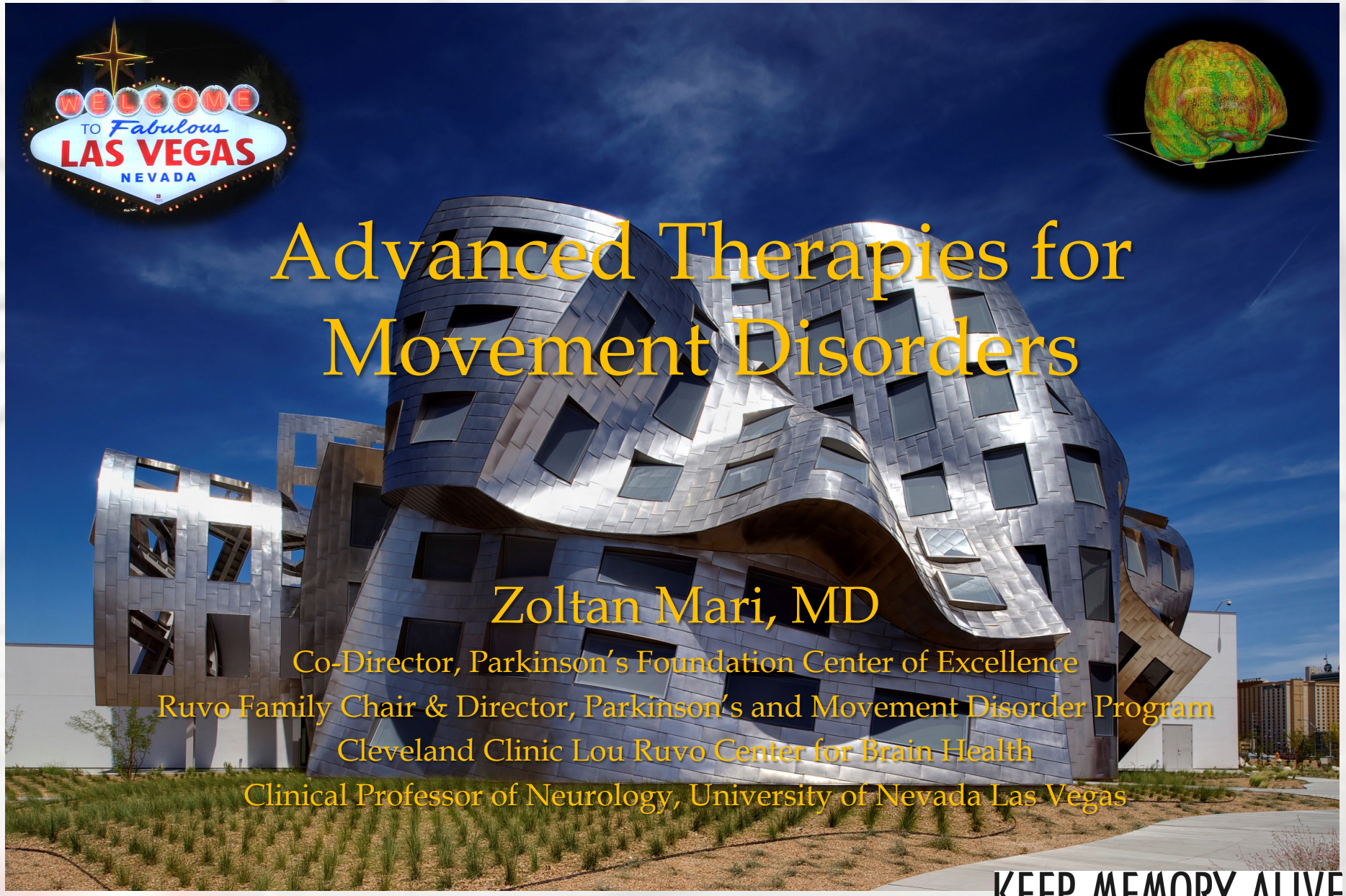


Advanced Therapies for Movement Disorders

Zoltan Mari, MD
Co-Director, Parkinson's Foundation Center of Excellence
Ruvo Family Chair & Director, Parkinson's and Movement Disorder Program
Cleveland Clinic Lou Ruvo Center for Brain Health
Clinical Professor of Neurology, University of Nevada Las Vegas

Cleveland Clinic

KEEP MEMORY ALIVE
Supporting the Mission of Cleveland Clinic Lou Ruvo Center for Brain Health
ALZHEIMER'S | HUNTINGTON'S | PARKINSON'S
MULTIPLE SYSTEM ATROPHY | MULTIPLE SCLEROSIS

Disclosures

- Z. Mari is a full-time staff at Cleveland Clinic and is representing his own opinions and NOT that of CC
- Z. Mari received (institutional) research support from:
  - National Institutes of Health
  - Michael J. Fox Foundation
  - National Parkinson Foundation (including PKG)
  - AbbVie/Solvay Pharmaceuticals
  - Great Lakes Neurotechnologies
  - AVID Radiopharmaceuticals
- Z. Mari has served as a paid consultant for GB Sciences, Sanofi Genzyme, NeuroReserve, Sensory Cloud, and Global Kinetics Corporation
- Z. Mari is founder and CMO for Neuraly, Inc & Z NeuroSciences, LLC

