

From Dogfish to Gila Monsters

Parkinson's Treatments of Tomorrow

Branch meeting
4 March 2020

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Central Nervous System drugs are tough

- Average of \$2.6bn to develop
- Take 18% longer than average
- Less than half as likely to succeed
- 40% longer to gain regulatory approval
- Priority review offered a third less often

Source: Tufts Center for the Study of Drug Development (CSDD)

Top indications for Pharma R&D

Position 2019 (2018)	Disease*	No. of active drugs 2019 (2018)	Trend
1 (1)	Cancer, breast	774 (727)	↑
2 (2)	Cancer, lung, non-small cell	586 (544)	↑
3 (3)	Cancer, colorectal	535 (503)	↑
4 (4)	Cancer, ovarian	442 (434)	↔
5 (5)	Cancer, pancreatic	438 (430)	↔
6 (8)	Alzheimer's disease	405 (381)	↑
7 (6)	Diabetes, Type 2	382 (407)	↓
8 (7)	Cancer, prostate	366 (381)	↓
9 (9)	Cancer, brain	360 (361)	↔
10 (11)	Cancer, melanoma	357 (346)	↔
11 (12)	Cancer, leukaemia, acute myelogenous	338 (326)	↔
12 (10)	Arthritis, rheumatoid	335 (352)	↓
13 (17)	Cancer, myeloma	283 (254)	↑
14 (15)	Cancer, head and neck	283 (258)	↑
15 (19)	Cancer, gastrointestinal, stomach	276 (242)	↑
16 (13)	Cancer, liver	273 (272)	↔
17 (18)	Parkinson's disease	271 (252)	↑
18 (14)	Pain, nociceptive, general	266 (262)	↔
19 (16)	Psoriasis	260 (256)	↔
20 (22)	Cancer, lymphoma, non-Hodgkin's	231 (215)	↔

Screenshot

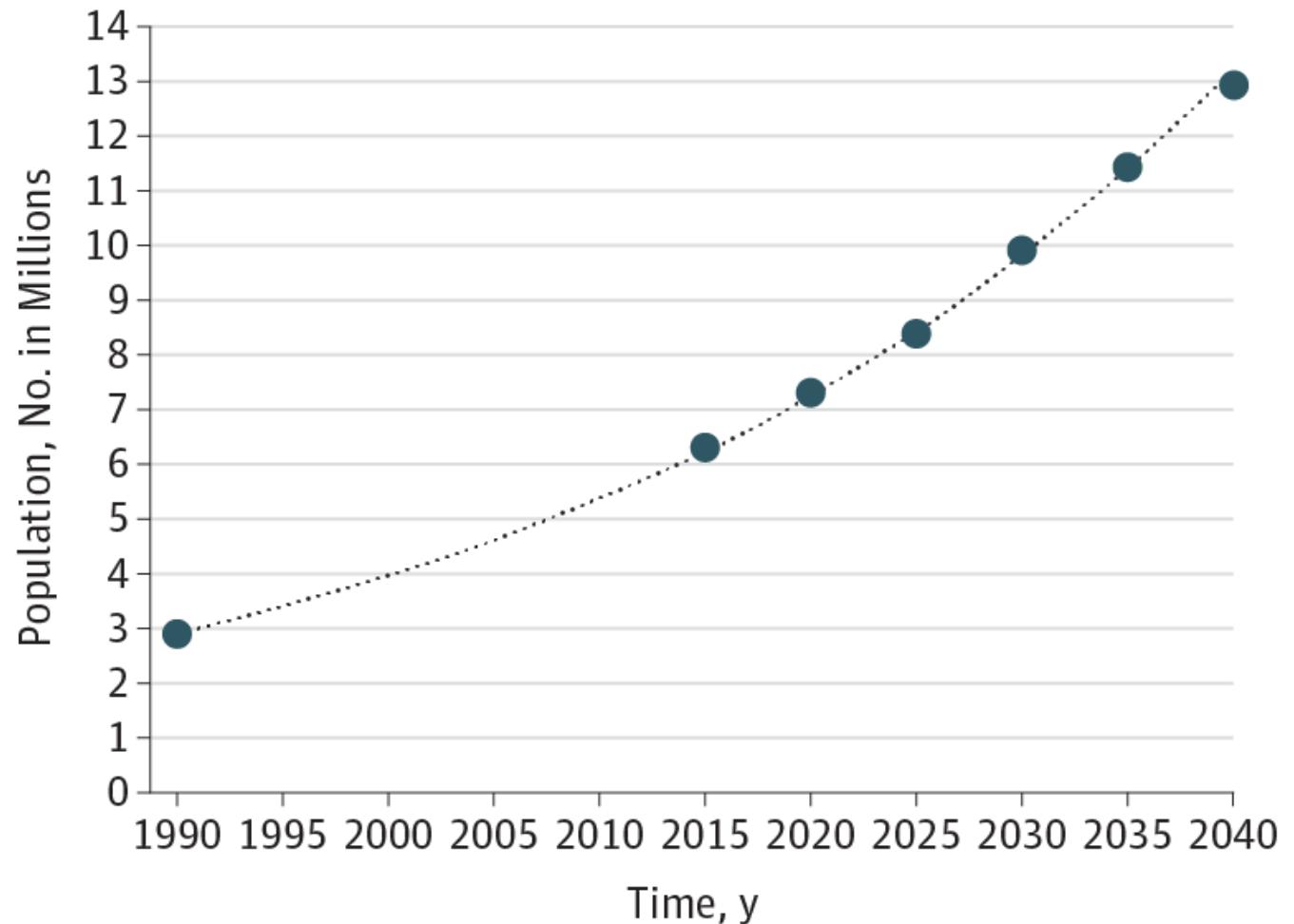
Top non-cancer indications for Pharma R&D

