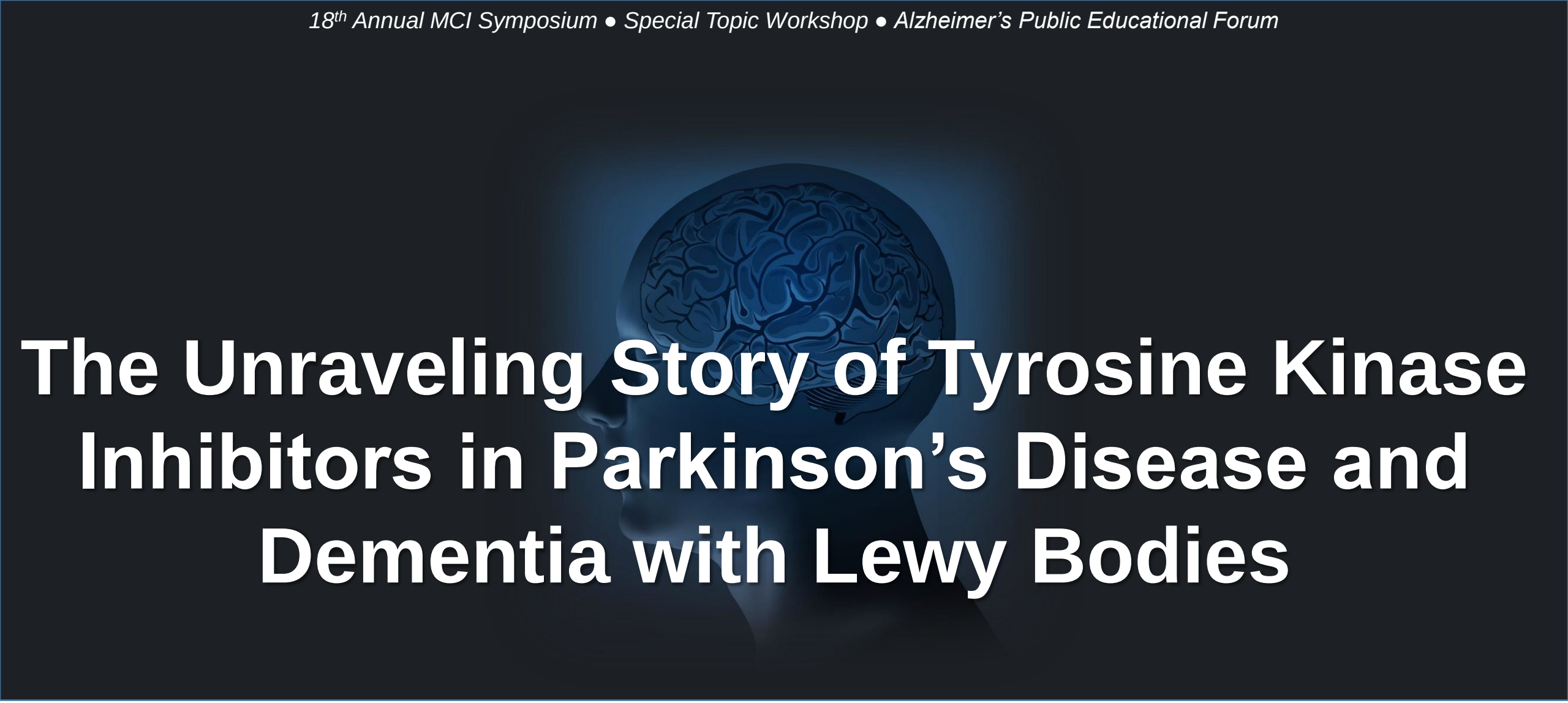

The Unraveling Story of Tyrosine Kinase Inhibitors in Parkinson's Disease and Dementia with Lewy Bodies

Georgetown University Medical Center

DISCLOSURES

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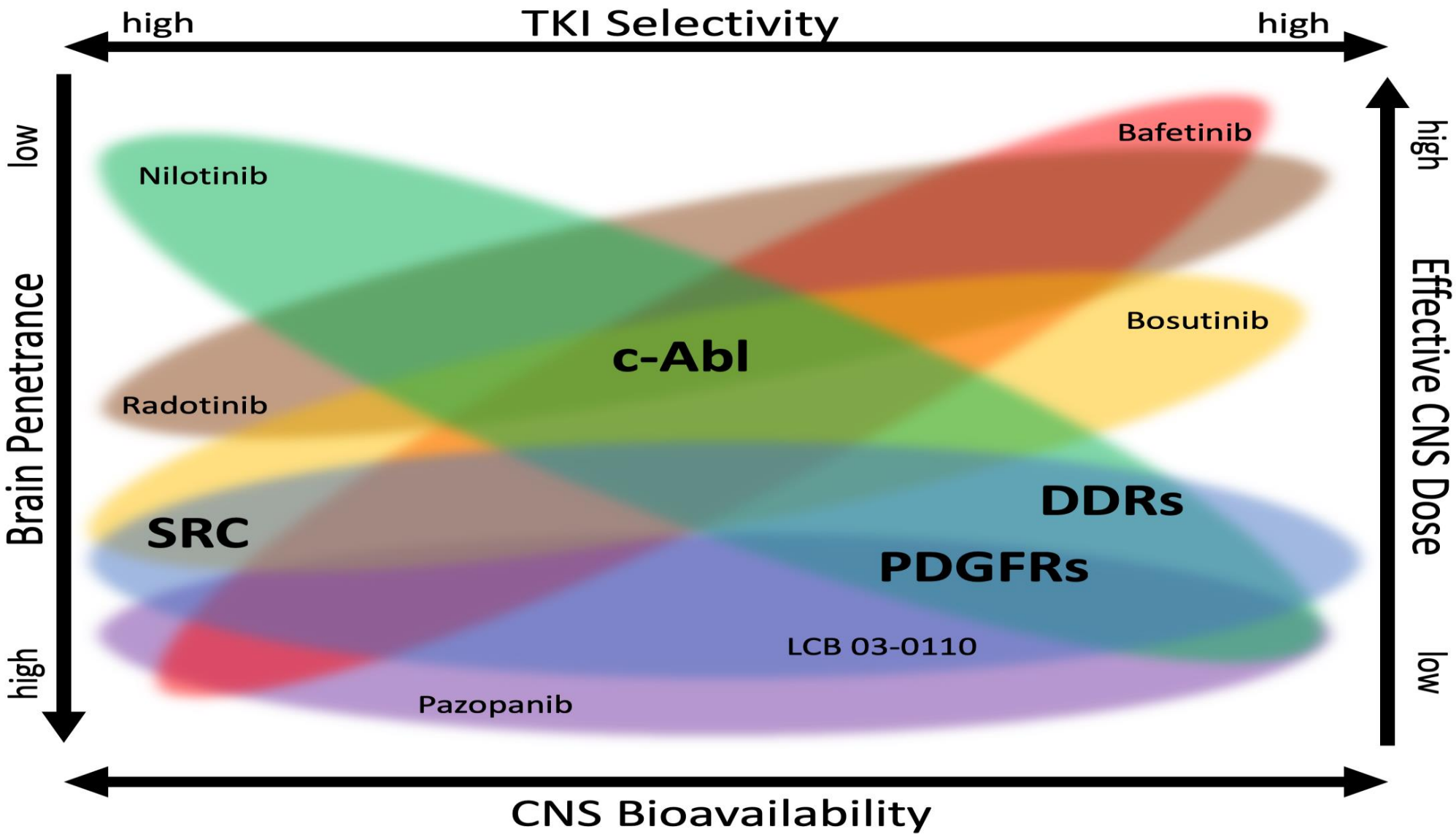
Charbel Moussa is an inventor on several issued and pending Georgetown University patent applications to use tyrosine kinase inhibitors (TKIs) for the treatment of neurological diseases.

Moussa receives research support from the National Institute on Aging, Alzheimer's Association, Alzheimer's Drug Discovery Foundation, Novartis (in-Kind) and research support and consulting fees from Sun Pharmaceuticals Research Corporation (SPARC)

Discoidin Domain Receptors (DDRs) Are Optimal Targets



Fowler et al, Drugs R D. 2019 Jun;19(2):149-166.

