Recent and Near Future Advances in Parkinson's Disease

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Ways to Treat PD

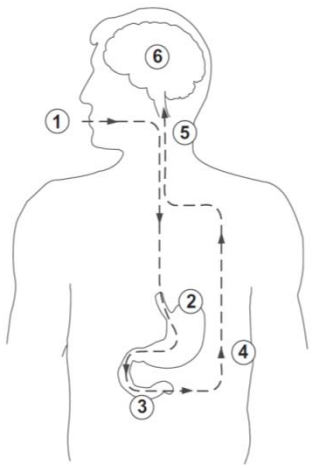
- Symptomatic Motor Treatment
  - Early therapy (UPDRS Part 2 and 3)
  - Add on therapy (On/Off diaries)
- Neuroprotection / Disease modifying
- Treatment for Specific Genetic PD
  - GBA, LRRK2
- Specific non-motor symptoms
  - psychosis, dementia, constipation, etc

Outline

- New L-dopa Preparations
- Opicapone (COMT inhibitor)*
- New Apomorphine Preparations
- Tavapadon (D1 agonist)
- Istradefylline - adenosine A2a antagonist*
- PD devices
- Genetic PD
- Disease modifying
  - ∝ synuclein Abx, K0969, gene therapies
- ~~Specific symptoms~~

Oral LD Therapy: Hurdles ($T^{1/2}$: 90 minutes)

1. **Swallowing oral therapy**
   Impaired swallowing (dysphagia) in advanced disease
2. **Stomach**
   Variable absorption of levodopa due to irregular gastric emptying
3. **Jejunum**
   Competition with dietary amino acids for active transport across the intestinal wall
4. **Peripheral tissues**
   Reduced levodopa bioavailability due to enzymatic breakdown by AADC and COMT
5. **Blood–brain barrier**
   Competition for transport across the blood–brain barrier with large neutral amino acids limits the amount of levodopa reaching the striatum
6. **Striatum**
   Conversion of levodopa to dopamine



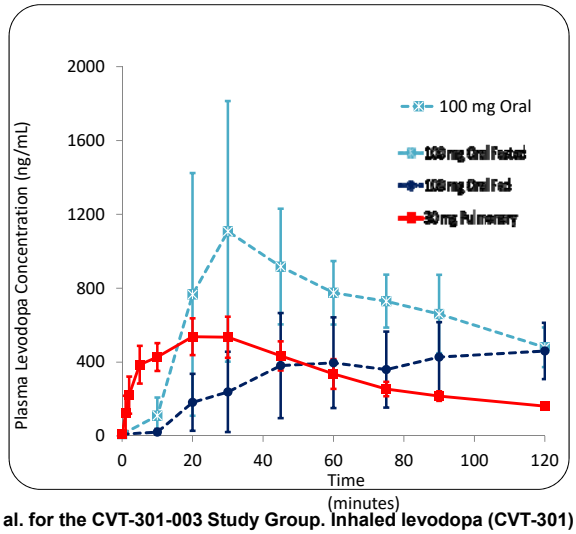
Novel L-dopa Preparations

- *Inbrija ®, inhaled L-dopa (Acorda)
- *Duopa ®, Continuous infusion gel (Abbvie)
- *Rytary ®, IPX0666 (Amneal)
- IPX203 (Amneal)
- NDO612, L-dopa Pump patch (Neuroderm)
- L-dopa subcutaneous pump (Abbvie)
- ~~Intec Accordion Pill~~
- SD-1077, deuterated L-dopa (TEVA)

Inbrija ®: Inhaled L-dopa (Acorda)

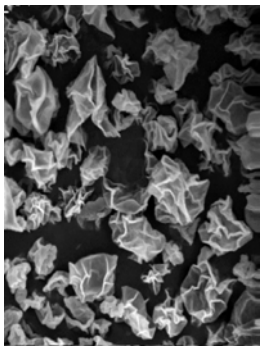
- Inhaled L-dopa dry powder FDA approved for rescue therapy
- Tmax by 15 minutes in all, usually 10 min.
- At 10 minutes, 10x absorption compared to oral
- To date no evidence of cumulative pulmonary side effects

Inhaled levodopa (CVT-301-001) serum pharmacokinetics



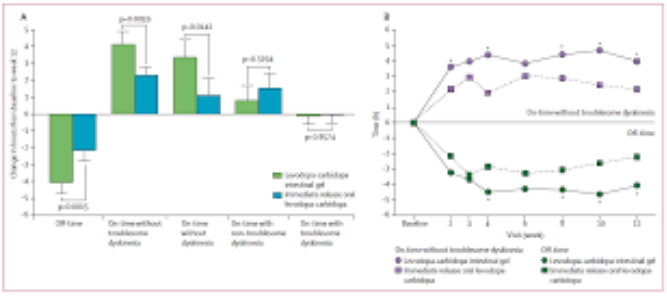
LeWitt PA et al. for the CVT-301-003 Study Group. Inhaled levodopa (CVT-301) provides rapid motor improvements after administration to Parkinson's disease patients when OFF Mov Disord 2015:30(supple1):260

Inbrija® : Inhaled L-dopa

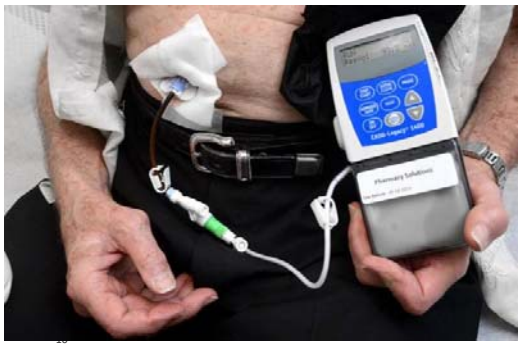


Homogeneous, drug loaded aerosol particles	⇨ Up to ~90% drug load
Capable of large dose	⇨ 10s mg/ inhalation
High efficiency dosing	⇨ ~70% nominal dose delivered
Breath actuated device	⇨ Precise dosing across flow rates, does not require coordinated breathing effort
Proven reliable and user friendly	Clinically validated in challenging patient populations

Duopa ® Jejunal Pump (Abbvie)

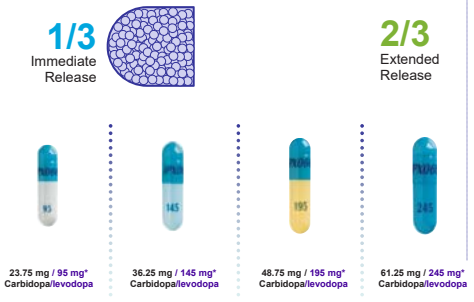


Neuropathy?

