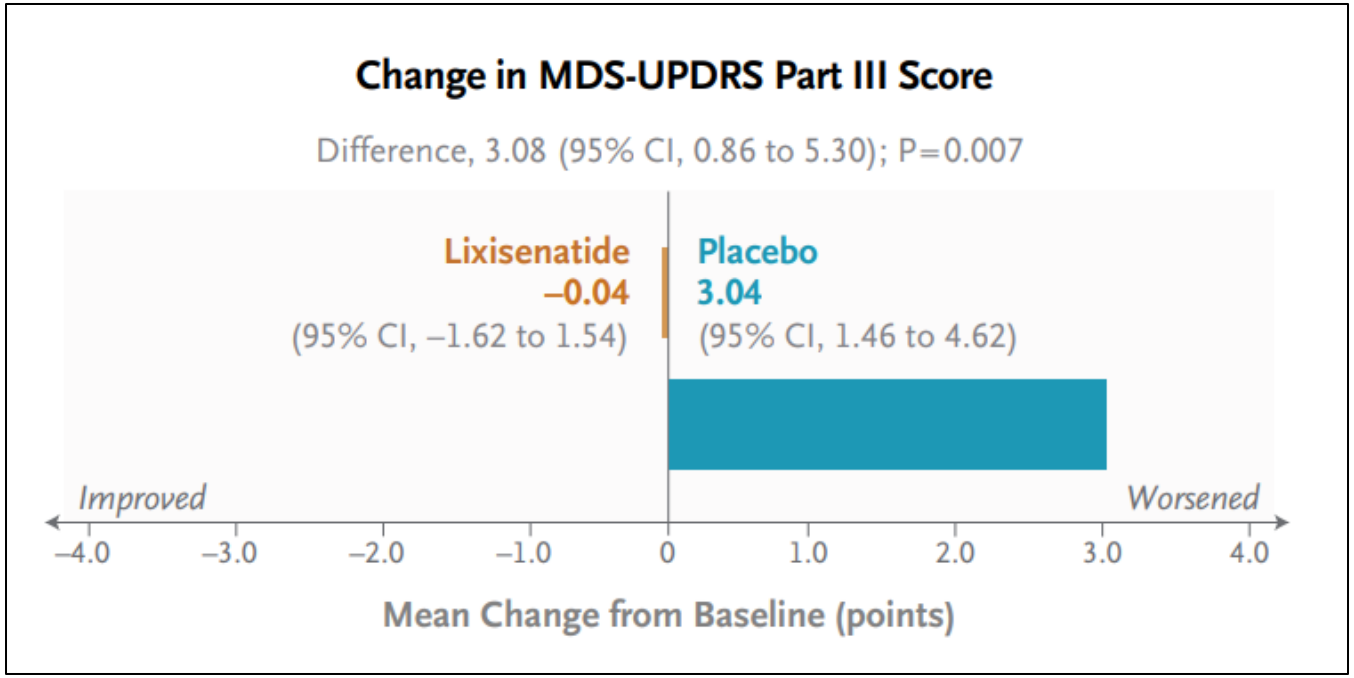
Demographics

- Patients ~ 60yrs old
- Disease duration ~1.4 yrs
- Levodopa dose ~ 325mg daily

GLP-1 agonists & Parkinson's – **LIXIPARK (2024)**

Primary Outcome

- MDS UPDRS III at 12 months



GLP-1 agonists & Parkinson's – **LIXIPARK (2024)**

Primary Outcome

- MDS UPDRS III at 12 months ✅

Secondary Outcomes ❌

Table 2. Efficacy Measures.