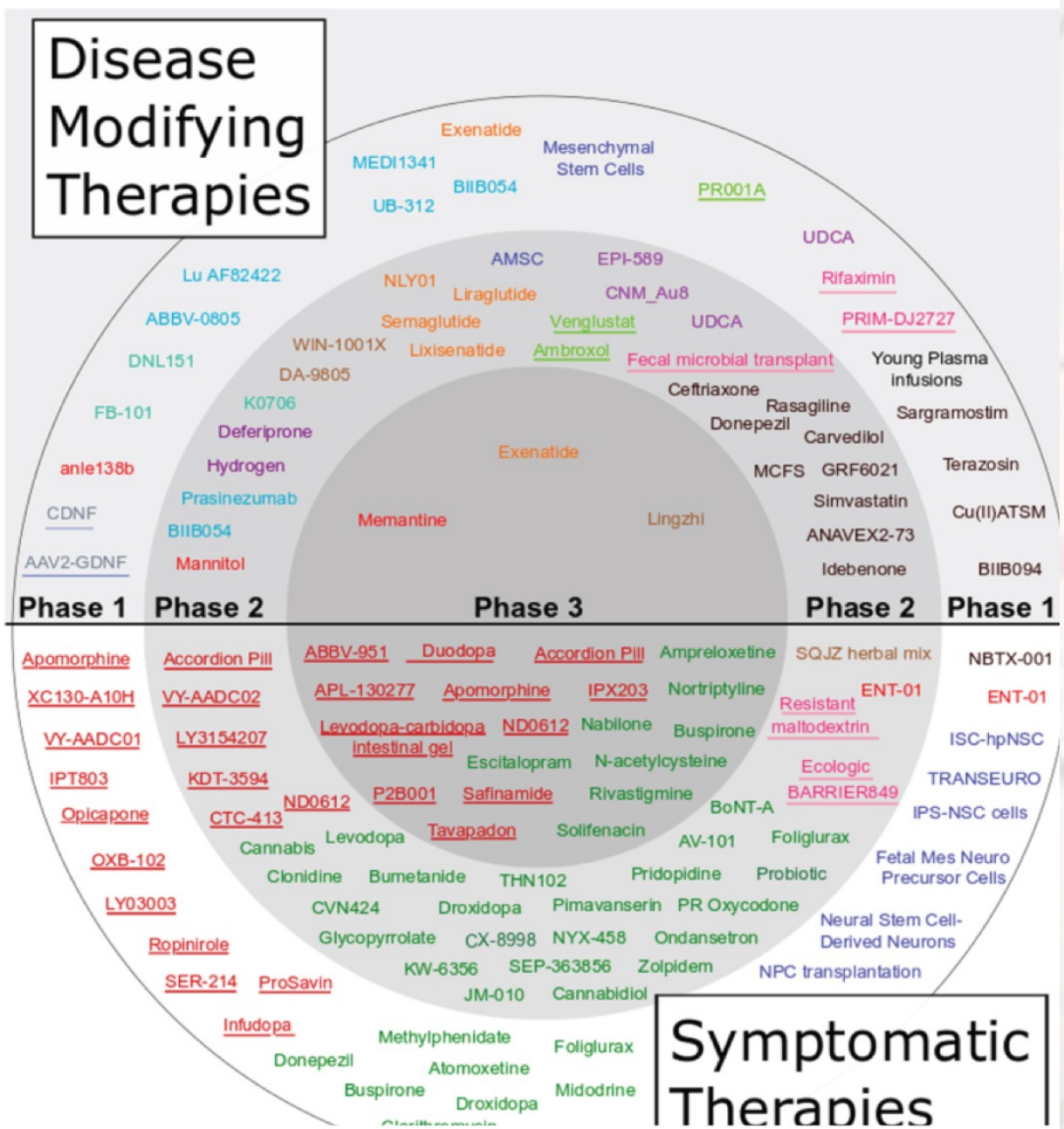
Outline

- Introduction and definitions
  - What are "Advanced Therapies"?
  - Why are they important?
- Rytary (while pill/covered earlier – some consider it "advanced")
- Pumps
  - Duopa (LCIG)
  - Subcutaneous pumps (currently experimental in the US)
    - Apomorphine
    - Carbidopa/levodopa (AbbVie, Neuroderm)
- Injectables/inhaleables/sublingual
  - Inbrija (inhaled C/L)
  - Kynmobi (under-the-tongue apomorphine)
  - Apokyn (subcutaneous apomorphine injection)
  - Apomorphine inhaleable (experimental)
- MRgFUS
- DBS

Introduction & Definitions

- Symptomatic versus disease modifying versus advanced treatments
  - All currently approved treatments for PD
  - Help improve symptoms: the appearance and impact – without affecting the underlying causes of disease
  - Symptomatic and disease modifying efficacy may not be exclusionary of each other
  - "Disease modifying" should be the truly "advanced", but that's not the current terminology
- We refer to symptomatic treatments as "advanced" typically when:
  - A treatment is using a complex/advanced treatment form (involving non-traditional delivery methods, surgery or other invasive procedure, etc)
  - Usually applicable at more advanced stages of disease – but note that it isn't the disease stage that qualifies patients for any advanced treatment, but it is the presence of specific set of symptoms and disabilities that the particular advanced treatment option is recommended
  - The proper use of the treatment (including patient selection, determination of candidacy, competent review and advice regarding the treatment, and successful/knowledgeable management and maintenance of the therapy) requires highly specialized expertise and experience (typically in the hands of a "movement disorder neurologist or specialist" (MDS = movement disorder specialist)
  - Vendor reps are very helpful in certain ways, including being accessible/available in emergencies, directing patients to resources and troubleshooting, but remember they're neither licensed nor experienced in actually managing advanced therapies, which should be strictly in the hands of a licensed provider!

PD drug therapies in the clinical trial pipeline: 2020



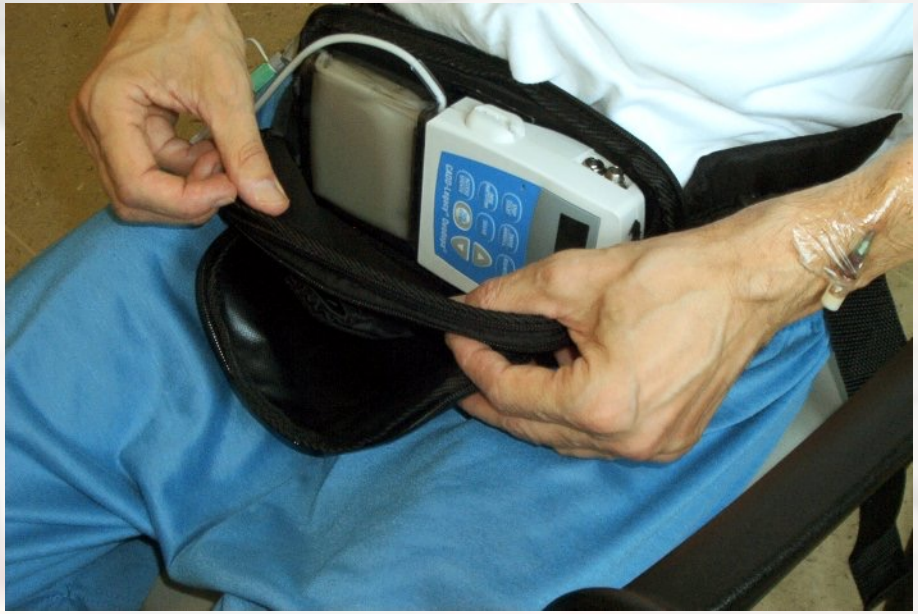
Agents in active PD drug trials, as of January 21, 2020 on ClinicalTrials.gov (by phase, DMT/ST and therapy category).