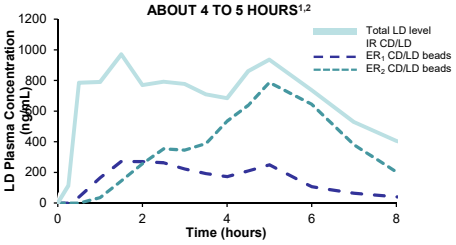


Extended Release C/L: RYTARY ® (Amneal)

AVAILABLE IN 4 CAPSULE STRENGTHS, EACH CONTAINING MULTI-BEAD TECHNOLOGY THAT PROVIDES AN IMMEDIATE- AND EXTENDED-RELEASE OF LD[1,2]

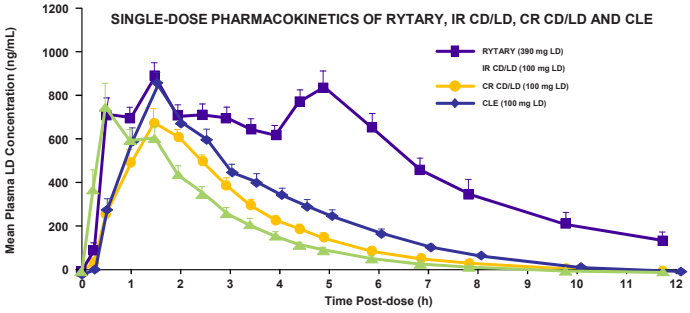


AFTER AN INITIAL PEAK AT ABOUT 1 HOUR, PLASMA CONCENTRATIONS ARE MAINTAINED FOR ABOUT 4 TO 5 HOURS[1,2]



Total and individual component LD plasma concentrations following a single dose of 2 x 195 mg RYTARY in 60 healthy subjects[1]

Extended Release C/L: RYTARY® (Amneal)

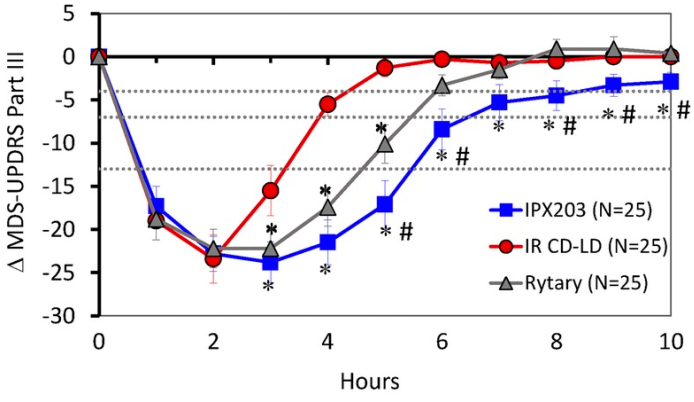


LD plasma concentration profiles collected after single-dose administration in healthy volunteers (n=22)

RYTARY provides an initial increase in LD concentration comparable to that with IR CD/LD and sustains the concentration for 1.9 to 2.5 hours longer than the other CD/LD products

Hsu A et al. *J Clin Pharmacol.* 2015;55(9):995-1003.

IPX203 ER CD-LD (Amneal) Investigational Phase 3 Trial



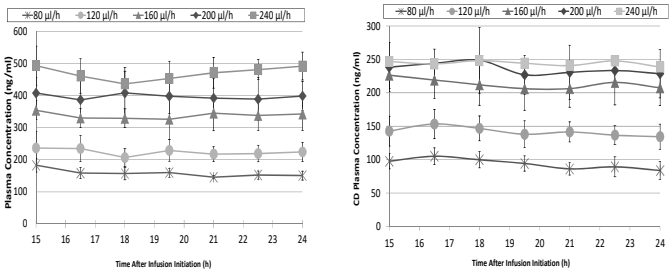
* $p<0.05$ compared with IR CD-LD
\# $p<0.05$ compared with Rytary

Trial ongoing here: subjects taking C/L IR with 2 hours "off" time

Modi N. Clin Neuropharm 2019

ND0612 – Subcutaneous L-dopa Infusion (Neuroderm / Mitsubishi)

Constant LD Plasma Concentrations Following Continuous SC Administration of ND0612



Plasma levodopa concentration **Plasma carbidopa concentration**

Caraco J, Oren S, LeWitt P. Near-constant therapeutic levodopa plasma concentrations maintained by continuous subcutaneous administration of ND0612, a novel formulation of levodopa/carbidopa.

Continuous Subcutaneous L-dopa Infusion (Neuroderm / Mitsubishi)

Pump-Patch status

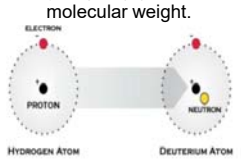
- Small Phase II trials have shown improved plasma concentrations 12/14
- ND0612H, achieved maximum daytime concentrations of 1,333ng/ml and 1,436ng/ml
- ND0612L achieved maximum daytime concentrations of 528ng/ml and 477ng/ml
- Crystal development has been a problem

ABBV-951: Subcutaneous Infusion (Abbvie)

Phase 2/3 Trial ongoing

Deuterated Drugs

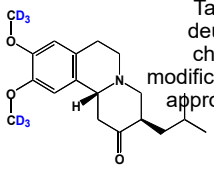
A non-toxic, naturally occurring form of hydrogen (H) with twice the molecular weight.



Advantages of D Substitution:

- No change in shape, size, charge, or target pharmacology of small molecules
- Can improve PK: 8x stronger C-D bond attenuates metabolism and increases half life
- Confers several potential advantages

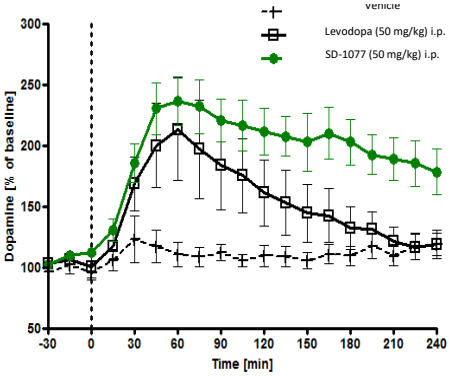
SD-809 (Deutetrabenazine)



Targeted deuterium chemical modifications in an approved drug

SD-1077: Deuterated Levodopa for the Treatment of Parkinson's Disease (PD)

Rodent Microdialysis Data

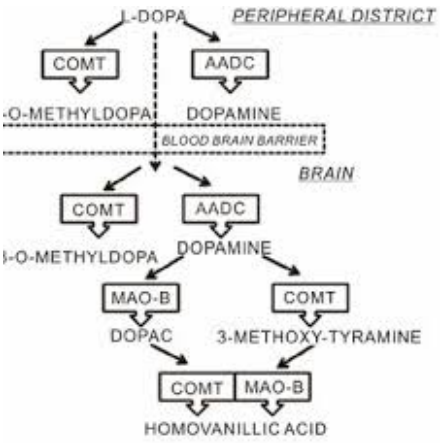


By prolonging the duration of action of dopamine in the brain, SD-1077 may address needs in the following patients:

Early-Stage PD: Potential to increase proportion of patients who use dopaminergic therapy
Mid-Stage PD: Potential to increase "on" time for patients without dyskinesia or reduce dyskinesia for patients with motor fluctuations
Late-Stage PD: Potential for use with continuous infusion pump

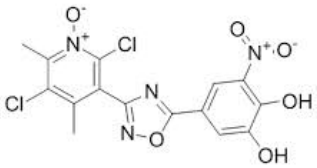
Catechol-O-methyltransferase (COMT inhibitors)