Discoidin Domain Receptors Are Upregulated in PD and AD

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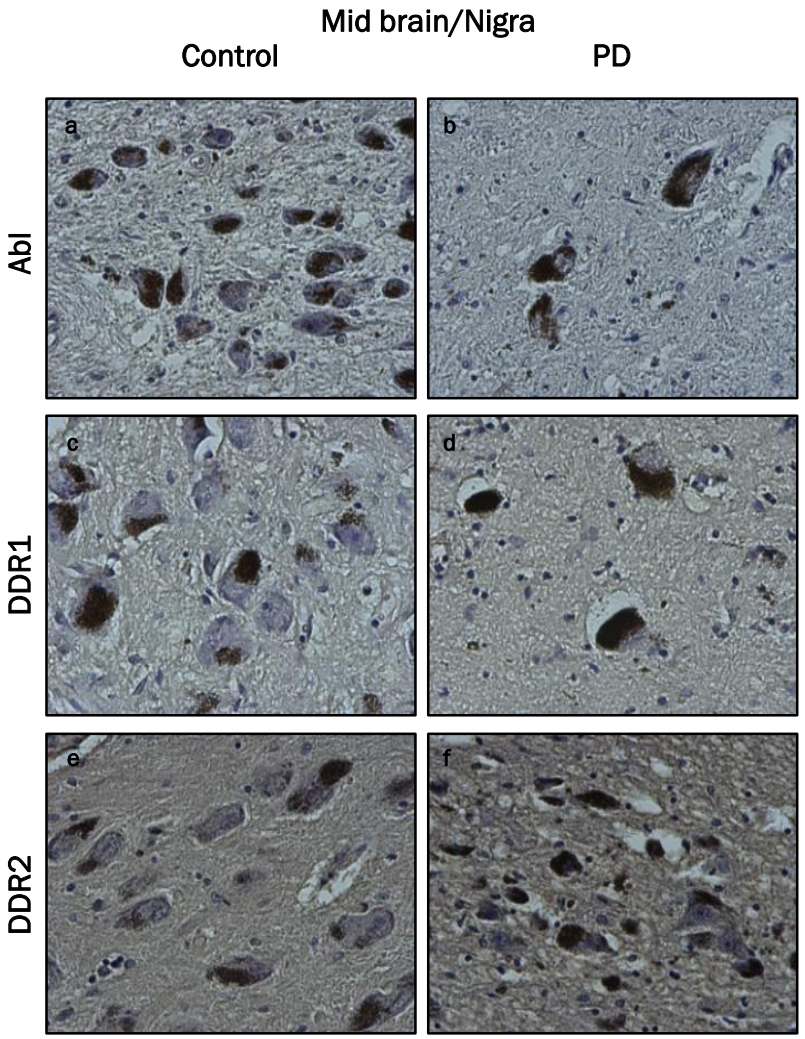
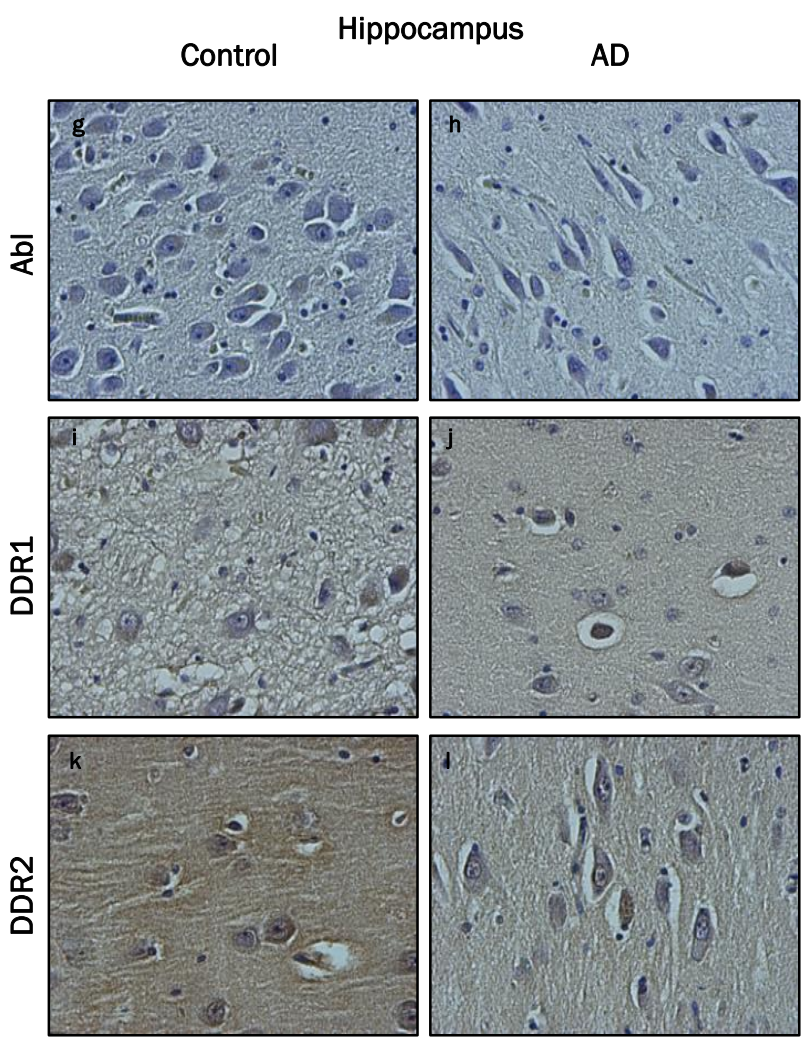
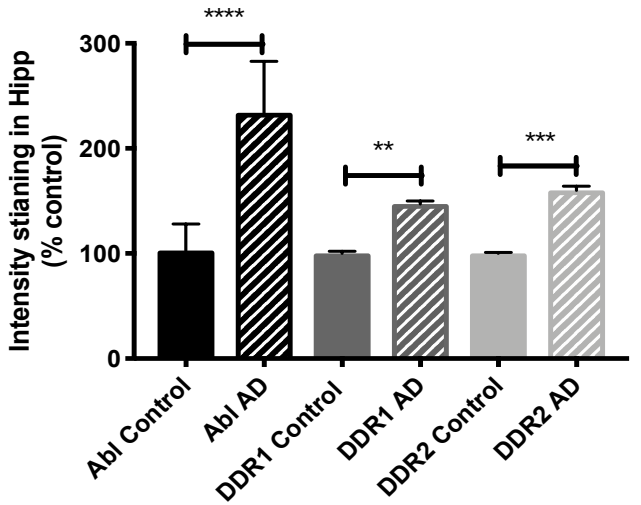
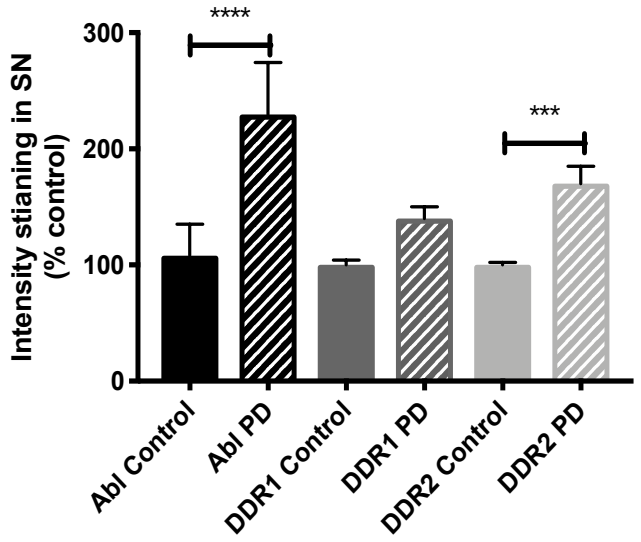
Post-Mortem Studies Show that DDRs Expression is Significantly Increased (~30%) in AD and PD Brains Compared with Age-Matched Controls (Hebron et al, J Neuroimmunol. 2017 Oct 15;311:1-9.)









Phase II Studies of Nilotinib in Parkinson's Disease

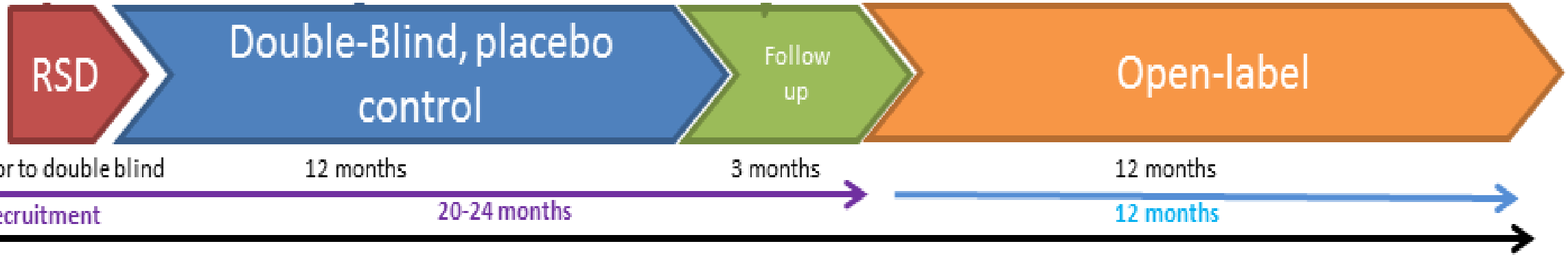
Phase II, Randomized, Double-Blind, Placebo-Controlled Study and Open Label Extension To Evaluate Nilotinib Effects on Safety and Biomarkers in Parkinson's Disease

(ClinicalTrials.gov Identifier: NCT02954978)

Nilotinib, 150mg
Nilotinib, 200mg
Nilotinib, 300mg
Nilotinib, 400mg
Placebo

Nilotinib, 150mg
Nilotinib, 300mg
Placebo

Nilotinib, 150mg
Nilotinib, 300mg



RSD Outcomes
Population Based
PK/PD single dose

Double Blind Outcomes
Primary: Safety, Tolerability and PK
Secondary: Biomarkers including, dopamine metabolism (No-NoGo)
Total and oligomeric alpha-synuclein and Ttau/ptau
Exploratory:
MDS-UPDRS, PDQ39 and MoCA

Open Label Outcomes
Primary: Safety
Secondary: MDS-UPDRS, PDQ39 and MoCA
Difference between:
nilotinib, 150mg vs 300mg
Difference between:
Early start (12M nilotinib to 12 M nilotinib)
Vs
Late start (12M placebo to 12M nilotinib)

Nilotinib in Parkinson's Disease (One Year Treatment)

Pagan et al, JAMA Neurology, 2019, Dec 16.