McFarthing et al. J Parkinson Dis. 2020; 10(3): 757-774.

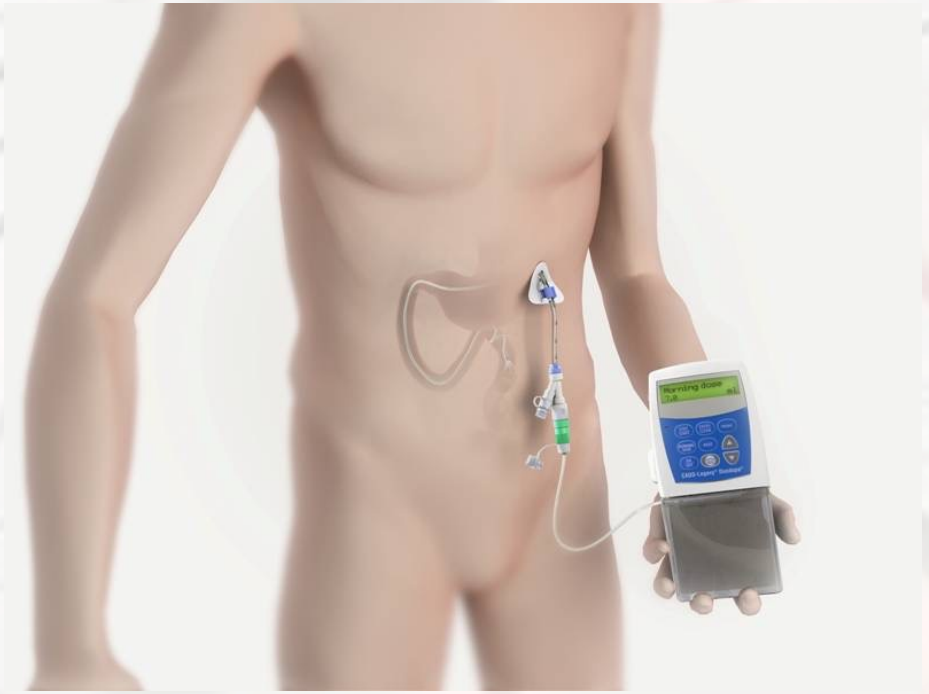
Duopa

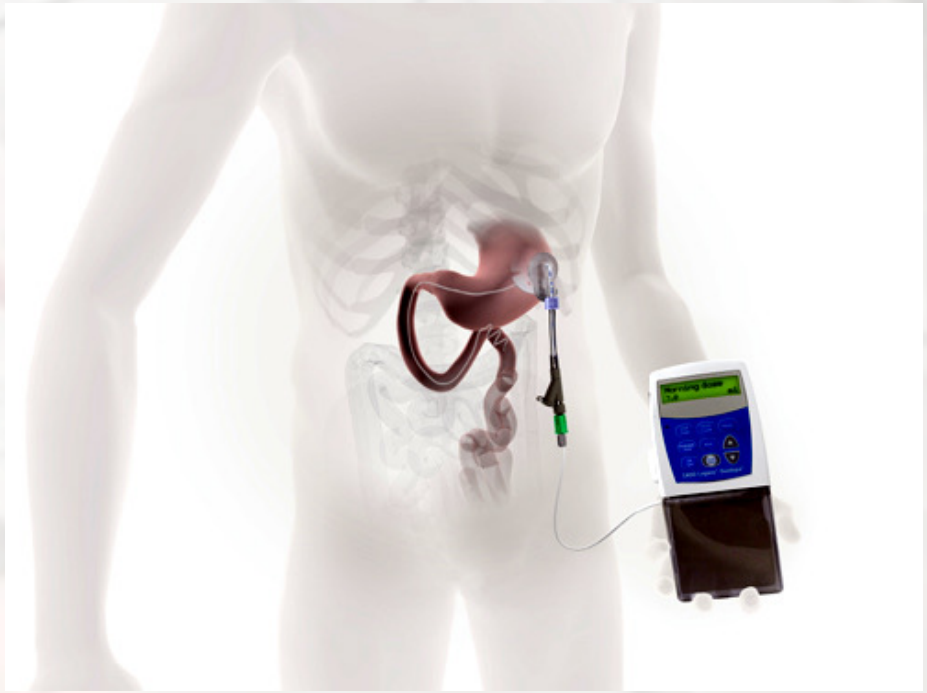

Duodopa®
Duodopa
Duodopa
Duodopa
Duodopa
Duodopa
Duodopa
Duodopa
Return to
Normality