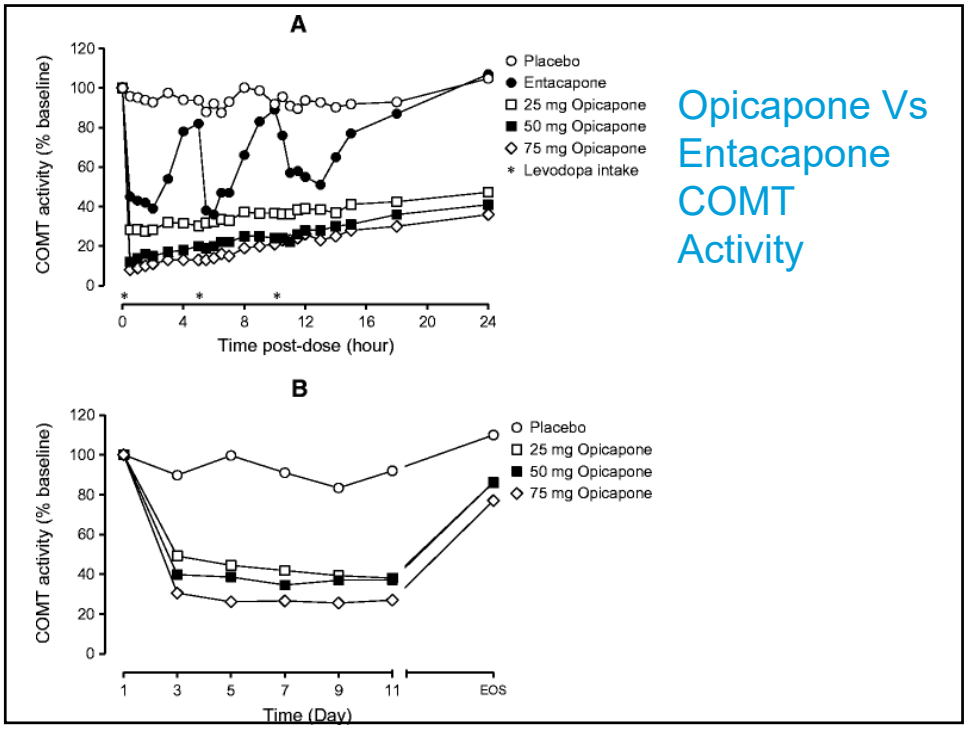
- Entacapone
  - Comtan®
    Stalevo®
- Tolcapone
  - Tasmar®
- **Opicapone**
  - **Ongentys®**



Opicapone / Ongentys® (Neurocrine / Bial)

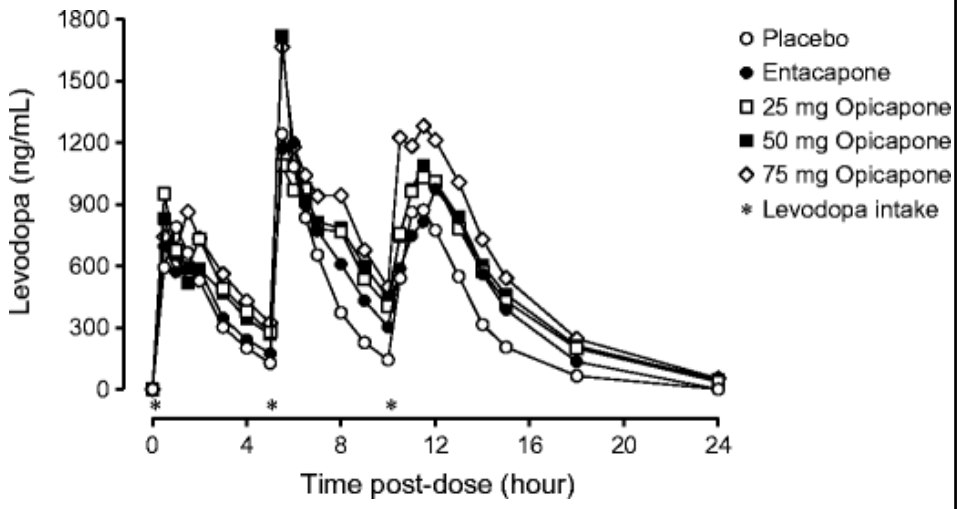
- BIAL Pharma, Portugal
  - Neurocrine
- "Third generation" COMT inhibitor
- T1/2: 1-2 hours
- T ½ on COMT inhibition > 100 hours
- Higher % COMT inhibition compared to entacapone





Opicapone Vs Entacapone COMT Activity

Opicapone Compared to Entacapone (L-dopa Concentrations)



Opicapone -Ongentys®
Neurocrine

- Phase III trials
  - About 1 hour less off time over placebo
  - Main AE: Dyskinesia 20% vs 6%
- FDA approved dose 50 mg qD
  - 25 with moderate hepatic failure

Studies not published yet

Apomorphine

- Chemically created in 1860s
- Potent, high affinity D1/D2 agonist
  - No affinity to opioid receptors
- Lipophilic quickly crosses the BBB
- Animal models show 10x higher levels in CNS
- Very strong anti-oxidant and probably inhibits apoptosis
- Poorly absorbed orally
- Very short $T_{1/2}$
- AE: Nausea and hypotension

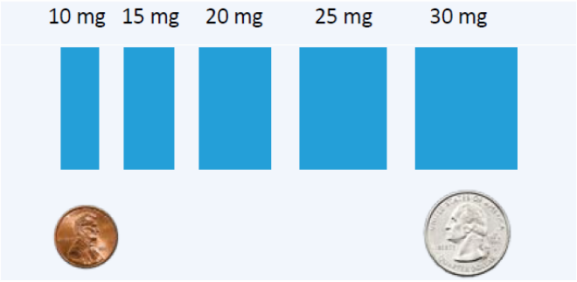
Apomorphine Preparations

- *Subcutaneous Injection (Apokyn® , Supernus
- *Sub-lingual (Kynmobi ® , Sunovion)
- Subcutaneous Infusions (Supernus)
- Inhaled apomorphine

Sublingual Apomorphine Kynmobi ®

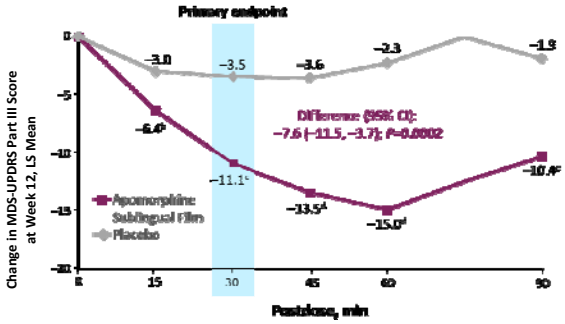
(Sunovion)

- Recently FDA approved for “off” periods in fluctuating PD
- Up to 5x/day
- Buffering system to offset acidity



Apomorphine Sublingual Film

- **CTH-300**: Pivotal, Phase 3, randomized, placebo-controlled study in 109 patients with idiopathic PD and "OFF" episodes[1,2]



- Efficacy: LS mean change in MDS-UPDRS Part III motor examination score at 30 minutes at week 12[a] was −11.1 for apomorphine sublingual film and −3.5 for placebo (*P*=0.0002)[1]

- [a]mITT population. [b]*P*<0.05. [c]*P*<0.001. [d]*P*<0.0001.
- CI, confidence interval; LS, least squares; MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; mITT, modified intention-to-treat; TEAE, treatment-emergent adverse event.
- **1.** Factor S, et al. *Mov Disord.* 2018;33(suppl 2):247; **2.** Pahwa R, et al. *Mov Disord.* 2018;33(suppl 2):372.