Efficacy Measure	Placebo (N=75)	Lixisenatide (N=77)	Difference
Primary end point — mean point estimate (95% CI)			
Change in score on MDS-UPDRS part III, on-medication state, 12 mo*	3.04 (1.46 to 4.62)	−0.04 (−1.62 to 1.54)	3.08 (0.86 to 5.30)
Secondary end points — mean point estimate (95% CI)			
MDS-UPDRS part III score, off-medication state after 2-month washout, 14 mo†‡	20.6 (18.5 to 22.8)	17.7 (15.7 to 19.7)	3.0 (0.1 to 5.8)
Change from baseline in MDS-UPDRS score, on-medication state			
Part III, 6 mo	1.66 (0.36 to 2.97)	0.54 (−0.93 to 2.00)	1.13 (−0.82 to 3.07)
Total, 12 mo	5.18 (2.90 to 7.45)	2.80 (0.29 to 5.31)	2.38 (−0.98 to 5.73)
Part I nm-EDL, 6 mo	0.69 (−0.10 to 1.48)	0.55 (−0.18 to 1.28)	0.14 (−0.93 to 1.21)
Part I nm-EDL, 12 mo	0.61 (−0.11 to 1.33)	1.25 (0.29 to 2.21)	−0.64 (−1.83 to 0.55)
Part II m-EDL, 6 mo	0.63 (0.03 to 1.23)	0.67 (−0.18 to 1.52)	−0.04 (−1.08 to 0.99)
Part II m-EDL, 12 mo	1.40 (0.65 to 2.15)	1.45 (0.58 to 2.33)	−0.05 (−1.19 to 1.09)
Part IV, 6 mo	0.2 (−0.2 to 0.6)	0.2 (0 to 0.5)	−0.03 (−0.50 to 0.44)
Part IV, 12 mo	0.2 (0 to 0.4)	0.2 (−0.1 to 0.6)	−0.06 (−0.44 to 0.33)
Change from baseline in levodopa equivalent daily dose at 12 mo — mg	31.3 (9.2 to 53.5)	35.8 (8.3 to 63.2)	−4.4 (−39.5 to 30.6)

GLP-1 agonists & Parkinson's – **SUMMARY OF RESULTS**

GLP-1RA	Dose/formulation	Phase I	Phase II	Phase III
Exenatide twice daily	Byetta injection 2ug / BMT	✓ Open label		
Exenatide once weekly	Bydureon injecton 2mg /placebo		✓ Bydureon formulation discontinued	
Exenatide once weekly	Bcise 2mg Pen / placebo			Results due 2024
Exenatide PEGylated	NLY01 5mg / placebo		✗ Post hoc analysis suggested <60yrs improved	
Exenatide SR	PT320 2.5ug		✗ Secondary outcomes suggest NMSS improved	
Exenatide	Bydureon inj 2mg / placebo		Trial of 60 patients - results expected 2024?	
Liraglutide	1.2mg / 1.8mg / placebo		✗ Secondary outcomes suggest NMSS improved	
Lixisenatide	20ug injection		✓ No secondary outcomes met	
Semaglutide	7mg / 14mg / placebo		Trial of 60 patients - results expected 2024?	

GLP-1 agonists & Parkinson's – should we continue to explore this drug class?

No

- Clinical trial results are not convincing / mixed

GLP-1 agonists & Parkinson's – should we continue to explore this drug class?

Yes

- Very strong pre-clinical across multiple animal toxin, transgenic models and human iPSC models of PD demonstrating GLP-1 agonists halt / improve / protect pathology of PD

GLP-1 agonists & Parkinson's – should we continue to explore this drug class?