Duopa



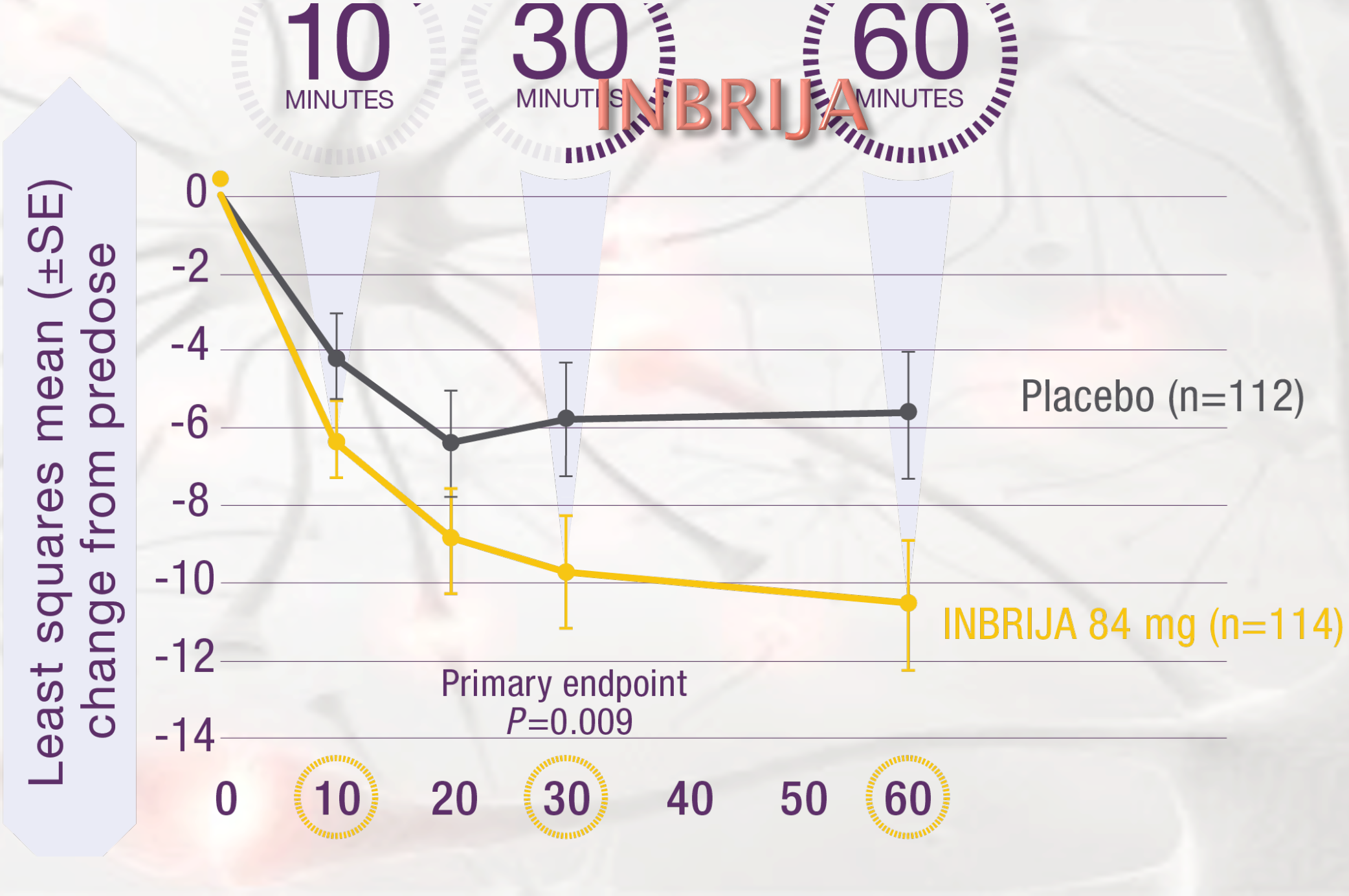
Duopa





INBRIJA

- Inhaled Levodopa
- Indicated for intermittent treatment of OFF episodes in patients with Parkinson disease treated with carbidopa/levodopa
- Initiate when OFF period symptoms start to return


10
MINUTES
30
MINUTES
60
MINUTES
INBRIJA
Least squares mean (±SE) change from predose
0
-2
-4
-6
-8
-10
-12
-14
Placebo (n=112)
INBRIJA 84 mg (n=114)
Primary endpoint
P=0.009
0
10
20
30
40
50
60

SUBLINGUAL APOMORPHINE CURRENTLY APPROVED .

SUBLINGUAL APOMORPHINE

- Many people do not like injections; moreover, sublingual route is easier to administer,
- Sublingual apomorphine (APL-130277) tested in phase 2/phase 3 studies, FDA approval pending
- Dose: 10-30 mg during OFF phase,
- ON state achieved in 15-30 min of dose in about 80% of patients,
- Mean duration of ON phase is 50 min and 60% remain ON for >90 min
- Common side effects are dizziness, somnolence and nausea.

KYNMOBI™

(apomorphine HCl) sublingual film

10 mg • 15 mg • 20 mg • 25 mg • 30 mg

Kynmobi

- Sublingual film indicated for off times in PD
- Improvement in motor symptoms at 15 minutes and last up to 90 minutes

Interaputaminal CDNF in PD

- CDNF is a neurotrophic factor shown to protect neurons.
- 17 subjects with PD were randomized to receive placebo or study medication every 4 weeks via an intraputamenal drug delivery device in Sweden and Finland.
- The phase I-2 in human was safe and well tolerated.
- The data for the extension phase of the study is expected to be available by the end of the year.

Sigrid Booms et al. MDS Virtual meeting 2020

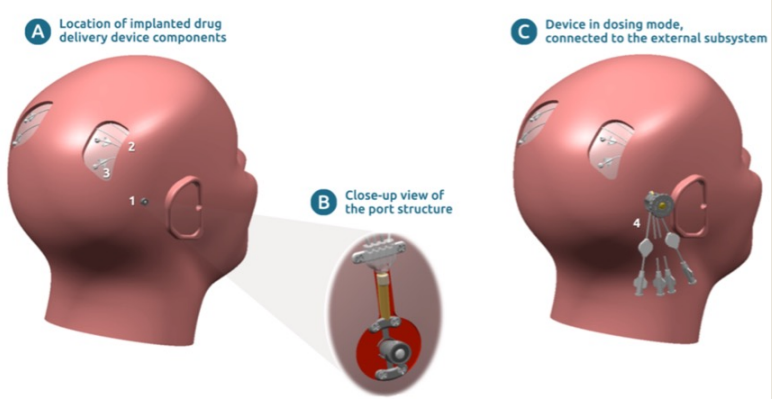


Figure 1. Drug Delivery System (DDS) used in the Phase I-II study.
(A) Location of different components after implantation surgery are shown. (B) Close-up view of the port structure. (C) Device in dosing mode, connected to the application set for drug dosing. List of components: 1 = transcutaneous skull-anchored port, 2 = subcutaneous lines connecting the port to the catheters, 3 = catheter entry sites (x4), the brain-dwelling parts of catheters are not shown, 4 = application set attached to the port [external infusion lines (not shown) will be connected to the application set for dosing].