Pooled Safety Analysis [a]

- Among 408 and 285 unique patients exposed to ≥1 dose of apomorphine sublingual film during titration and maintenance treatment phases, 60% and 75%, respectively, reported ≥1 TEAE

Preferred Term	Titration Phase	
	Patients, % (N=408)	Events
Any TEAE	60	844
Nausea	21	115
Dizziness	11	53
Somnolence	11	74
Yawning	11	75
Headache	8	41

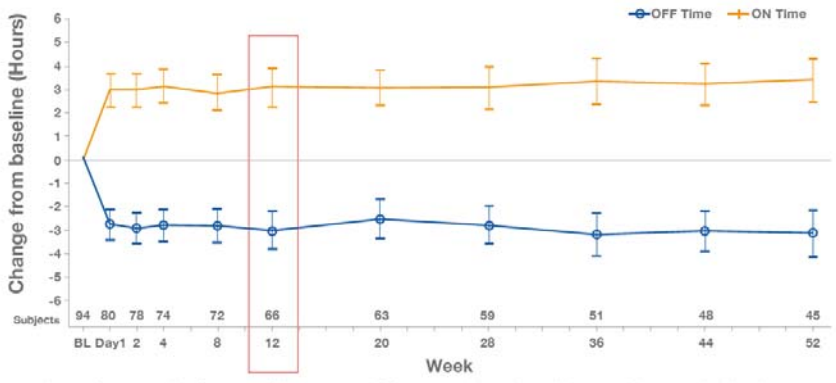
Preferred Term	Maintenance Treatment Phase	
	Patients, % (n=285)	Events
Any TEAE	75	802
Nausea	17	59
Somnolence	7	25
Dizziness	6	19
Fall	5	15
Fatigue	5	17
Lip swelling	5	17
Oral mucosal erythema	5	16
Vomiting	5	15
Yawning	5	16

- Clinical studies contributing patients to this analysis included CTH-105, CTH-201, CTH-300, and CTH-301.

Subcutaneous Apomorphine Infusion (completed Phase 3 Trials)

- **Used in Europe for decades (Britania)**
- **Supernus**
- **FDA NDA recently filed**

Apomorphine Pump: Reduction in OFF time increase in ON time without troublesome dyskinesia



Mean change from Baseline (95% Confidence Interval) for OFF and ON time without troublesome dyskinesia over 24 hours, mITT Population

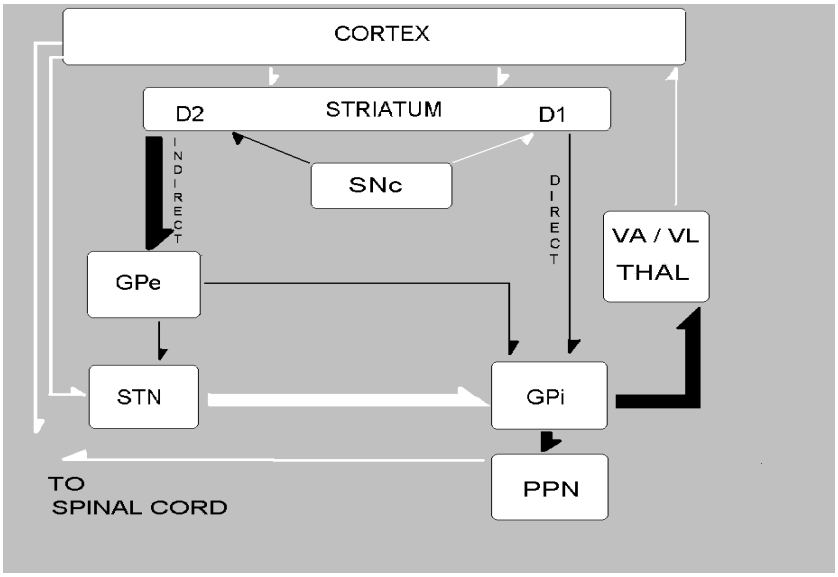
Apomorphine Pump Adverse Events : Related

	Titration Period (N=99)	Maintenance Period through Week 52 (N=85)	Overall[a] (N=99)
Infusion site nodule	61 (61.6)	37 (43.5)	77 (77.8)
Dyskinesia	28 (28.3)	15 (17.7)	38 (38.4)
Infusion site erythema	20 (20.2)	11 (12.9)	27 (27.3)
Nausea	23 (23.2)	8 (9.4)	29 (29.3)
Somnolence	16 (16.2)	10 (11.8)	25 (25.3)
Dizziness	15 (15.2)	7 (8.2)	20 (20.2)
Headache	9 (9.1)	5 (5.9)	14 (14.1)
Infusion site pruritis	8 (8.1)	6 (7.1)	13 (13.1)
Fatigue	5 (5.1)	7 (8.2)	12 (12.1)
Infusion site bruising	8 (8.1)	4 (4.7)	12 (12.1)
Infusion site pain	6 (6.1)	4 (4.7)	10 (10.1)
Fall	4 (4.0)	7 (8.2)	10 (10.1)

Dopamine Agonists

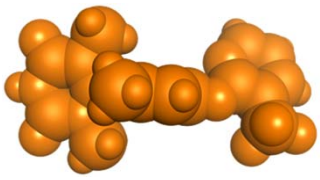
- Pramipexole - Mirapex®
- Ropinirole - Requip®
- Rotigotine transdermal - Neupro®
- Apomorphine
- Bromocriptine
- Pergolide - Permax ®
- **Tavapadon (D1 specific agonist)**

PD Basal Ganglia



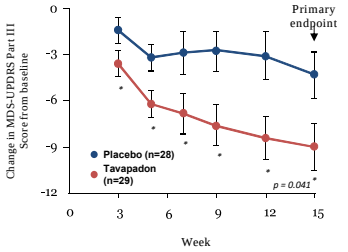
Tavapadon – D1 specific agonist
(Cereval)

Less dyskinesia?
Less sedation?
Less impulse control disorder?



Tavapadon – Phase 2 Early PD Data

Phase 2 Data: Tavapadon in Early PD[1]
(Primary Endpoint: MDS-UPDRS III Motor Score)



In Phase 2, tavapadon demonstrated 4.8 point MDS-UPDRS III difference vs. placebo at week 15 (p=0.04, MMRM)

Note: Average dose of tavapadon = 9 mg; 11 patients on 15 mg top dose at week 15. Baseline Part III scores of 24.3 (tavapadon) and 25.8 (placebo).