Yes

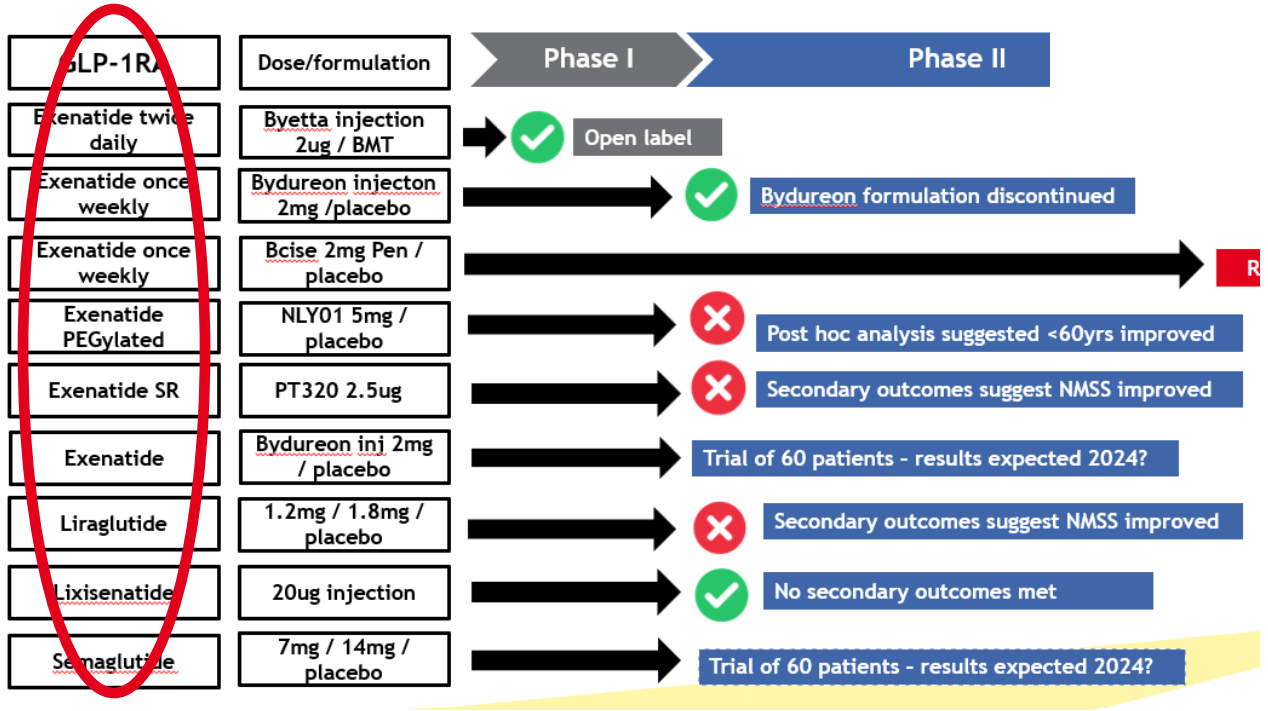
- Very strong pre-clinical across multiple animal toxin, transgenic models and human iPSC models of PD demonstrating GLP-1 agonists halt / improve / protect pathology of PD

- Heterogenous methodology of trials

GLP-1 agonists & Parkinson's – should we continue to explore this drug class?

Yes

- Very strong pre-clinical across multiple animal toxin, transgenic models and human iPSC models of PD demonstrating GLP-1 agonists halt / improve / protect pathology of PD
- Heterogenous methodology of trials