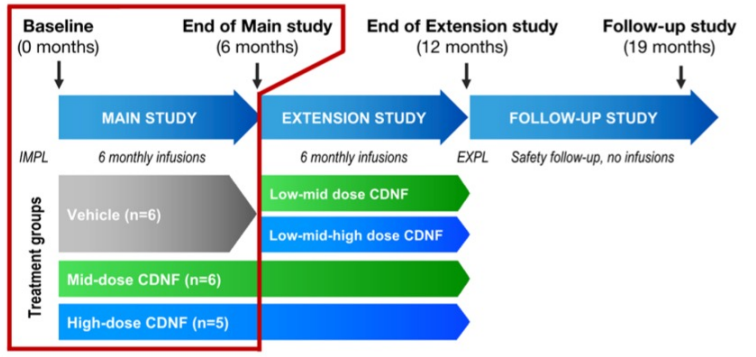
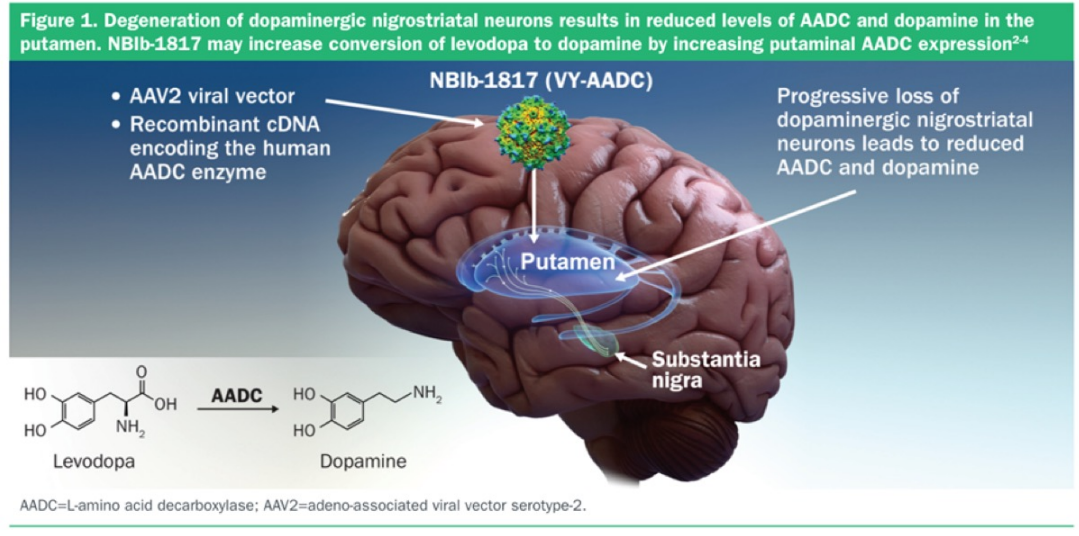


Figure 2 . Dosing regimen in the CDNF Phase I-II main study.
All subjects started with either placebo or low-dose CDNF for the two first infusions, and then continued on placebo or mid or high-dose CDNF in the Main study. In the Extension study, all patients received six additional monthly infusions of CDNF. Vehicle group received ascending low-mid-high doses while Mid-dose group remained on mid dose and High-dose group remained on high dose. Arrows indicate PET imaging timepoints. IMPL = device implantation; EXPL = device explantation. The results presented in this poster are from the randomized, placebo-controlled Main study part highlighted in red.

AADC gene therapy

- AAV2 gene therapy encoding human aromatic L-amino acid decarboxylase (AADC)
- VY-AADC01 administered surgically was well tolerated.
- Phase I studies showed clinical benefit with significant reduction on PD medications
- No SAE were reported today
- A phase 2 randomized double blind trial, Restore-1 is ongoing.



VY-AADC01 administered using a single posterior trajectory per putamen was well tolerated.

Stewart Factor et al. MDS Virtual meeting 2020

Subcutaneously infusion of levodopa/carbidopa

- Abbvie trial, 24 h/day CSCI.
- Single arm, open label, Phase Ib study with 20 subjects.
- The study showed improvement of PD symptoms across all waking days especially in the early morning.


Daily Time-Course of Efficacy of Continuous Subcutaneous Infusion of Foslevodopa/Foscarbidopa in Advanced Parkinson's Disease Patients From a Phase 1b Study

Sven Stodtmann,[1] Matthew R. Rosebraugh,[1] Weining Z. Robieson,[1] Maurizio F. Facheris[1]

[1]AbbVie, Inc., North Chicago, IL, USA; [2]AbbVie GmbH & Co KG, Germany

Presented at the Movement Disorder Society 23rd International Congress of Parkinson's Disease and Movement Disorders • Virtual • September 13-16, 2020

BACKGROUND

METHODS

METHODS (CONTINUED)

RESULTS

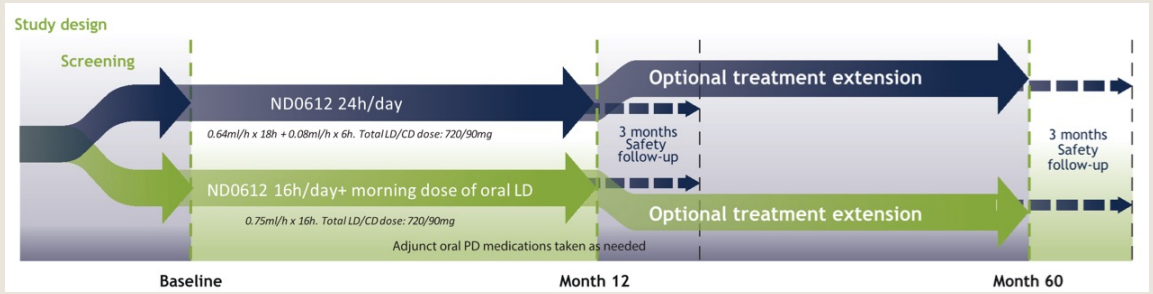
CONCLUSION

DISCLOSURES

ACKNOWLEDGMENTS

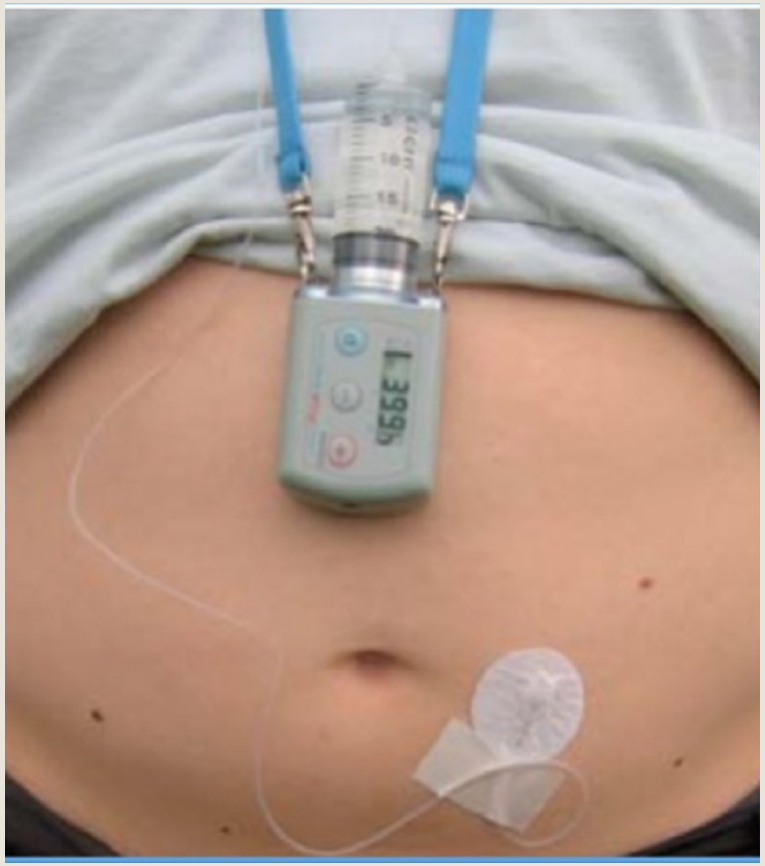
Subcutaneously infusion of levodopa/carbidopa