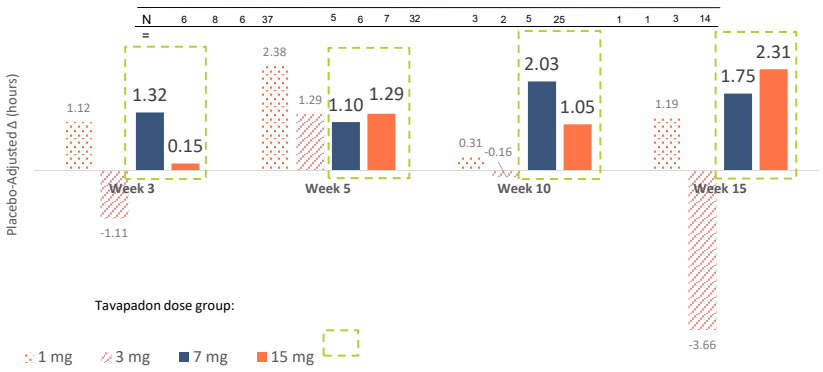
Additional Tavapadon Phase 2 Data[1]

- When adjusted to exclude patients with baseline MDS-UPDRS II of 0 or 1, **showed improvement of ~2 points over placebo on MDS-UPDRS Part II[2]**
- Most common AEs included headache and nausea (can be mitigated with titration)
- Incidence of known D2/D3 side effects:
  - Somnolence: 14%
  - Nausea: 31%
  - Hallucinations: 0%[3]
  - Hypotension-Related Events: 7%
  - Dizziness: 7%

Tavapadon demonstrated 5.8 point improvement over placebo at week 15 on MDS-UPDRS Part II + III (p = 0.02, MMRM)

Tavapadon Phase 2 Adjunct to L-dopa: Increase ON-Time without Troublesome Dyskinesias

Tavapadon demonstrated at least 1 hour of improvement in ON-time without troublesome dyskinesias



Tavapadon showed clinically meaningful benefit within therapeutic dose range of 5 mg to 15 mg

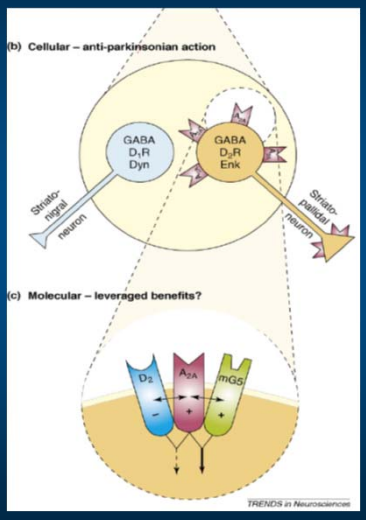
Adenosine A2a Antagonists

- Istradefylline (Nourianz®, Kyowa)
- Tozadenant, (Biotie)
- Preladenant, (Merck)
  - Discontinued after Phase III trials
- Vipadenant (Biogen/Vernalis)
  - Discontinued
- ST-1535
  - Animal studies
- Caffeine

http://clinicaltrials.gov/

A2a Receptors

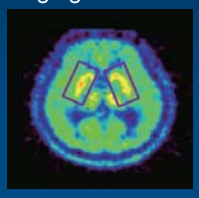
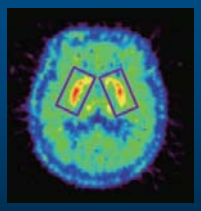
Striatum



- A2a receptor is a G-protein coupled receptor
- Highly expressed in the striatum with low levels in the cortex
- Interact functionally with D2 receptors in the striatopallidal (indirect) pathway
  - A2a –D2, A2A-D3 and A2A-mGlu5 heteromers have been found
  - This pathway is thought to be overactive in PD
  - The interaction with D2 receptors provides the basis for the utilization of A2A antagonists to treat PD

Schwarzschild MA et al., TRENDS in Neurosciences, 2006;29(11):647-54.

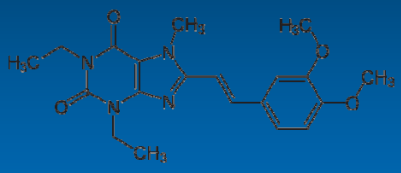
Istradefylline / A2a Receptors in PD

	A2a Receptor PET imaging[1]	Receptor Subtypes	CNS Distribution	Affinity of Istradefylline for Receptors Ki
NI		A1	Widely distributed	>1000
		A2a	Striatum, globus pallidus (external), nuc accumbens, olfactory tubercle	12
PD		A2b	Widely distributed (low density)	150
		A3	Widely distributed (low density)	>10,000

1. Mishina M et al. *Int Rev Neurobiol*. 2014;119:51-69

Istradefylline, Nourianz®

- Kyowa Kirin
- In 2008, FDA issued a non-approvable letter and expressed concerns as to whether the efficacy results sufficiently supported its clinical utility
- In 2013, approved in Japan
- In 2019, FDA approved
- 20mg-40mg qD



Istradefylline

Author	Phase	Dose (mg) once daily	Reduction in OFF (hrs) vs. placebo	*P*-value
Hauser 2003	exploratory	20 or 40	1.7	0.004
LeWitt 2008	2	40	1.2	0.005
Stacy 2008	2	20	0.64	0.026
Stacy 2008	2	60	0.77	0.024
Hauser 2008	3	20	0.70	0.03
Guttman 2006	3	10, 20, 40	—	NS
Mizuno 2013	3/4	20, 40	.76 /.73	0.003

Istradefylline Adverse Events

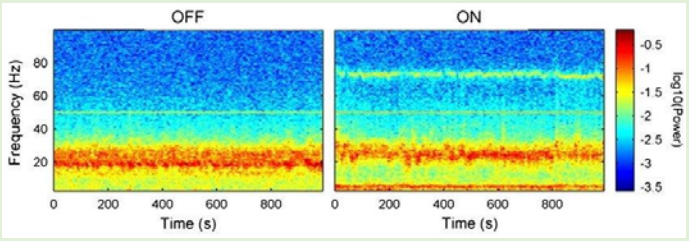
Adverse Reactions	Placebo (n=426)(%)	Istradefylline 20 mg/day (n=356)(%)	Istradefylline 40 mg/day (n=378)(%)
Nervous system disorders			
Dyskinesia	8	15	17
Dizziness	4	3	6
Gastrointestinal disorders			
Constipation	3	5	6
Nausea	5	4	6
Diarrhea	1	1	2
Psychiatric disorders			
Hallucinationa	3	2	6
Insomnia	4	1	6
Metabolism and nutrition disorders			
Decreased appetite	1	1	3
Investigations			
Blood alkaline phosphatase increased	1	1	2
Blood glucose Increased	0	1	2
Blood urea increased	0	1	2
Respiratory disorders			
Upper respiratory tract inflammation	0	1	2
Skin and subcutaneous tissue disorders			
Rash	1	1	2