6 (8)	Alzheimer's disease	405 (381)	↑
7 (6)	Diabetes, Type 2	382 (407)	↓
12 (10)	Arthritis, rheumatoid	335 (352)	↓
17 (18)	Parkinson's disease	271 (252)	↑

Source: Pharmaprojects Pharma R&D annual review 2019

Why are companies interested in Parkinson's?

- Prevalence is increasing
 - 1990 – 2.5m
 - 2016 – 6.1m
 - 2040 – 12.9m
- It's a chronic condition
- It's primarily a disease of old age
- There is currently no “cure”



Total number of academic
publications on Parkinson's in 2019

8,094

How many Parkinson's therapies
are in research and development?

291*

*at least....

Source: Parkinson's Hope List

RELIEVE
symptoms

112

Source: Parkinson's Hope List

**DISEASE
MODIFYING**

RETARD
disease progress
REPLACE
what's been lost

179

Parkinson's therapies by phase

PHASE	2019	2020
Research programme	17	14
Discovery	53	55
Pre-clinical	74	66
Phase 1	48	63
“Proof of concept”	4	4
Phase 2	65	65
Phase 3	19	20
Regulatory review	2	2
TOTAL	282	291

Source: Parkinson's Hope List

The Phase 3 problem

- 20 programs are in Phase 3
- Only two are potential disease modifiers
 - Exenatide
 - Lingzhi (Ganoderma), Chinese mushroom extract



Source: Parkinson's Hope List

How many active clinical trials are registered for Parkinson's?

750

Alzheimer's	- 682
Type 2 Diabetes	- 1265
Rheumatoid arthritis	- 508

Source: www.clinicaltrials.gov

Dogfish and Gila Monsters

Dogfish (*Squalus acanthius*)



How did dogfish get their name?

What is the collective noun for dogfish?