- Neuroderm trial with CSCI of ND0612
- Phase 2b, international, open label study over one year
- 24 h/day and 16 h/day infusion tested total daily dose of 720 mg of levodopa
- Mild to moderate infusion site reactions were common
- A phase 3 double-blind pivotal efficacy trial (BouNDless) is being initiated



Continuous subcutaneous apomorphine infusion (CSAI)

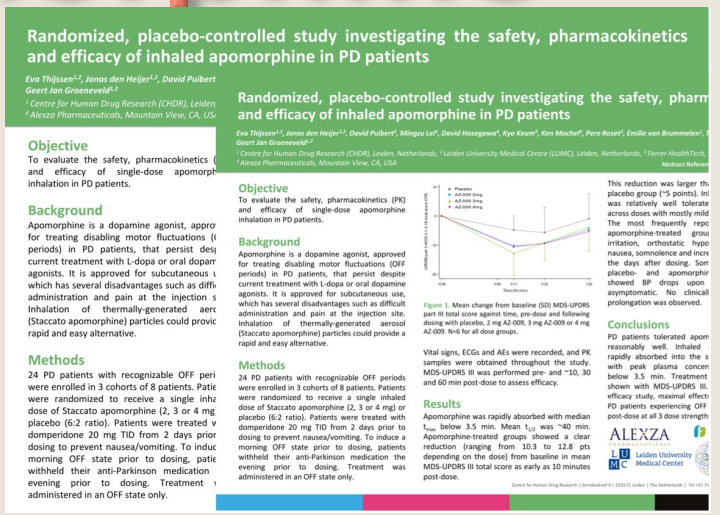
- CSAI has been used world wide to treat motor fluctuation in PD
- Not available in the USA yet
- The recent open label multi center trial in us in 99 patients with PD showed that the CSAI was safe and well-tolerated during one year follow up
- The New Drug Application was submitted to FDA for review



https://doi.org/10.1038/npjparkd.2016.23

Inhaled Apomorphine

- Randomized, placebo-controlled study in 24 PD patients
- Absorbed rapidly tmax less than 3.5 min



Randomized, placebo-controlled study investigating the safety, pharmacokinetics and efficacy of inhaled apomorphine in PD patients

Eva Thijssen[1,2], Jonas den Heijer[1,2], David Puibert[1], Mingzu Le[4], David Hasegawa[4], Kyo Kaum[2], Ken Mochel[4], Pere Rosel[5], Emilie van Brummelen[2], Geert Jan Groeneveld[1,2]

[1] Centre for Human Drug Research (CHDR), Leiden, Netherlands, [2] Leiden University Medical Centre (LUMC), Leiden, Netherlands, [3] Ferrer HealthTech, [4] Alexza Pharmaceuticals, Mountain View, CA, USA

Abstract Referen

Objective

To evaluate the safety, pharmacokinetics (PK) and efficacy of single-dose apomorphine inhalation in PD patients.

Background

Apomorphine is a dopamine agonist, approved for treating disabling motor fluctuations (OFF periods) in PD patients, that persist despite current treatment with L-dopa or oral dopamine agonists. It is approved for subcutaneous use, which has several disadvantages such as difficult administration and pain at the injection site. Inhalation of thermally-generated aerosol (Staccato apomorphine) particles could provide a rapid and easy alternative.

Methods

24 PD patients with recognizable OFF periods were enrolled in 3 cohorts of 8 patients. Patients were randomized to receive a single inhaled dose of Staccato apomorphine (2, 3 or 4 mg) or placebo (6:2 ratio). Patients were treated with domperidone 20 mg TID from 2 days prior to dosing to prevent nausea/vomiting. To induce a morning OFF state prior to dosing, patients withheld their anti-Parkinson medication the evening prior to dosing. Treatment was administered in an OFF state only.

Figure 1. Mean change from baseline (SD) MDS-UPDRS part III total score against time, pre-dose and following dosing with placebo, 2 mg AZ-009, 3 mg AZ-009 or 4 mg AZ-009. N=6 for all dose groups.

Vital signs, ECGs and AEs were recorded, and PK samples were obtained throughout the study. MDS-UPDRS III was performed pre- and ~10, 30 and 60 min post-dose to assess efficacy.

Results

Apomorphine was rapidly absorbed with median t_{max} below 3.5 min. Mean $t_{1/2}$ was ~40 min. Apomorphine-treated groups showed a clear reduction (ranging from 10.3 to 12.8 pts depending on the dose) from baseline in mean MDS-UPDRS III total score as early as 10 minutes post-dose.

This reduction was larger th placebo group (~5 points). In was relatively well tolerate across doses with mostly mild The most frequently repo apomorphine-treated grou irritation, orthostatic hypo nausea, somnolence and incre the days after dosing. Sor placebo- and apomorphir showed BP drops upon asymptomatic. No clinicall prolongation was observed.