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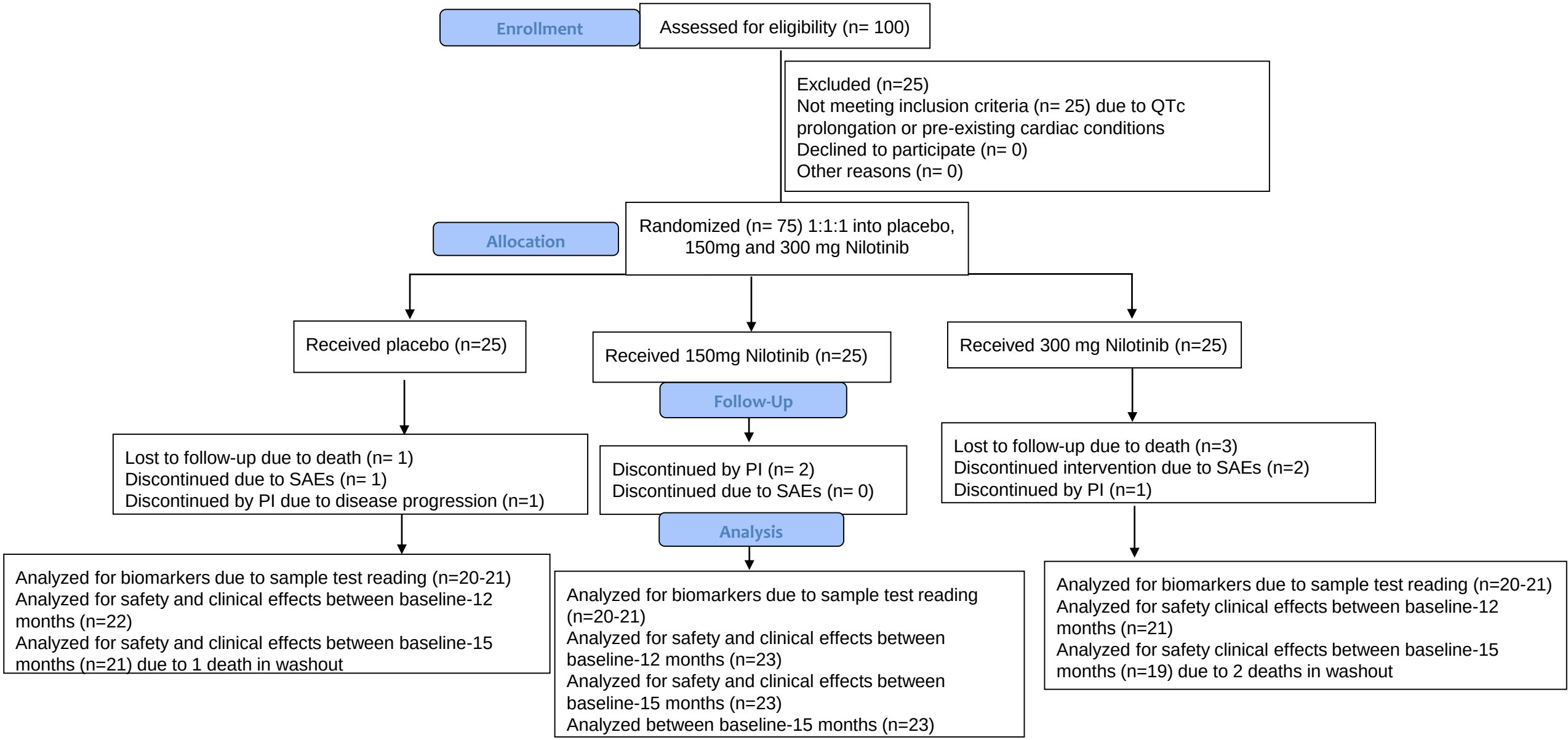

Sufficient CSF Nilotinib Levels to inhibit DDR1 but not Abl

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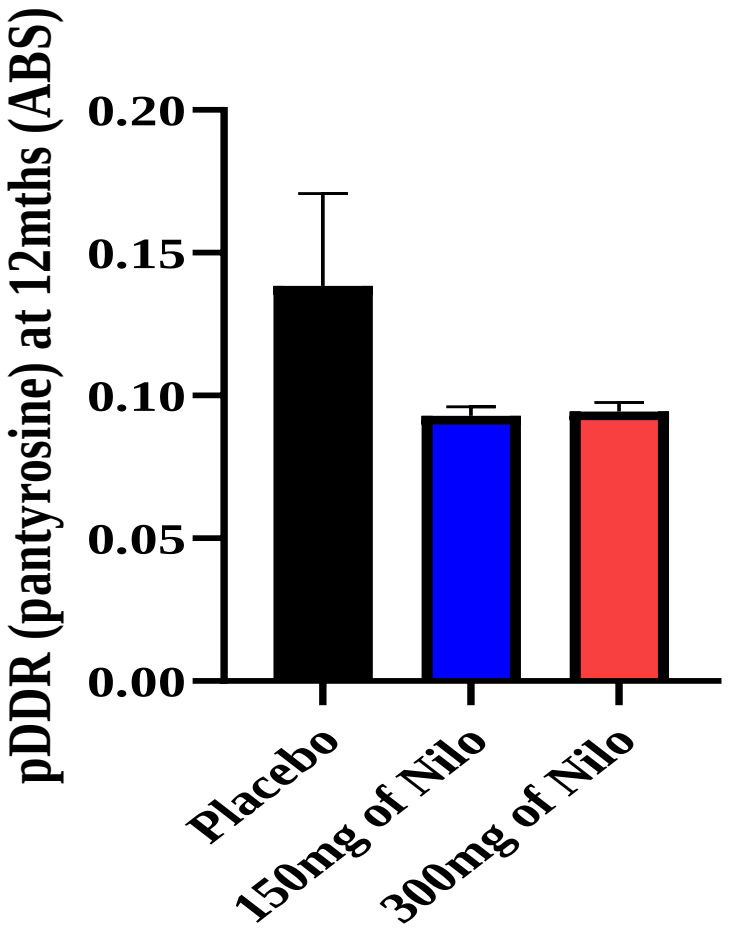
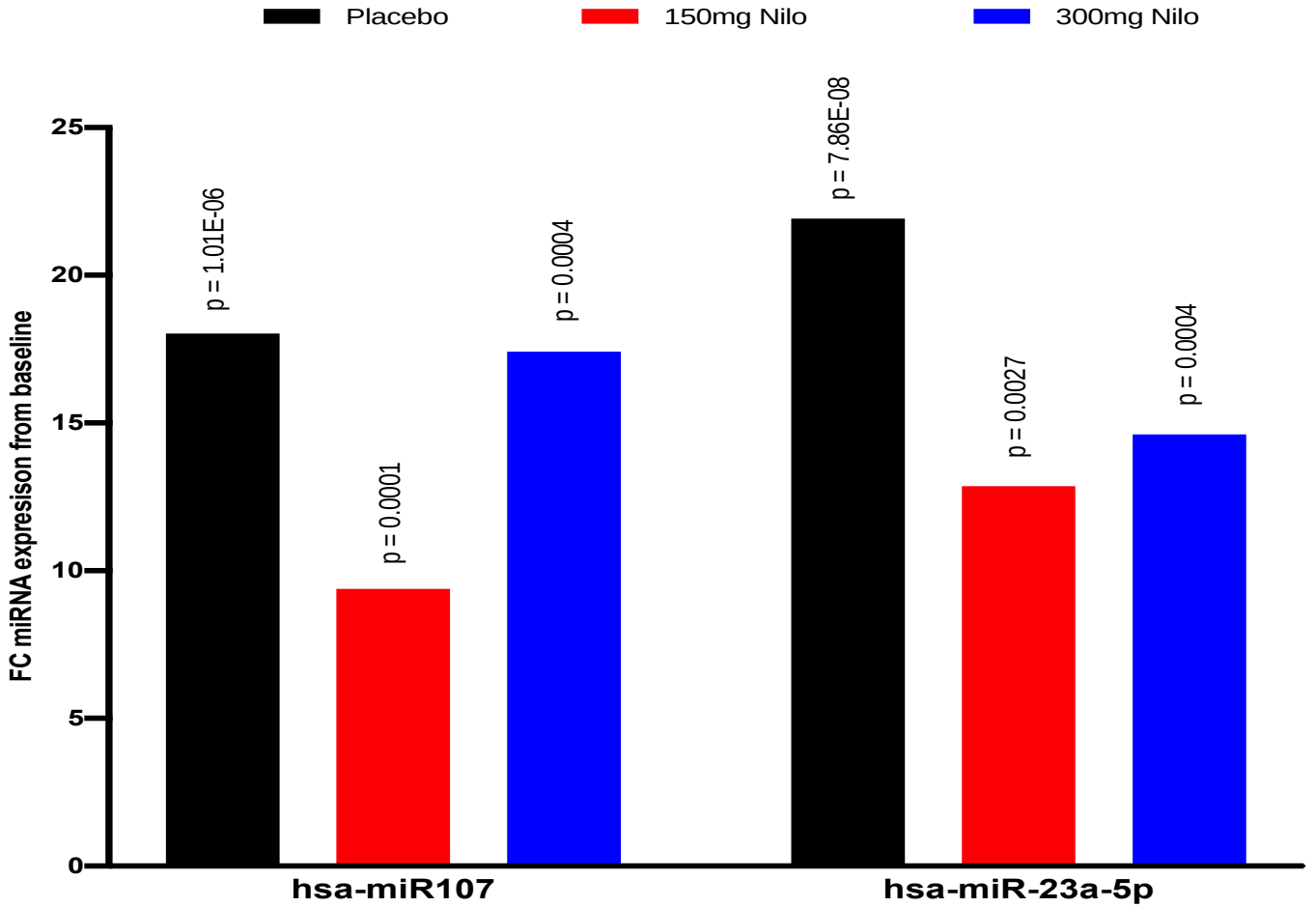
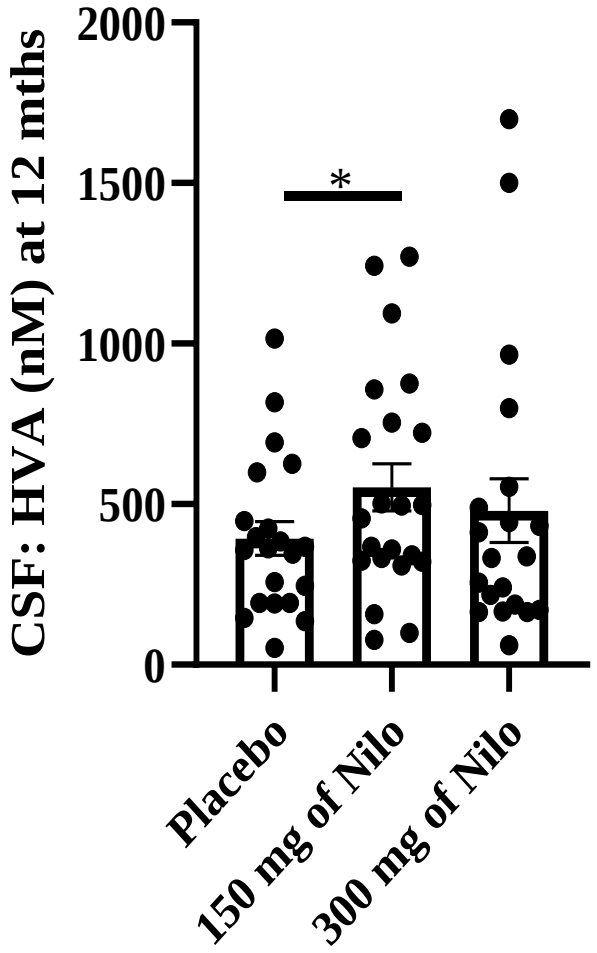
Nilotinib CSF Concentration (2-5nM) is 2-4 times Higher than the IC_{50} Required to Inhibit Discoidin Domain Receptor (DDR)-1 (IC_{50} to inhibit DDR1=1 nM)- ELISA and Whole Genome CSF miRNA Sequencing Support DDR1 inhibition.