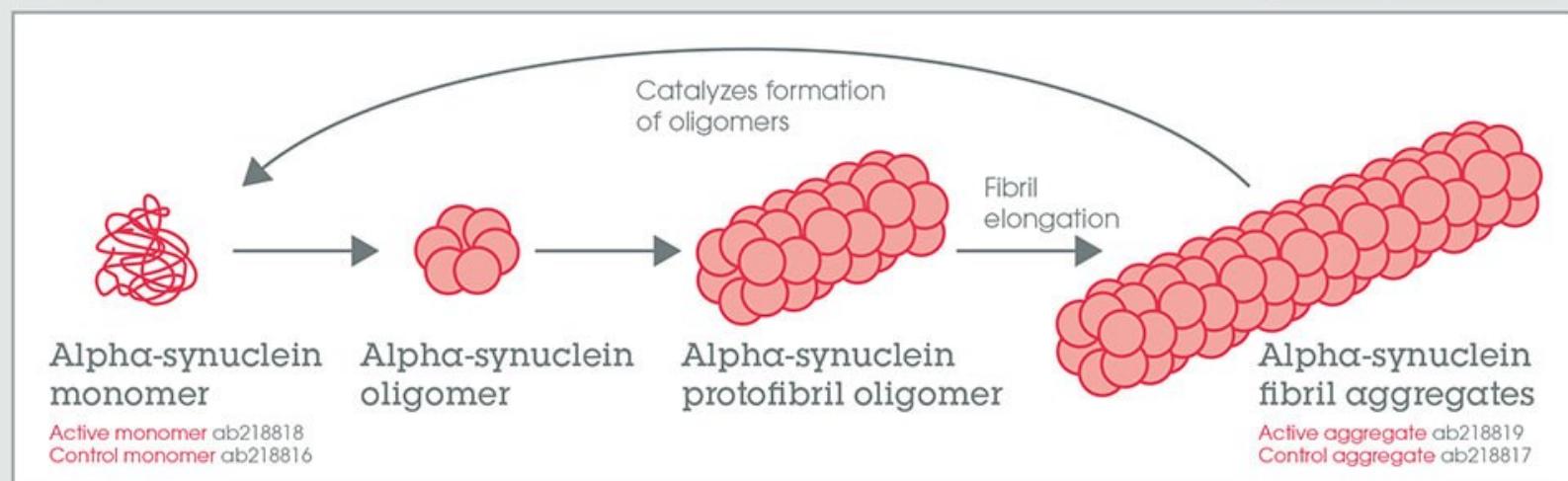
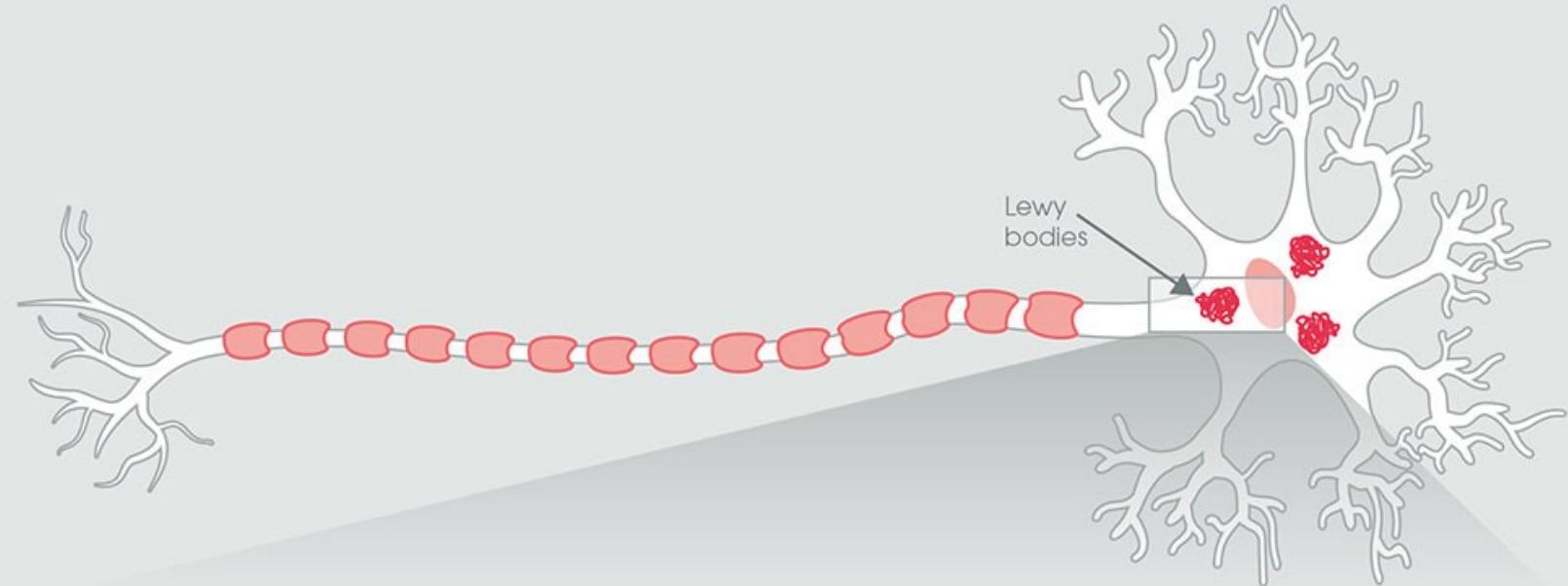
Dogfish (*Squalus acanthius*)