Conclusions

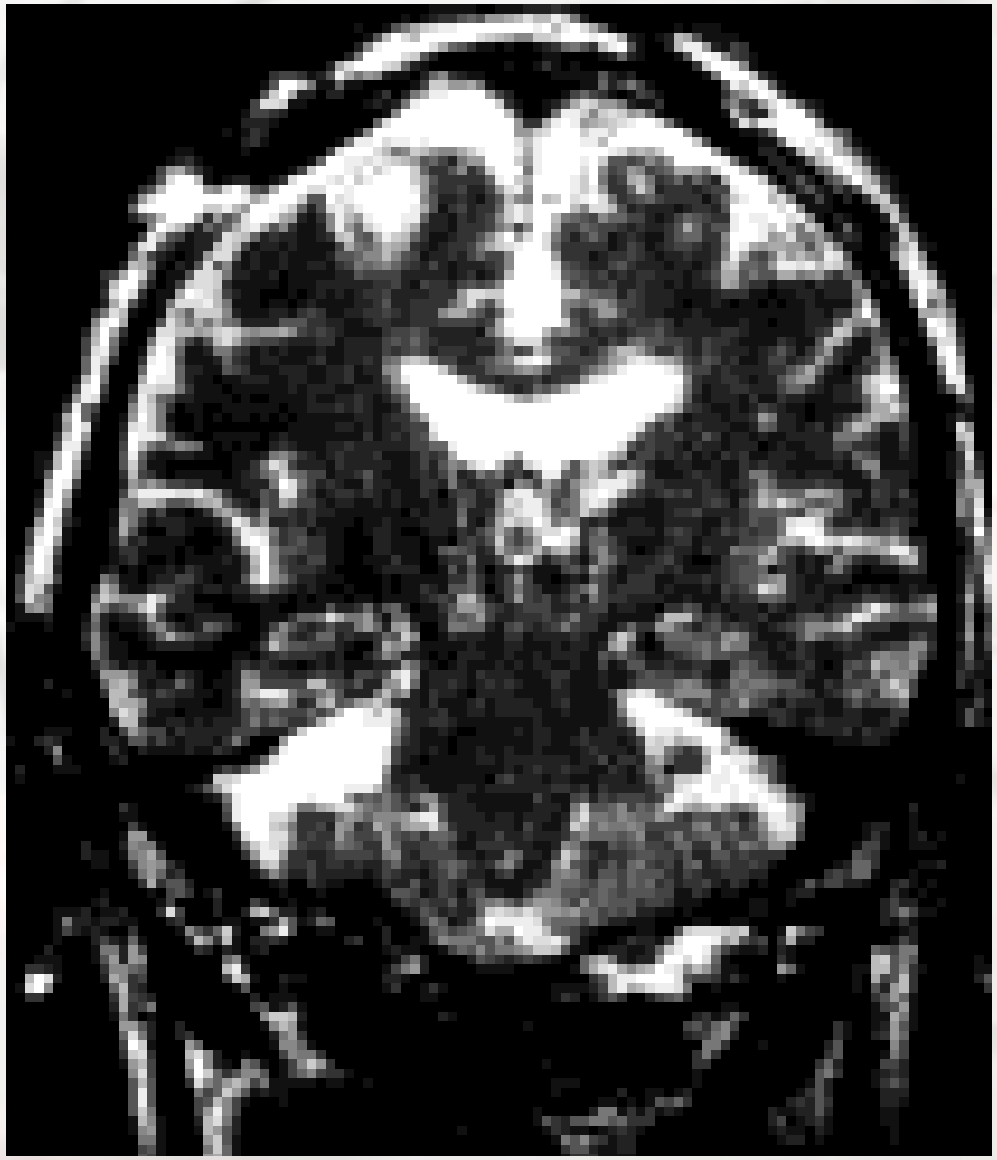
PD patients tolerated apom reasonably well. Inhaled rapidly absorbed into the s with peak plasma concen below 3.5 min. Treatment shown with MDS-UPDRS III. efficacy study, maximal effects PD patients experiencing OFF post-dose at all 3 dose strength

ALEXZA

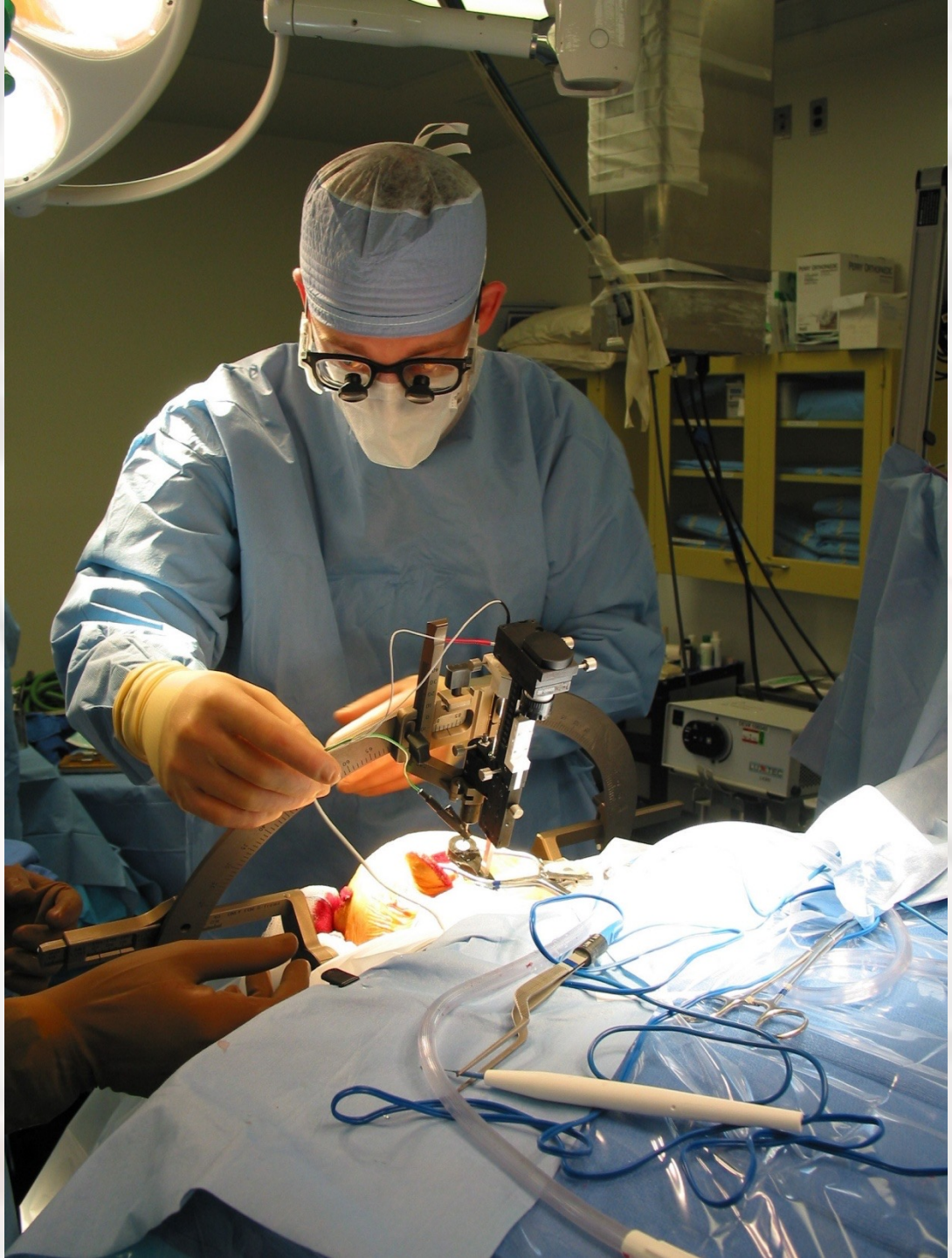
Leiden University Medical Center

- It showed improvement of the symptoms and relatively well tolerated
- AE: throat irritation, orthostatic hypotension, yawning, nausea, somnolence an and dyskinesia.