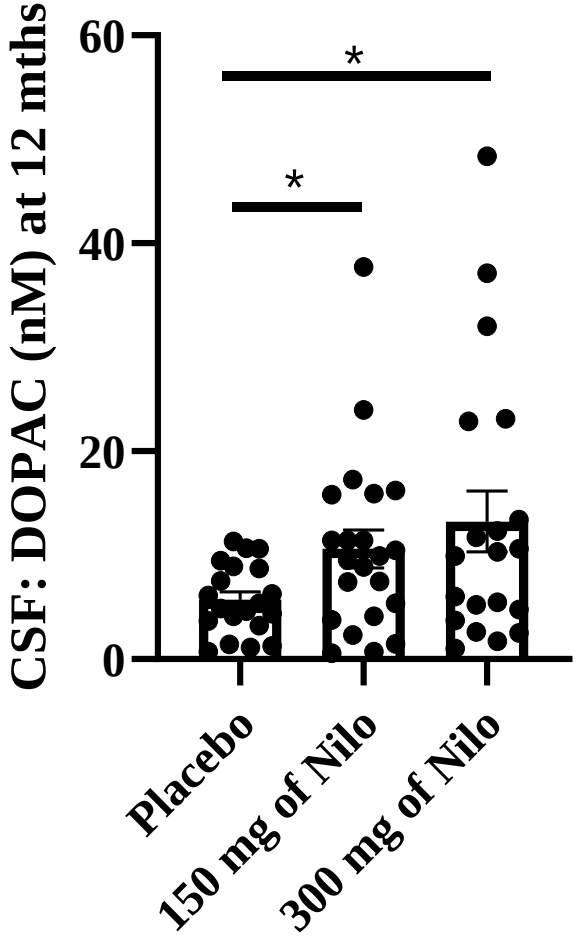


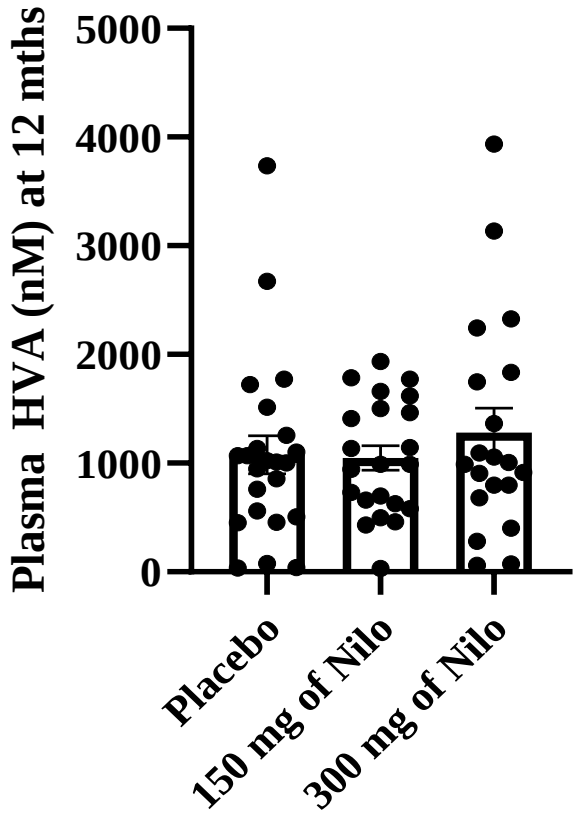


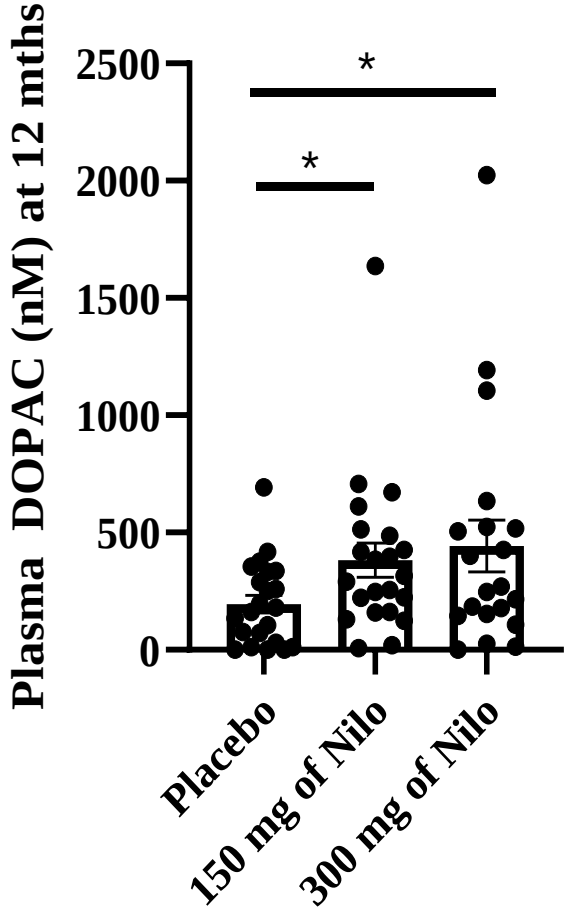
Nilotinib Increases Dopamine Levels in PD (One Year Treatment) Pagan et al, JAMA Neurology, 2019, Dec 16.