- The *Squalidae* family
- Can live as deep as 900m
- Spiny dogfish have venomous spines on each dorsal fin
- Gestation period up to 2 years
- The dogfish liver produces squalamine



Squalamine

- Squalamine prevents “sticky” α -synuclein aggregation by inhibiting membrane binding



Squalamine

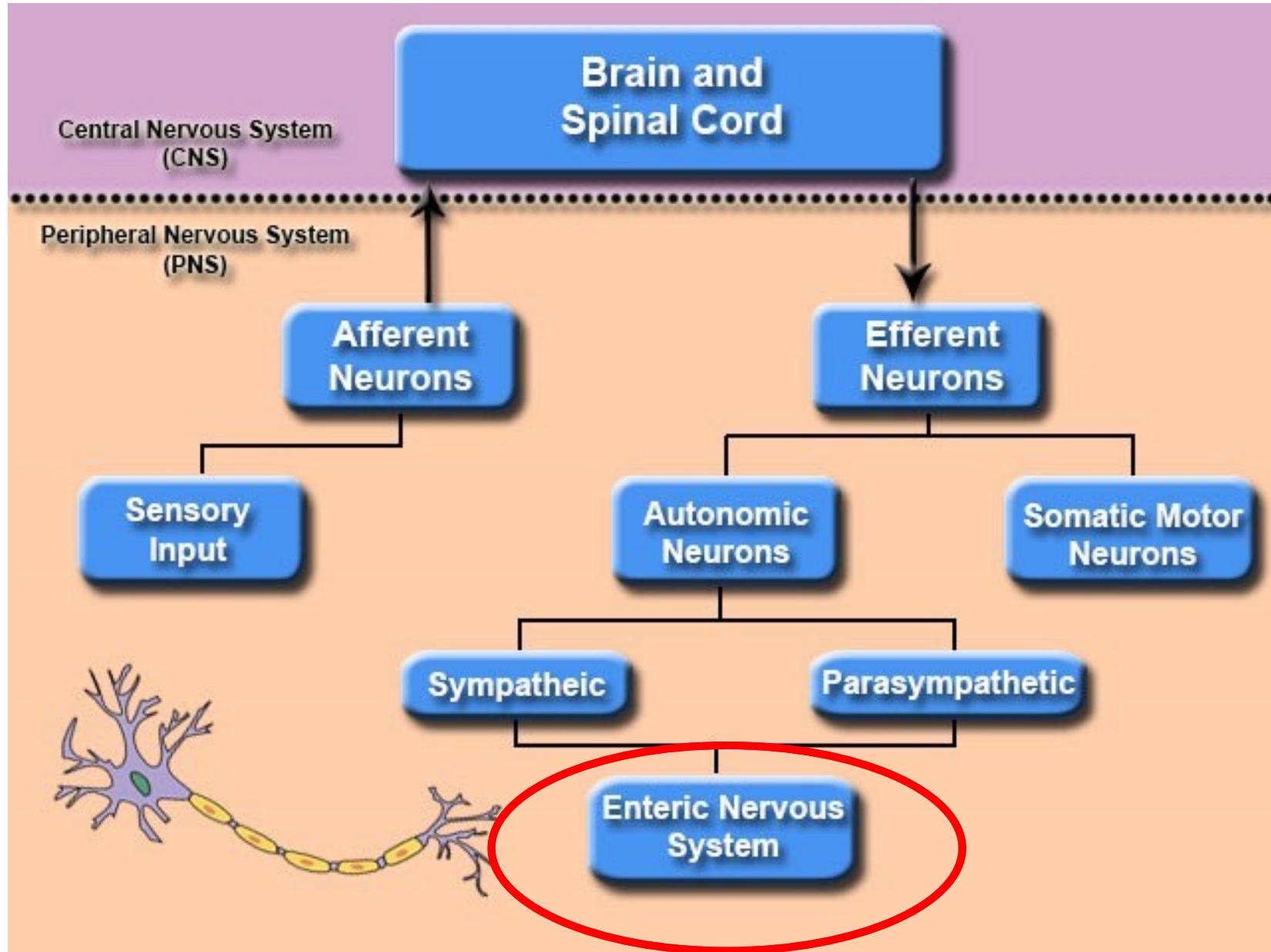
- Squalamine prevents “sticky” α -synuclein aggregation by inhibiting membrane binding
- But it doesn’t cross the blood-brain barrier