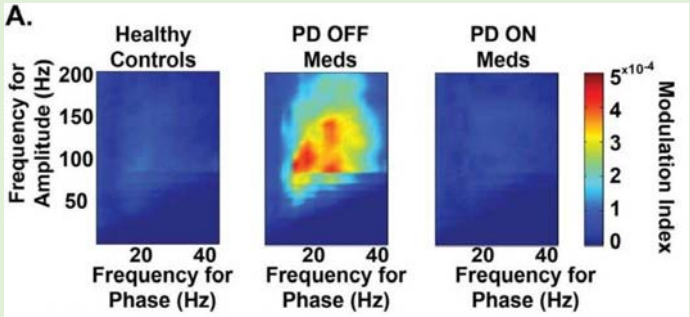
PD Devices

- Deep Brain Stimulation
  - Medtronic - Activa, Percept
  - Abbvie – St. Jude
  - Boston Scientific - Vercise
- Focused Ultrasound
- Vestibular Thermal Stimulation
- Phototherapy

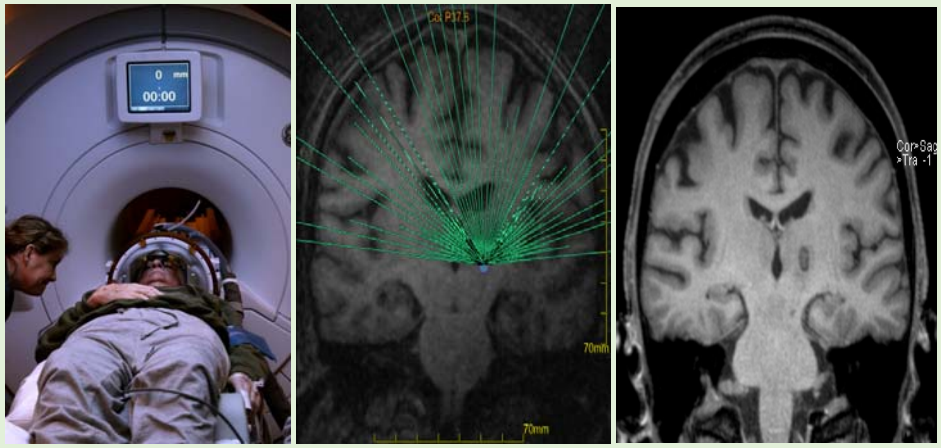
Directional Leads: adjust lateral/medial
Abbvie / Boston Scientific

Local Field Potential Feedback
Brainsense™ - Medtronic





Transcranial MR-guided Focused Ultrasound

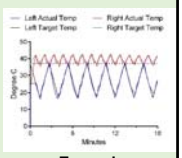


Focused Ultrasound (Exablate - Insightec)

- Class 1 data (FDA approved) for VIM ET
- Class 1 data (FDA approved) for PD VIM
- Ongoing studies for PD Gpi
- Little data for PD STN

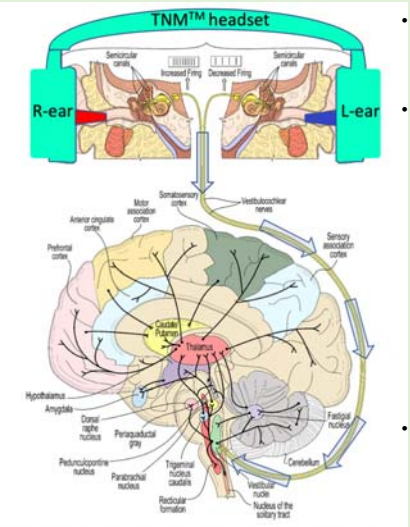
Brainstem Modulation Via ThermoNeuroModulation (TNM™) Scion Neurostim

- Caloric vestibular stimulation (CVS)
  - Safely used diagnostically for over a century
  - The central role for the vestibular system in health and well-being and its pervasive connectivity suggest wide range of therapeutic applications for CVS
  - Exploration into its therapeutic utility of CVS has been limited by feasibility for repeated and/or controlled stimulation using irrigation approaches.
- The TNM™ solid-state time-varying caloric vestibular stimulation (tvCVS) device
  - Enables longitudinal home use
  - Provides tightly-controlled time-varying waveforms
    - Prevent adaptation to the stimulus
    - Mitigate side-effects by controlling the time-rate of change
  - Approved for market entry in the US (ages 12 and up) and Europe (adults) for the prevention of episodic migraine. It is otherwise limited by U.S. Federal law to investigational use.
  - Designated by the FDA as non-significant risk for studies in PD and a Breakthrough Device for the treatment of symptoms in PD

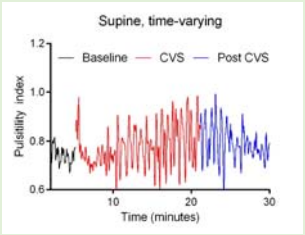


Example waveform of tvCVS with the TNM device

Neuromodulation via tvCVS

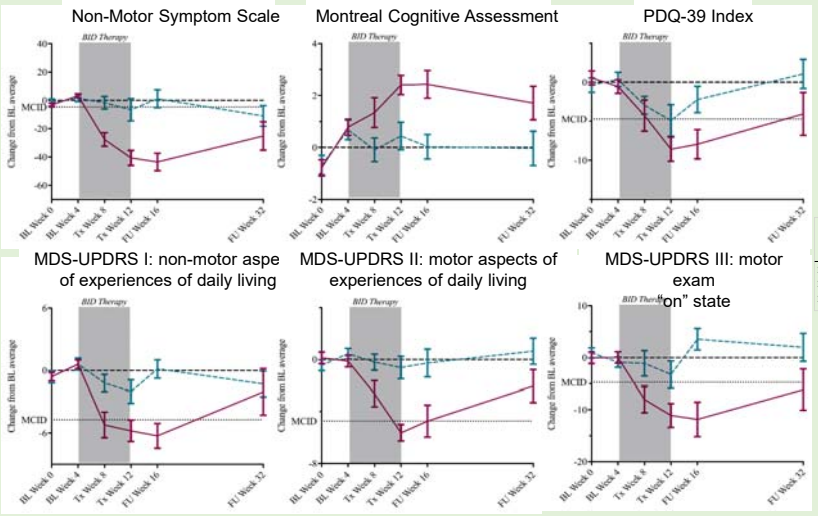


- The tvCVS stimulus directly and specifically targets the vestibular system and uses endogenous sensory pathways to convey applied stimulus.
- The high connectivity of the vestibular system enables vestibular stimulation to act on multiple brain targets in parallel making it an ideal conduit for neuromodulation.