Nilotinib Doubles Endogenous Dopamine Levels in Moderately Advanced PD Patients – Receiving Levodopa but no MAOB-inhibitors



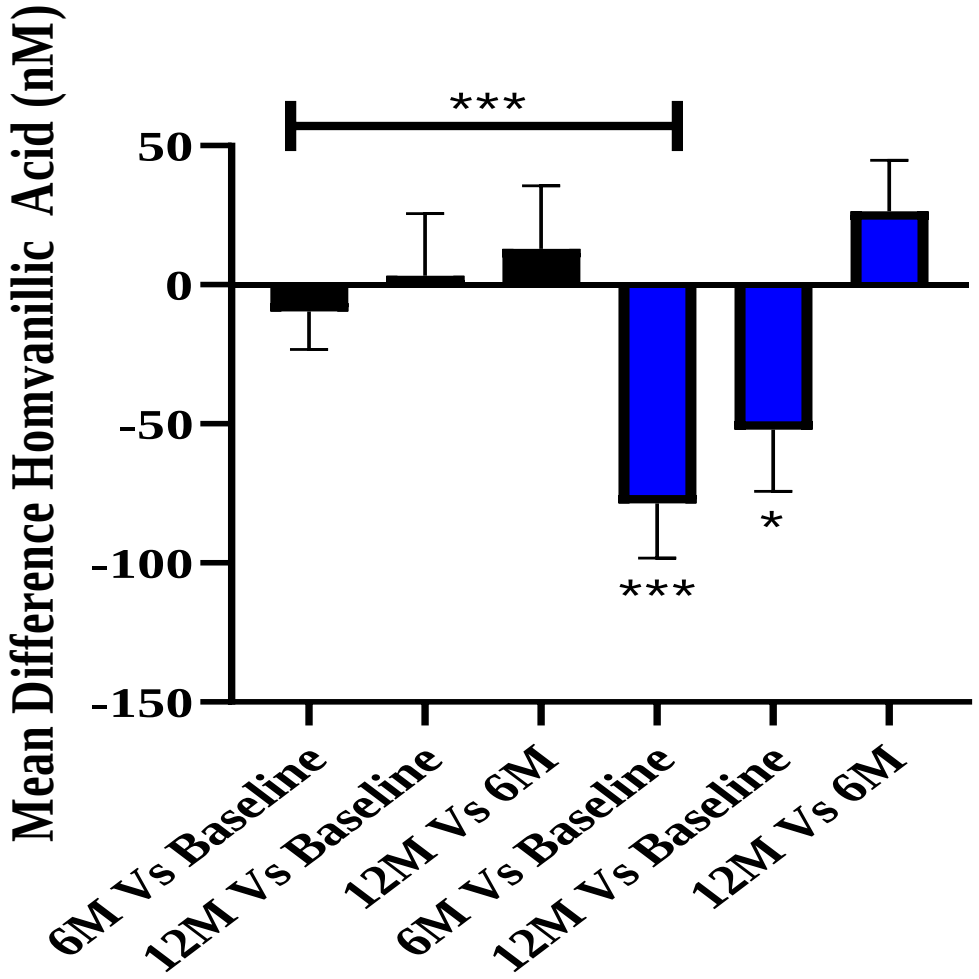


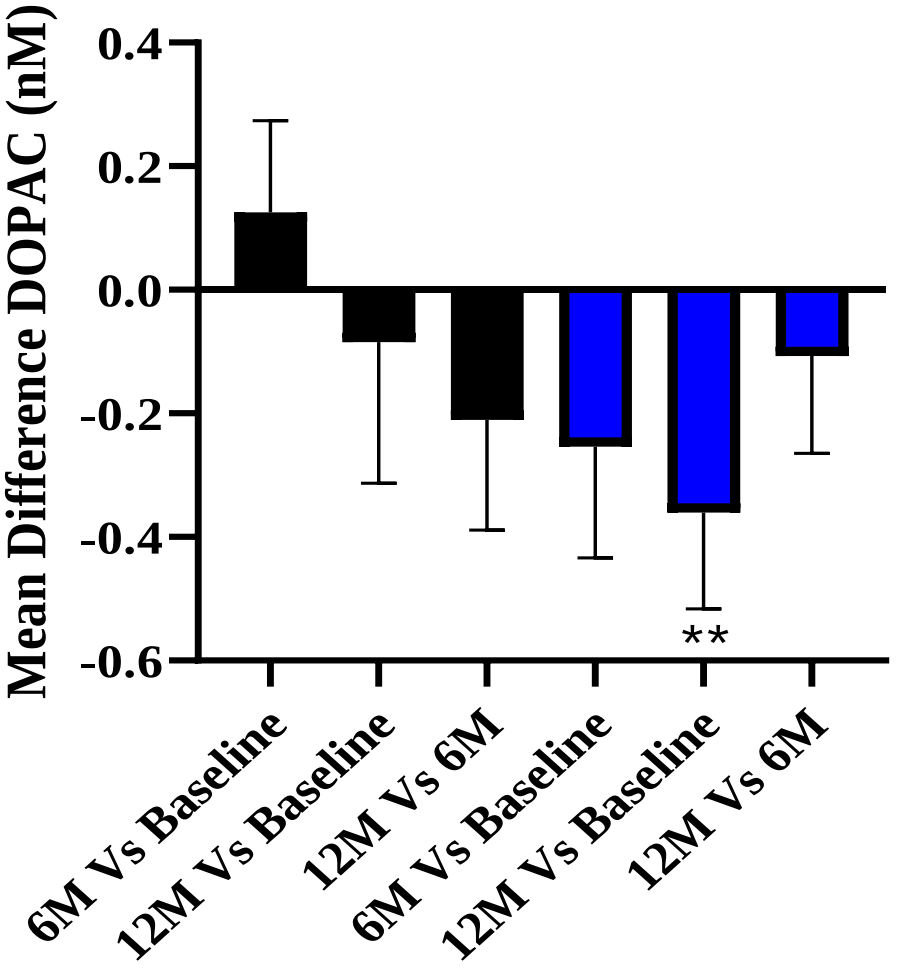




Nilotinib Increases Dopamine Levels in AD (One Year Treatment)

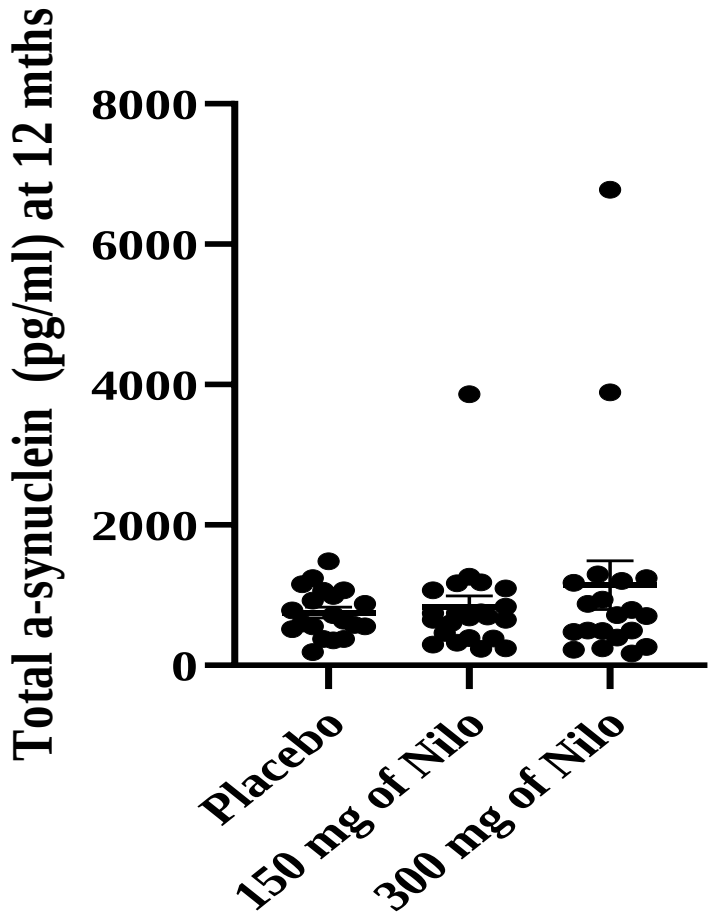
Nilotinib Reduces Dopamine Catabolism in the CSF of Levodopa (and other PD-medications) Naïve Alzheimer's Patients