Blood-brain barrier



Squalamine

- Squalamine prevents “sticky” α -synuclein aggregation by inhibiting membrane binding
- But it doesn’t cross the blood-brain barrier
- So – target the enteric nervous system, specifically constipation



Enterin Inc - the Rasmet study

- Synthetic version of squalamine known as ENT-01 or Kenterin
- Phase 2a open label
- 34 PD patients with constipation
- Multiple escalating dose, fixed dose for 7 days, 14 day washout
- 82.4% of patients reached the primary efficacy endpoint
- Side effects – mild nausea (47%); diarrhoea (40%)
- Kenterin is now in a Phase 2b trial

Results

	Baseline	Fixed dose
↑ CSBM	1.2	3.6
↑ SBM	2.6	4.4
↓ Suppository use	1.8	0.3
↑ Consistency	2.7	4.1
↑ Ease of passage	3.2	3.7
↓ Quality of life	1.4	1.2
↓ Patient assessment	1.3	1.1

- CSBM – complete spontaneous bowel movements
- SBM - spontaneous bowel movements
- PAC-QOL - patient assessment of constipation – quality of life
- PAC-SYM – patient assessment of constipation - symptoms

Trodusquemine – squalamine and more

- It prevents α -synuclein aggregation
- Trodusquemine crosses the blood-brain barrier
- It inhibits the interaction of α -synuclein oligomers and fibrils



Gila monsters *Heloderma suspectum*

- What is the collective noun for a group of lizards?



Type 2 diabetes

- Resistance to, and lack of, insulin leading to high blood sugar
- Glucagon-like peptide 1 (GLP-1) reduces blood sugar levels by enhancing insulin release
- GLP-1 has a very short half-life in the blood
- The Gila Monster has venomous saliva – containing exendin, a GLP-1 agonist with a much longer half-life