- tvCVS produces robust oscillations and entrainment of cerebrovascular dynamics. The entrainment and frequency of this effect suggests engagement of a pontine pacing center. The cerebrovascular effects are hypothesized to engage several mechanism that promote brain health.

tvCVS : therapeutic gains across multiple symptoms in PD



Sample Size

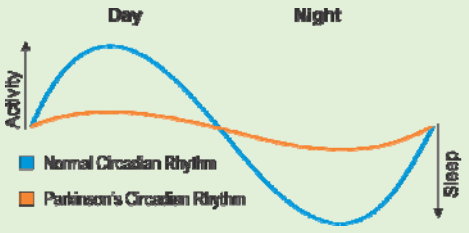
	Placebo	Active
BL - Tx Week 12	17	16
FU Week 16	17	13
FU Week 32	15	12

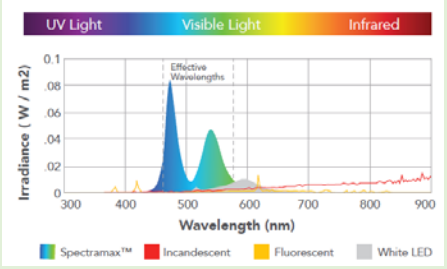
MCID: minimal clinically important difference

Wilkinson et al., 2019 *Parkinsonism Relat Disord* 65:261-266

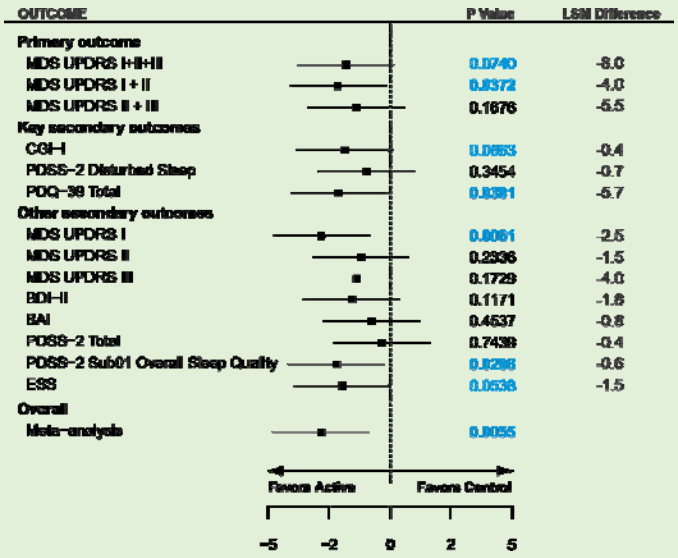
University of Kent

Light Therapy in PD: Spectromax (Photopharmics)





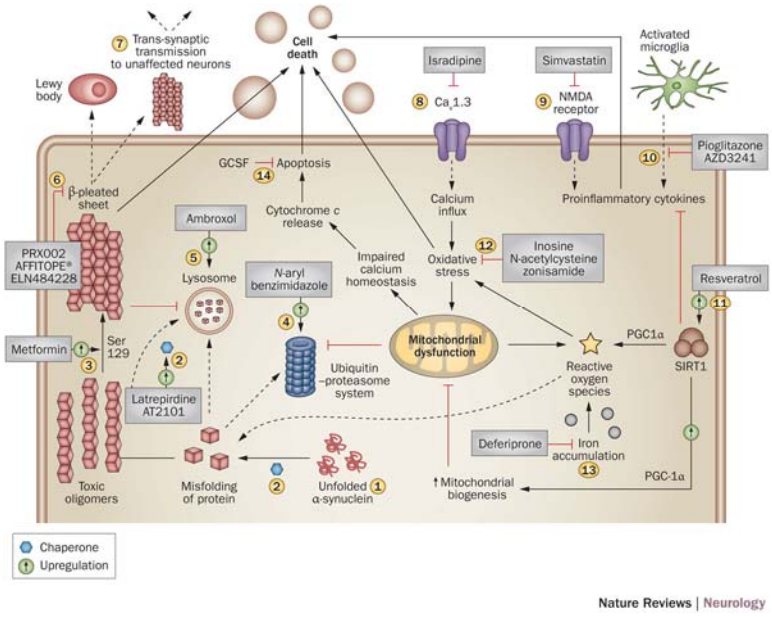
Phase 2 trial: 6-month, N=92, double-blind, RCT



Phase 3 trial starting

Disease Modifying Therapies

Proposed mechanisms involved in the Parkinson disease pathogenesis, and targets for intervention



Neuroprotective R.I.P.

- Pioglitazone, PPAR agon
- GPI-1485, Neuroimmunophilin
- Riluzole, Glut agonist
- Propargylamine
- CEP-1347, anti apoptotic
- GDNF, neurotrophic
- CoQ10, mitochondrial
- Vitamin E, antioxidant
- Glutathione, antioxidant
- CERE-120
- Mitoquinone, mitochondria
- Pramipexole, DA agonist
- Cogane, GDNF mod
- Creatine, mitochondria
- Isradipine, Ca antagonist
- Inosine, antioxidant Nrf2

Disease Modifying Therapies

- Iron Chelator
- GLP-1 agonists
- Cell Transplant Therapies
- Abl Tyrosine Kinase Inhibitors
- Alpha-Synuclein reducers
  - (Immunotherapy)
- Gene Therapies

Deferiprone (Apotex)

- Oral small molecule iron chelator
- Small Phase 2 trial reduced SN iron content
- 140 subject Phase 2b study completed
- 372 subject Phase 2/3 study ongoing

- Also studied in Alzheimer's, PANK2, ALS

Martin-Bastida et al., 2017 Devos et al., 2014

"Glucogon-like peptide (GLP-1) analogues

- Promote insulin release
- Reduce CNS cell death in multiple models
  - Increase mitochondrial function, inhibits protein aggregation

Compounds:

- Liraglutide (Victoza, NovoNordisk)
- Exendin-4
- Exenatide (Byetta, Bydureon)
- Semaglutide (Ozempic, Novo Nordisk)

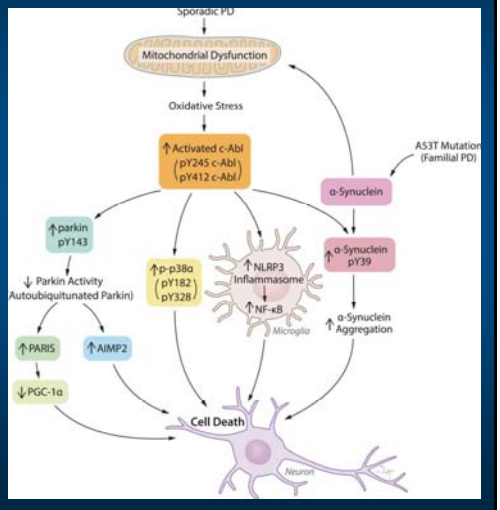
Author/year	Transplant site / dose	Immunosuppressed	N (# female)	PD duration (years)	Outcomes	Safety/tolerability
Human embryonic mesencephalic tissue						
Lindvall 1989 Sawle 1992 Wenning 1997 Freed 1992 Peschanski 1994 Defer 1996 Spencer 1992 Freeman 1995 Brundin 2000	Variable – caudate +/- putamen, unilateral vs bilateral 1-7 donor embryos 1 study used adjunct - tirilazad mesylate	Y	multiple	5-22	Improvement in some but not all clinically - Included improved ADLs, H&Y, decreased medication, improved ^{18}FDOPA uptake at graft sites	Generally well tolerated and most studies had no SAEs Variability in post-transplant dyskinesia
Carotid body tissue						
Arjona 2003 Minguez-Castellanos 2007	Bilateral putamen or caudate/putamen	N	13 (6)	11 ± 4 years	15 ± 21.5% improvement (p=0.034) at 1 year (range 5-74%) No significant change in ^{18}F-DOPA PET	1 lacunar infarct; 1 cortical hemorrhage/seizure No GID
Human retinal pigment epithelial cells						
Bakay 2004 Farag 2009 Stover 2005, 2008	Unilateral putamen	N	6 (NR)	10.2	48% improvement in UPDRS motor "off" score and decreased "off" time	No SAEs deemed to be treatment-related No GID
Adrenal medullary tissue						
Backlund 1985	Unilateral or bilateral caudate (1 thalamic)	N	>90	3->14	Initial reports dramatic and positive but later trials demonstrated modest improvement	No SAEs reported in initial studies Later studies with significant morbidity and mortality
Porcine embryonic mesencephalic tissue						
Schumacher 2000 Fink 2000 Deacon 1997	Unilateral caudate and putamen	Y	12 (3) 60.8 ± 6.5	14.0 ± 5.9 years	Total UPDRS "off" improved but UPDRS part 3 scores "off" medication did not improve No significant change in ^{18}FDOPA PET	1 death, unrelated No GID noted
Human parthenogenetically derived neural stem cells (NSCs)						
Garitaonandia 2018 Gonzalez 2019 Kern 2019	Bilateral caudate, putamen, SN 30, 50, or 70 million cells	N	12 planned		Preliminary results report improvement at 6 months in Hauser Motor Diary; PD Quality of Life Score-39; Clinical Global Impression	No related SAEs
Wang 2018	NCT 03119636 Ongoing		50 planned			
Human induced pluripotent stem cells (hiPSC)						
Takahashi 2017	Staged transplantation to bilateral putamen 2.4 million cells per side - Allogeneic	Y	Ongoing: 5-10 planned		None yet reported	No SAEs reported from first surgery
Schweitzer 2020	Staged transplantation to bilateral putamen 4 million cells per hemisphere - Autologous	N	1 (0) 69yo	10	PD symptoms stabilized or improved at 18-24 months	Safety/tolerability No SAEs