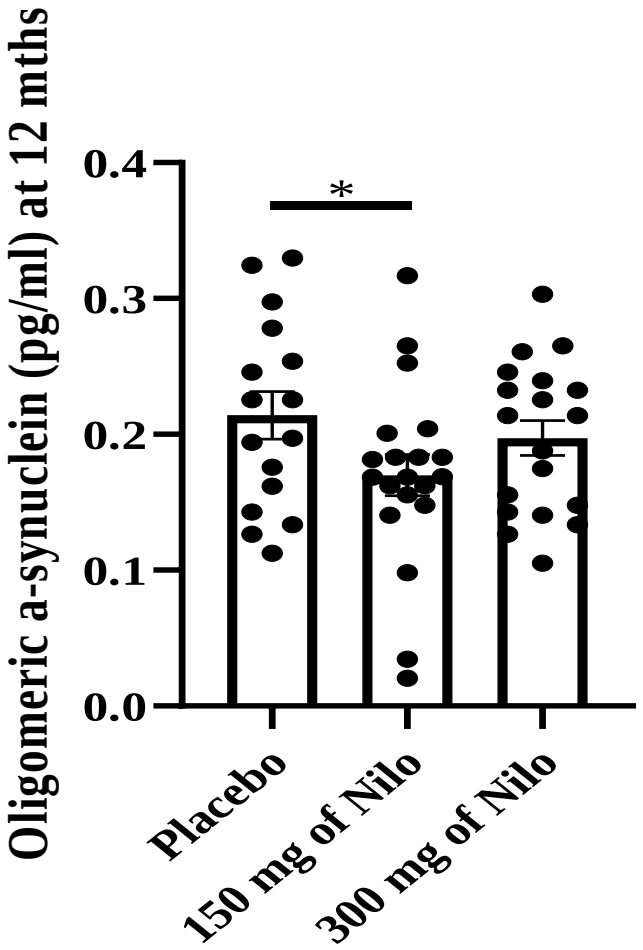


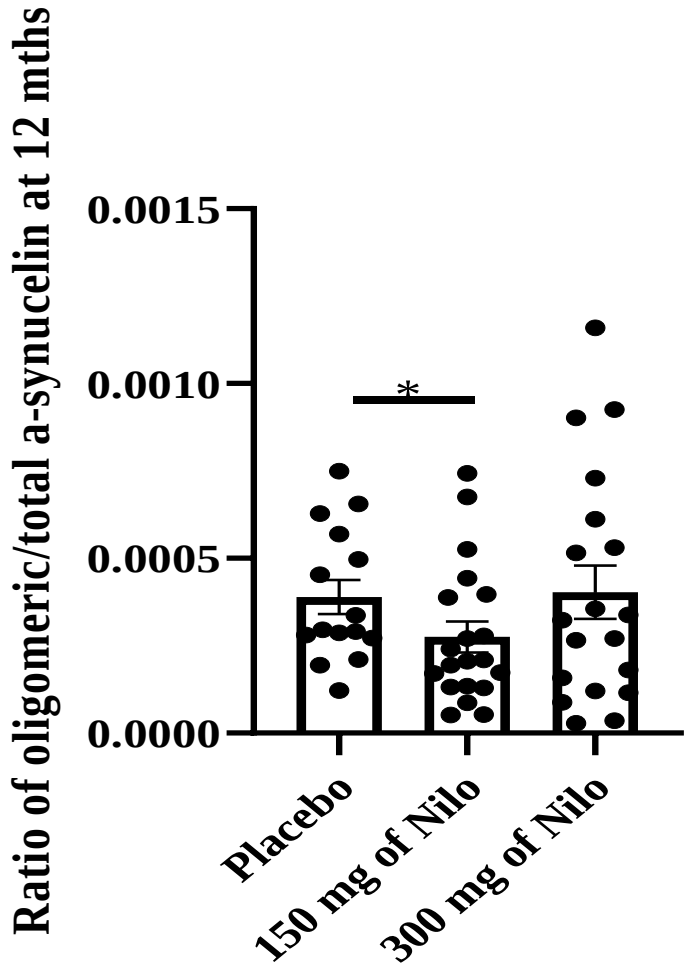


Nilotinib Reduces Oligomeric alpha-Synuclein in PD (One Year Treatment) Pagan et al, JAMA Neurology, 2019, Dec 16.

Nilotinib (150mg) Reduces CSF Toxic alpha-Synuclein Oligomers in Moderately Advanced PD Patients

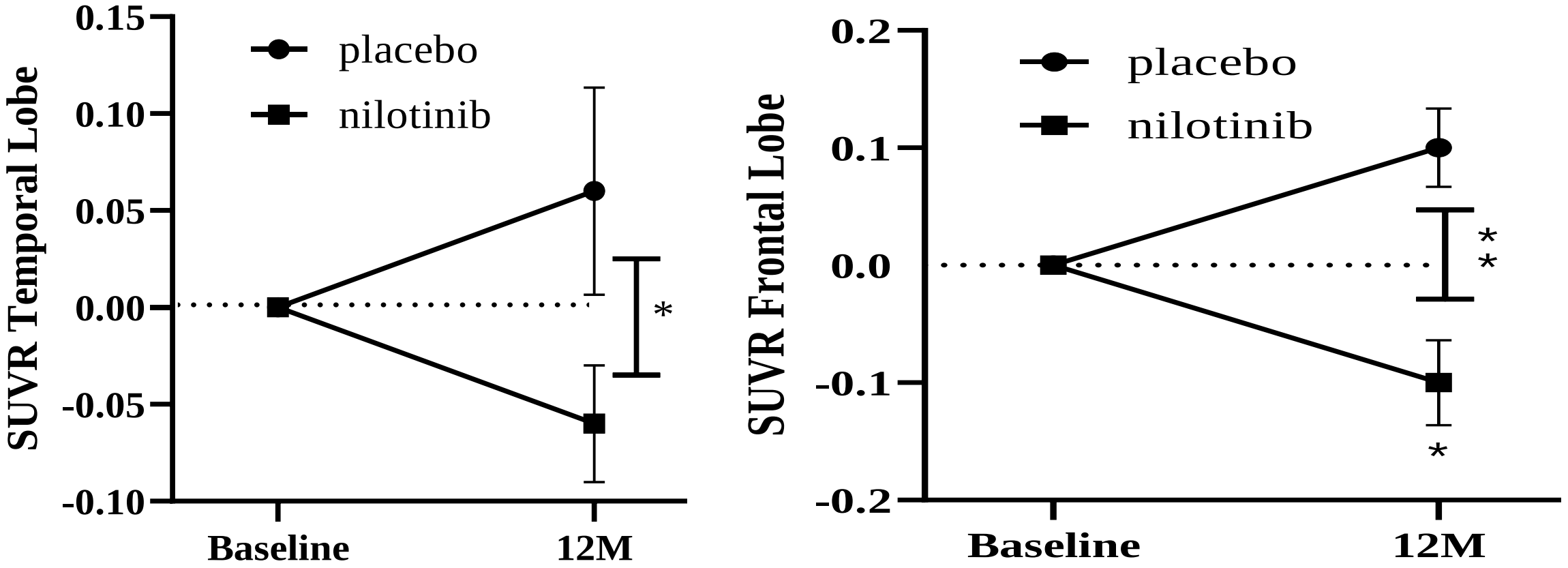






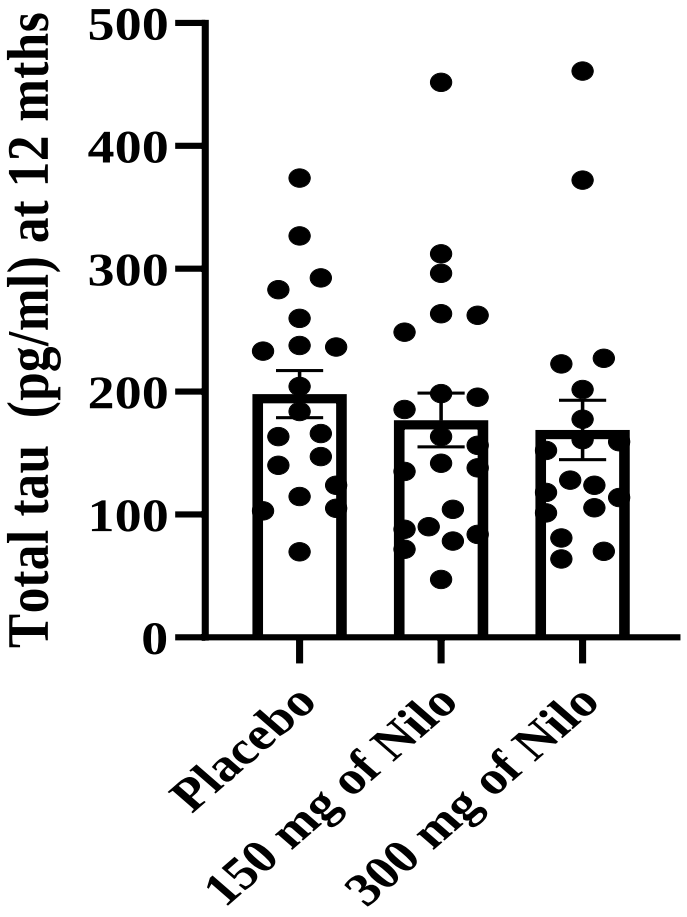
Nilotinib Reduces Amyloid Burden in AD (One Year Treatment)

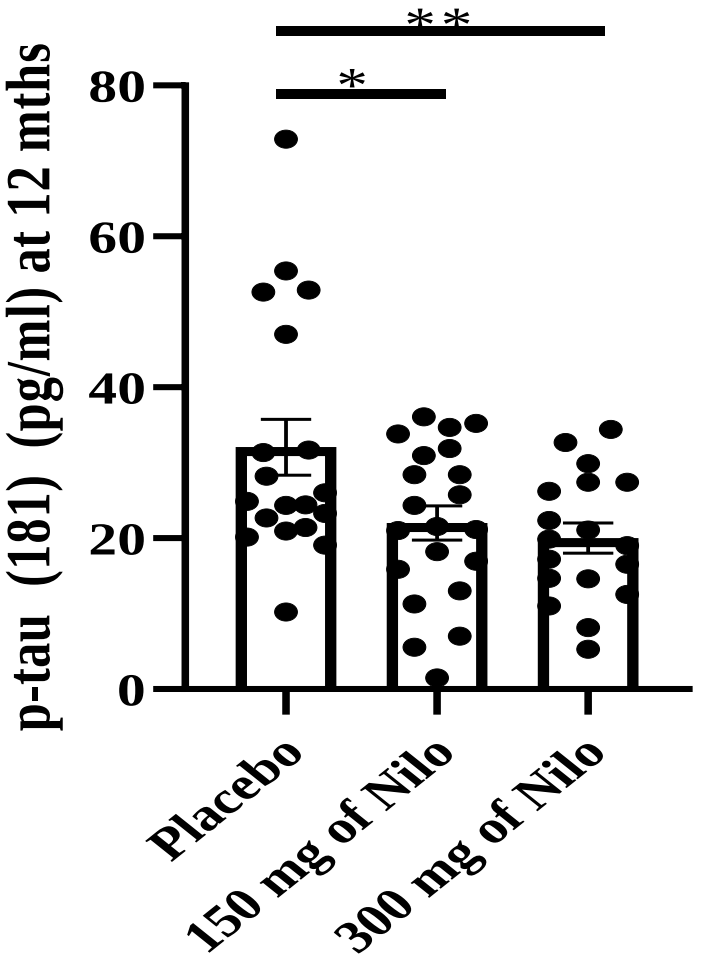
Nilotinib Reduces Amyloid Burden via Aβ Positron Emission Tomography (PET-Florbetaben F18)