Once-weekly 

BYDUREON BCise®
exenatide extended-release
injectable suspension 2 mg

victoza

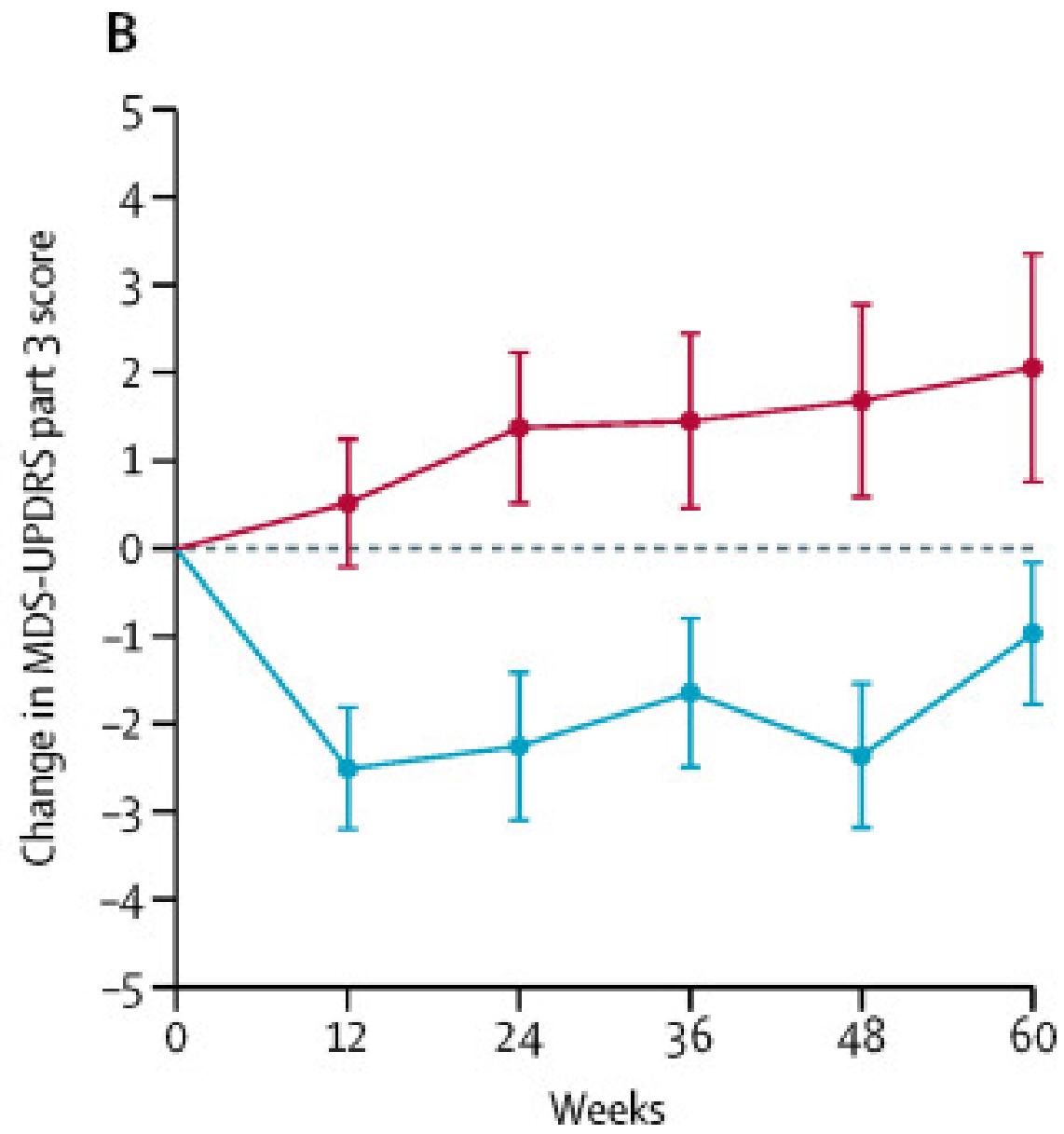
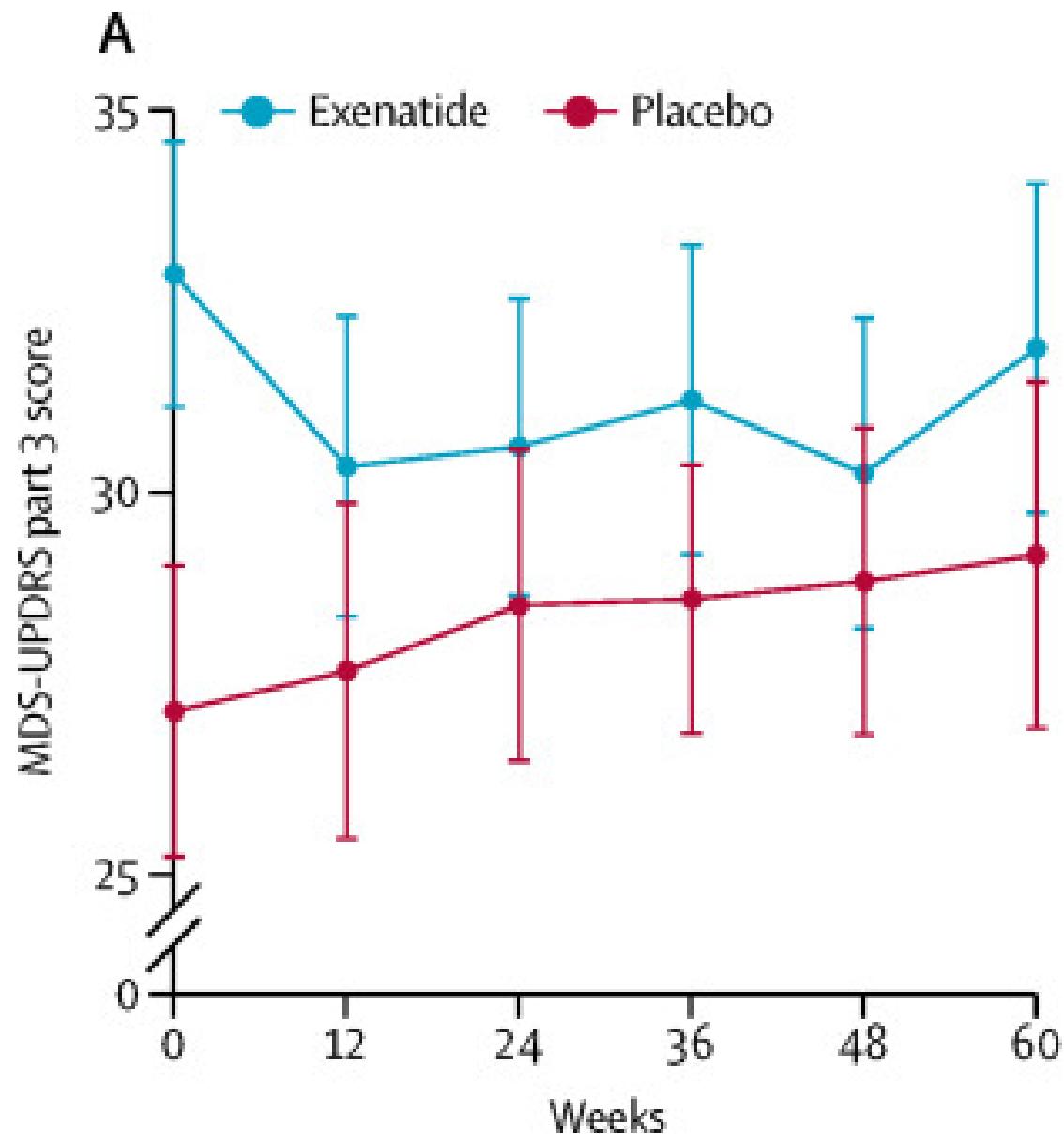
Byetta®
(exenatide) injection

 **Lyxumia®**
lixisenatide

ONCE-WEEKLY
OZEMPIC®
semaglutide injection 0.5mg | 1mg

RYBELSUS®
semaglutide tablets

Exenatide is neuroprotective



Clinical trials for GLP-1 agonists

DRUG	LOCATION	PHASE
Exenatide	London	3
Exenatide	Stockholm	2
Exenatide	S Korea	2
Exenatide	Baltimore	2
Exenatide	Florida	1
Liraglutide	California	2
Lixisenatide	Toulouse	2
Semaglutide	Oslo	2

Conclusions

- There is still a lot going on
 - New therapies
 - Clinical trials
 - Research
- Parkinson's is attractive to Pharma
- It's tough and expensive
- Not enough late stage drugs
- The investment is very large
- We can have HOPE

Thank you