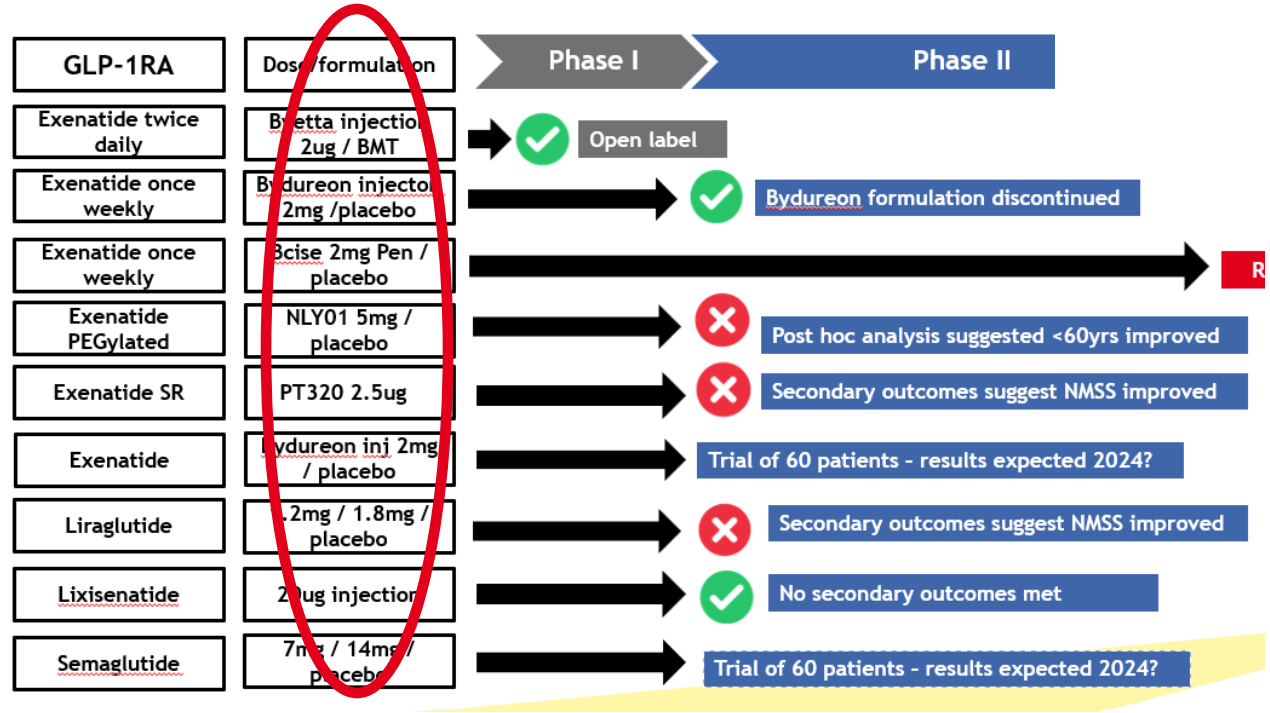


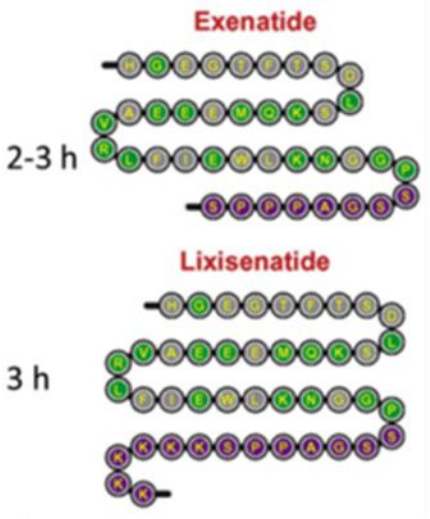
Outcome measures: MDS-UPDRS III, MDS-UPDRS II & III, MATTIS-DRS
Duration of exposure: 36 weeks, 48 weeks, 60 weeks, 96 weeks
Patient selection: "Early" PD vs Established PD; <60yrs vs >60yrs; insulin resistance vs all patients
Placebo "unblinding": influencing results

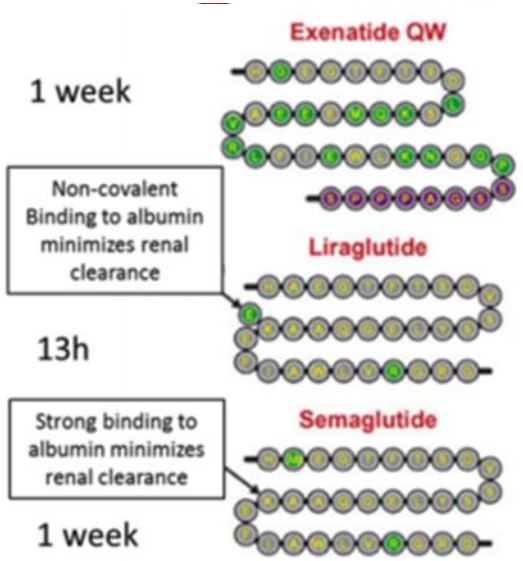
GLP-1 agonists & Parkinson's – should we continue to explore this drug class?