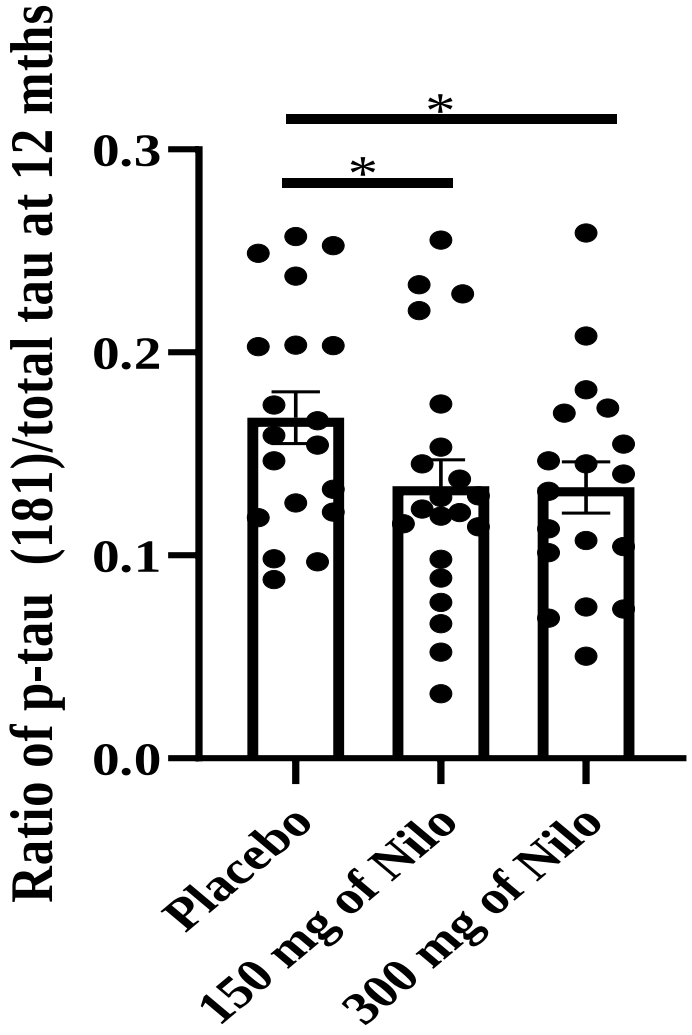


Nilotinib Reduces Phospho-tau 181 in PD (One Year Treatment) Pagan et al, JAMA Neurology, 2019, Dec 16.

Nilotinib Reduces CSF Toxic ptau in Moderately Advanced PD Patients







Clinical Effects of Nilotinib - 12 months
The Placebo Effects!

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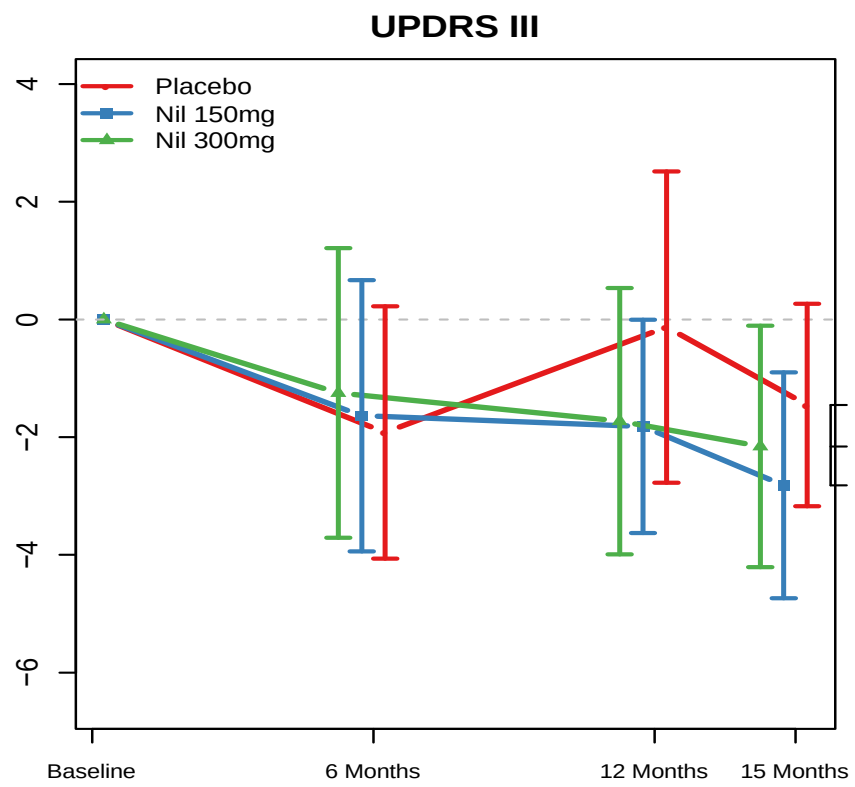
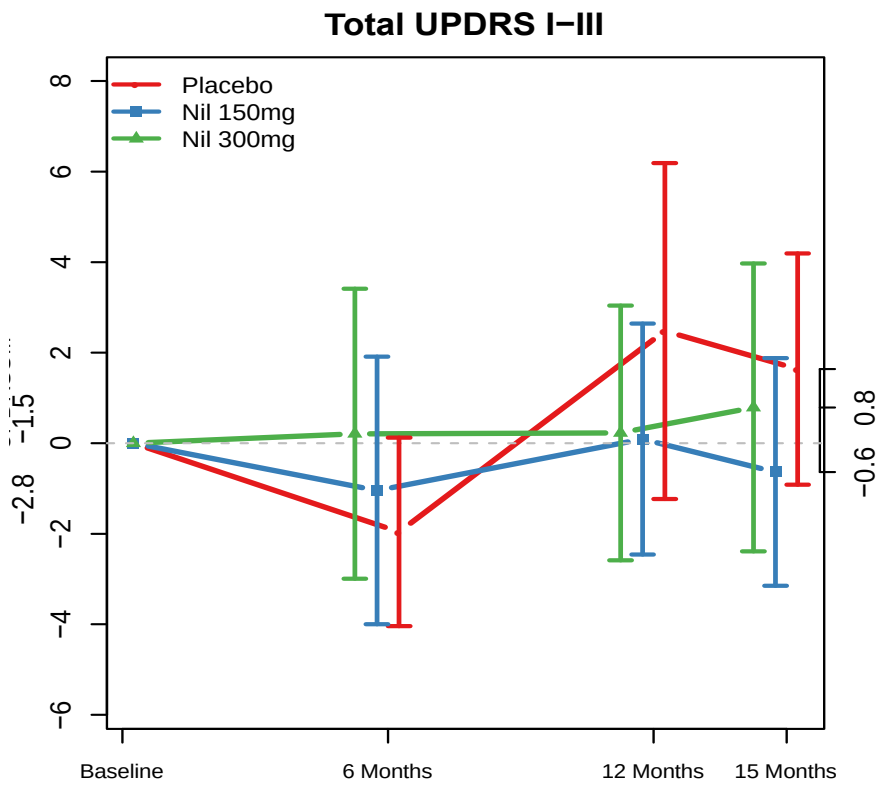
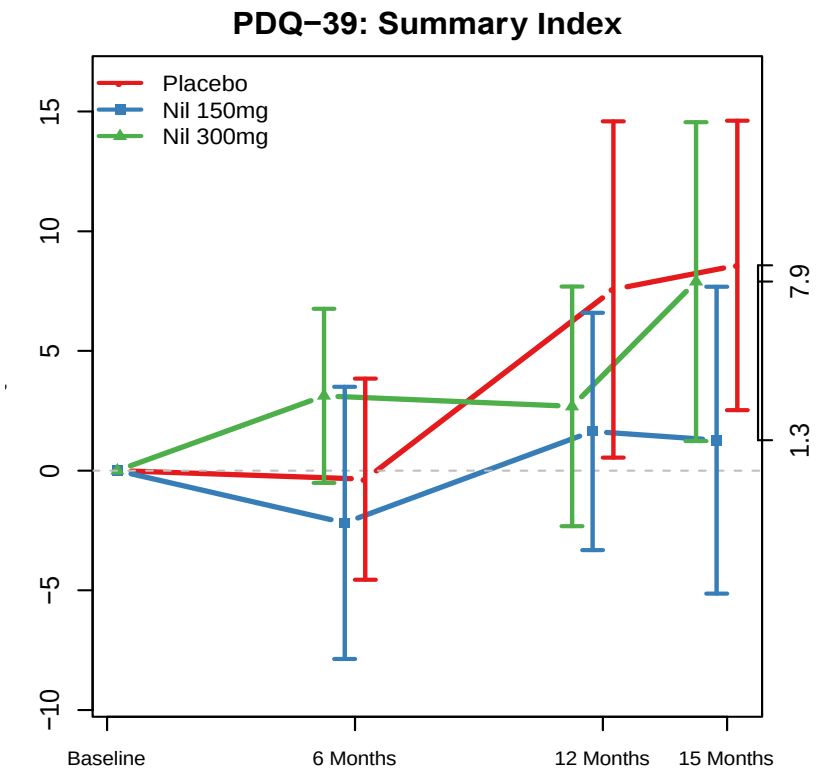
<u>One Year Treatment</u> Nilotinib Shows Weak Effects on Motor and Non-Motor Symptoms in PD patients on optimal SOC (ON-testing)- Maybe Due to Placebo Effects