Ongoing Cell Transplant Trials for PD

Trial (NCT number)	Transplantations initiated	Donor cells (cryopreserved product)	Number of transplant recipient (age)	Disease duration	Disease severity	Primary endpoint
TRANSEURO* (0189839)	Completed	Human fetal VM tissue (no)	11 (30–68 years)	2–13 years	Early to moderate	Efficacy
STEM-PD (NA)	No	hESC-derived mesDA progenitors	8 (<70 years)	5–15 years	Moderate	Tolerability and feasibility
NYSTEM-PD (NA)	No	hESC-derived mesDA progenitors	10 (45–72 years)	5–15 years	Severe	Safety, tolerability and feasibility
CiRA (NA)	Yes	hiPSC-derived mesDA progenitors	5–10 (50–69 years)	>5 years	Severe	Safety and tolerability
Chinese Academy of Sciences (03119636)	Yes	Stem cell-derived neural precursors	50 (50–80 years)	>5 years	Severe	Safety
Bundang CHA Hospital, Korea (01860794)	No	Human fetal VM neural precursors	15 (18–70 years)	NA	Severe	Safety and tolerability

Abl Tyrosine Kinase Inhibitors (Used for CML, ALL)

- Abl activity Inc in PD
  - Oxidative stress
  - Protein aggregation
- Compounds:
  - K0706*
  - Nilotinib* (Tasigna®)
  - Bafetinib (INNO-406)
  - Imatinib (Gleevac®)
  - Radotinib*

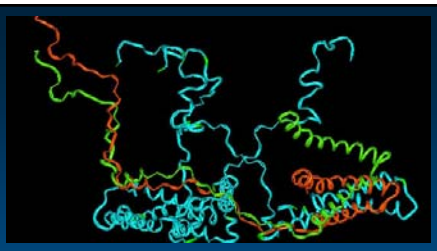


K0706 Sun Pharma

- May cross BBB better than other drugs
- PROSEEK Trial
  - 500 Subject Phase 2 trial for early PD
  - Can only have 2 years symptoms and can only be on rasagaline

Recruitment ongoing

Alpha-Synuclein in PD



- 144 AA protein in multiple configurations
- Abundant on nerve synapses
- Mutation/Gain of Function is rare cause of PD (PARK1)
- Major constituent of Lewy bodies
- Aggregated protein can spread “causing” normal protein to aggregate
- Aggregated protein also seen in MSA
- Multiple functions including dopamine release

Treatments Targeting α-synuclein

Drug	Company	Status	Comment
BIIB054	Biogen	Phase 2 SPARK trial enrolled	Ongoing
PRX0002/ Ro7046015	Prothena/Roche	Phase 2 PASADENA trial ongoing	Ongoing
MEDI1341	Astrazeneca/ Takeda	Phase 1 study complete	
PD01 AFFITOPE®	AFFiRiS	Phase 1 complete MSA Phase 1 started	Mono-epitopic vaccine (active)
NPT200-11/UCB0599	Neuropore/UCB	Phase 1 planned	Binds to α-syn to prevent aggregation
NPT088	Proclara	Alzheimer Phase 1 started	Binds to α-syn, B-amyloid, tau

Gene Therapies in PD

- Nerve Growth Factors
  - Glial derived neurotrophic factor GDNF (various vectors)*
  - Neurturin –AAV2*
  - Brain derived neurotrophic factor (BDNF)
- Enzymatic Genes
  - Aromatic acid decarboxylase (AADC)
  - Combination: AADC, tyrosine hydroxylase, GTP cyclohydroxylase, (VMAT-2)
  - Glutamic acid decarboxylase (GAD)

* Negative human trials

Enzyme Gene Therapies

Product	Company	Status	Comment
AADC-AAV2 VY-AADC02	Voyager / Neurocrine	Small i/ii trial showed clinical benefit	Single implant into bilat. putamen
AADC, TH, CH-1 lentivirus Prosavin (OXB-101)	Oxford BioMedica / Axovant	Small i/ii trial showed mild clinical benefit and good long term f/u	Bilat Putamen, Gene order changed and new i/ii trials starting
GAD-AAV	MeiraGTx	Small Phase 2 controlled study positive	Increases GABA-injected into bilat STN

Christine 2009, Palfi 2014, Kaplitt 2007

Treatment Targeted PD Genes

- Glucocerebrosidase (GBA1)
- Leucine-rich repeat kinase 2 (LRRK2)
- Alpha-synuclein (SNCA)

Glucocerebrosidase (GBA1)

- Venglustat (GZ/SAR402671, Sanofi/Genzyme)
  - Allosteric inhibitor of of glucosylceramide to reduce accumulation of glucosylceramide
  - Phase 2 studies finishing
- LTI-291 (Lysosomal Therapeutics)
  - small-molecule activator of glucocerebrosidase
  - Phase 1b studies completed
  - FDG-PET study improvement vs placebo
- PR001 (Prevail Therapeutics)
  - AAV9 vector GBA1 gene therapy

Leucine-rich repeat kinase 2 (LRRK2) (Dardarin)

- DNL201/DNL151 (Denali)
  - Oral LRRK2 inhibitor
  - Phase 1 safety in normals and small 1b in PD completed

Conclusions

- 24 FDA approved treatments for PD
- Symptomatic Pipeline robust
  - Mostly new delivery systems
  - Several new meds in known classes
  - Fewer novel mechanisms of action
- Disease modifying treatments?

Thank You