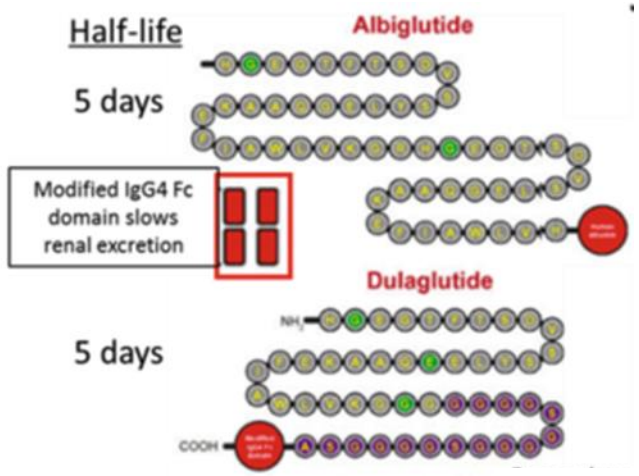
Yes

- Very strong pre-clinical across multiple animal toxin, transgenic models and human iPSC models of PD demonstrating GLP-1 agonists halt / improve / protect pathology of PD
- Heterogenous methodology of trials
- Not clear what is the "right" drug and dose?







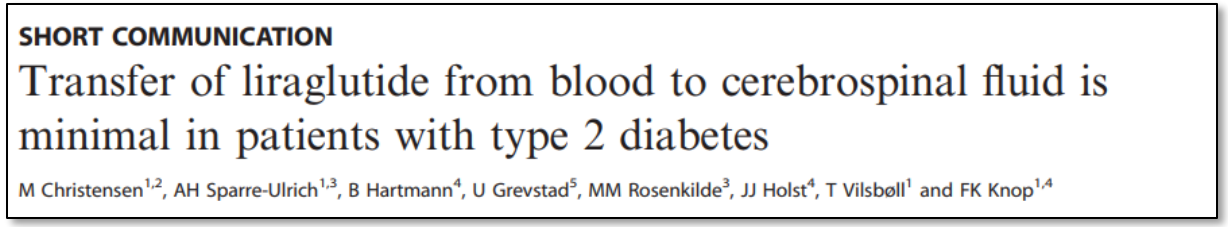


GLP-1 agonists & Parkinson's – should we continue to explore this drug class?

Yes

- Very strong pre-clinical across multiple animal toxin, transgenic models and human iPSC models of PD demonstrating GLP-1 agonists halt / improve / protect pathology of PD
- Heterogenous methodology of trials
- Not clear what is the "right" drug and dose?
- Human comparative BBB is lacking

Exenatide (Bydureon): ~ Penetrates CSF ~ 2.5% serum level



Liraglutide: Does not penetrate CSF

GLP-1 agonists & Parkinson's – should we continue to explore this drug class?

Going forward

- Collaboration and data sharing across GLP-1 clinical trials to identify gaps in knowledge and biomarkers of target engagement
- Newer dual and Triple agonists (GLP-1 / GIP / Glucagon) show greater promise and may be more effective molecules

Thank you

Department of Clinical and Movement Neurosciences, NHNN, London

Thomas Foltynie

Andrew Lees

Huw Morris

Iciar Aviles-Olmos

John Dickson

Kate Maglagan

Simon Skene

Translational Gerontology Branch, Intramural Research Program, NIH, Baltimore

Nigel H Greig

Yazhou Li

David Tweedie

Laboratory of Neurosciences, Intramural Research Program, NIH, Baltimore

Dimitrios Kapogiannis

Seema Gulyani

Maja Mustapic

Sahil Chawla

The Francis Crick Institute, London

Sonia Gandhi

Minee-Liane Choi

Wei-Jia Zhang

Gurvir Virdi

James Evans

Aaron Wagen

Laura Sanchez