DBS Electrodes in STN



Limousin et al. 1998



Z. Mari: PD Rx

CURRENT DEEP STIMULATION DEVICES

Medtronic

St. Jude's infinity device

Boston Scientific Vesice

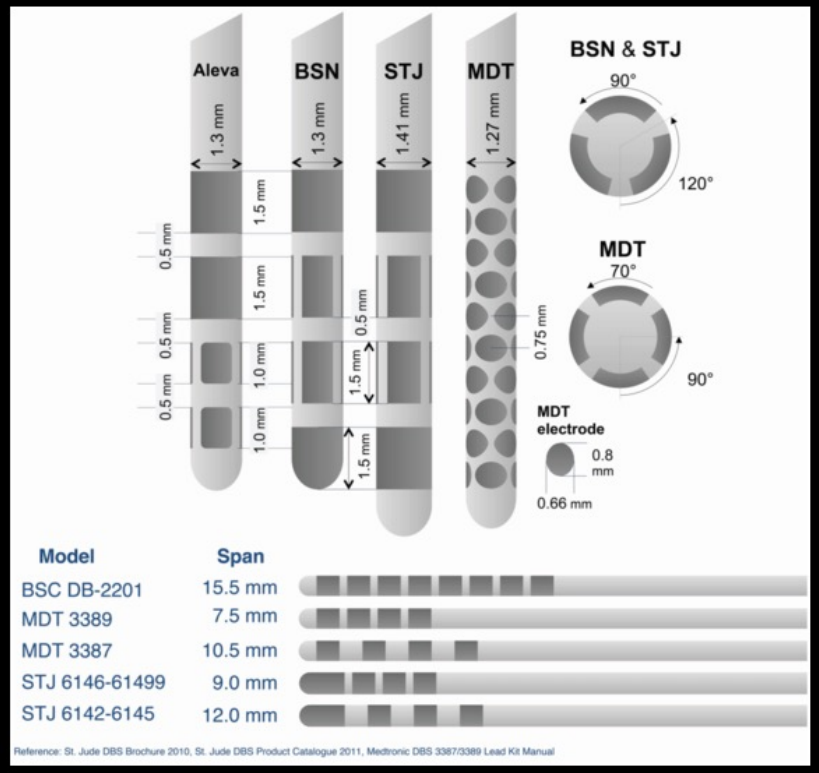
Patient Selection: a "good" patient for DBS

A Parkinson's patient who:

- Has advanced Parkinson's disease
- Responds well to levodopa medications, either now or in the past had sustained good response
- Fluctuations in levodopa response exist (on/off), often with dyskinesia
- Does not exhibit signs of dementia
- Is otherwise a good surgical candidate

Exclusion Criteria

- Major psychiatric illness
- Cognitive impairment
- Substantial medical problems or lab abnormalities
- Cardiac pacemaker
- Previous intracranial surgery
- Age over 70 years (relative criterion)



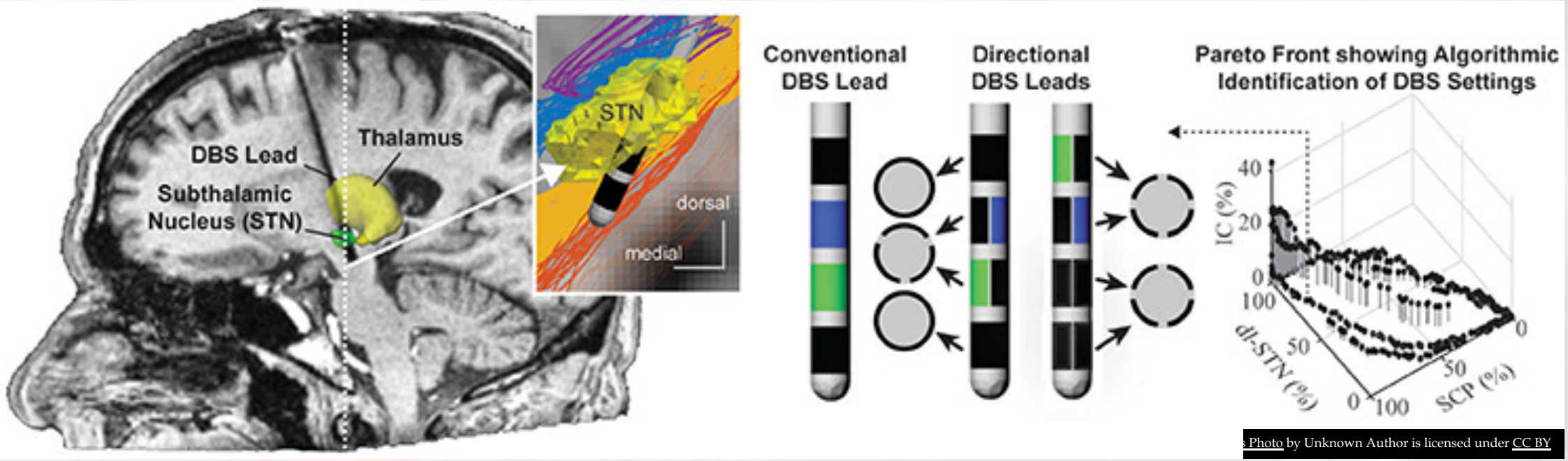
Conventional quadripolar electrode

Directional multipolar electrode

Eight lead electrode (individually set for different stimulation levels)

THE TWO LEADS IN THE MARKET WITH DIRECTIONAL LEAD TECHNOLOGY

- St. Jude infinity device
- Boston Scientific vesice device



MEDTRONIC BRAIN SENSE

- Percept DBS neurostimulation system works on the ability to chronically capture and record brain signals while delivering therapy to patients with neurologic disorders.
- Track patient brain signals and correlate these with patient-recorded actions or experiences, such as symptoms, side-effects, or medication intake.
- Enables more personalized, data-driven neurostimulation treatment.

- Feedback loop
- Digital PD diaries
- Currently I (ZM) do not recommend it for its limited/unclear practical benefit versus increased battery drain