Clinical Effects of Nilotinib > 12 months (Two-Year Treatment)

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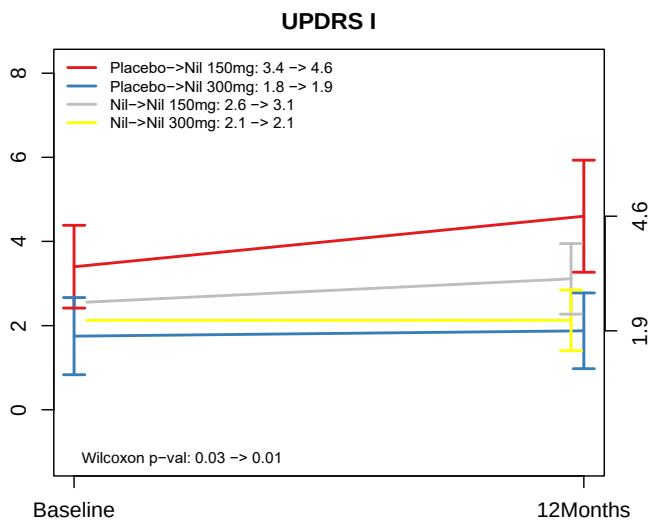
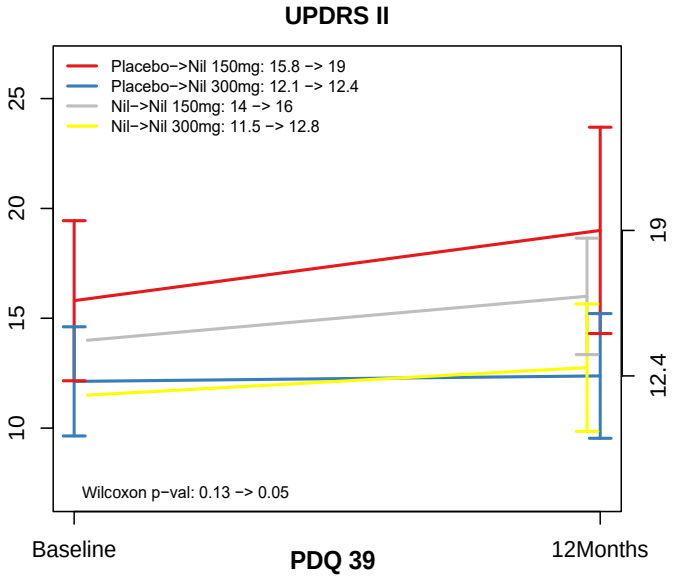
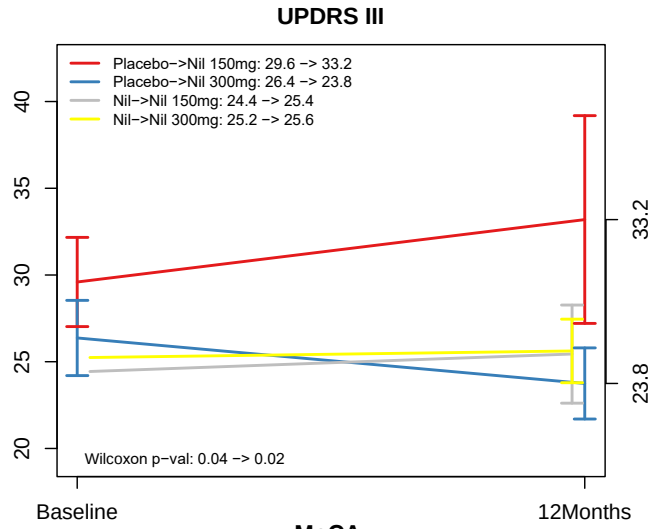
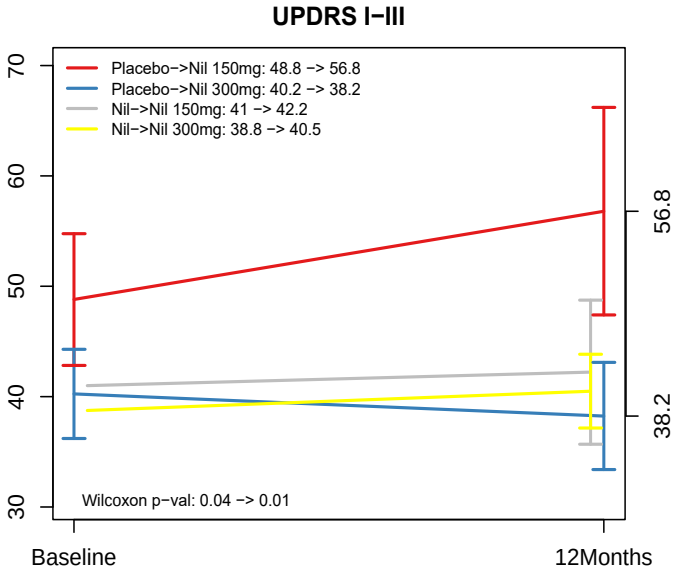
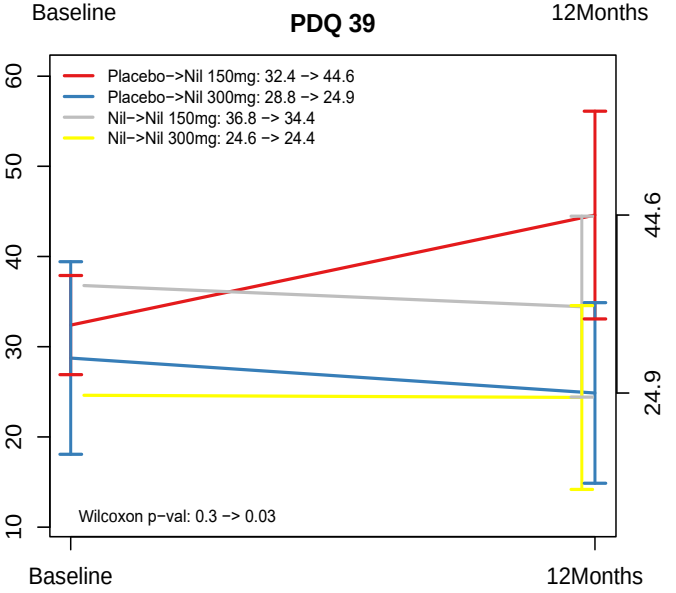
Early Start Nilotinib Stops PD Progression in 150 and 300 mg Groups, But 300 mg Nilotinib Significantly Improves Motor, Non-Motor and Cognitive Symptoms Compared with 150mg Nilotinib in the Late Start Nilotinib Group that Received Placebo in Year 1 in PD patients on optimal SOC (ON-testing)

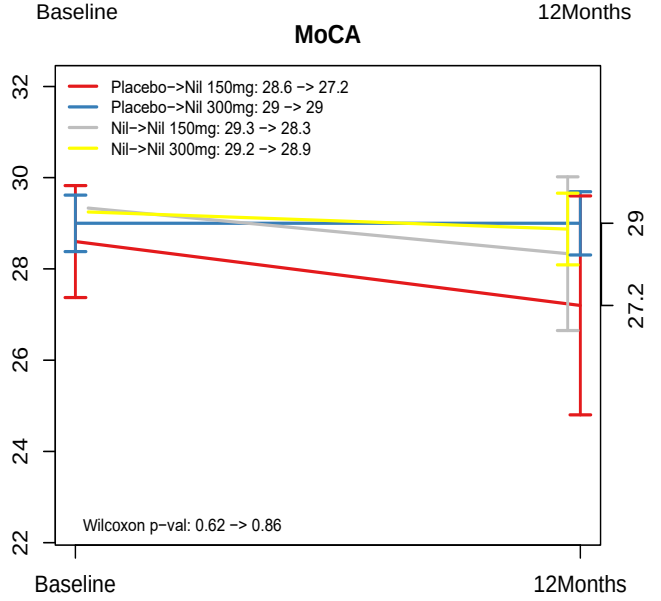




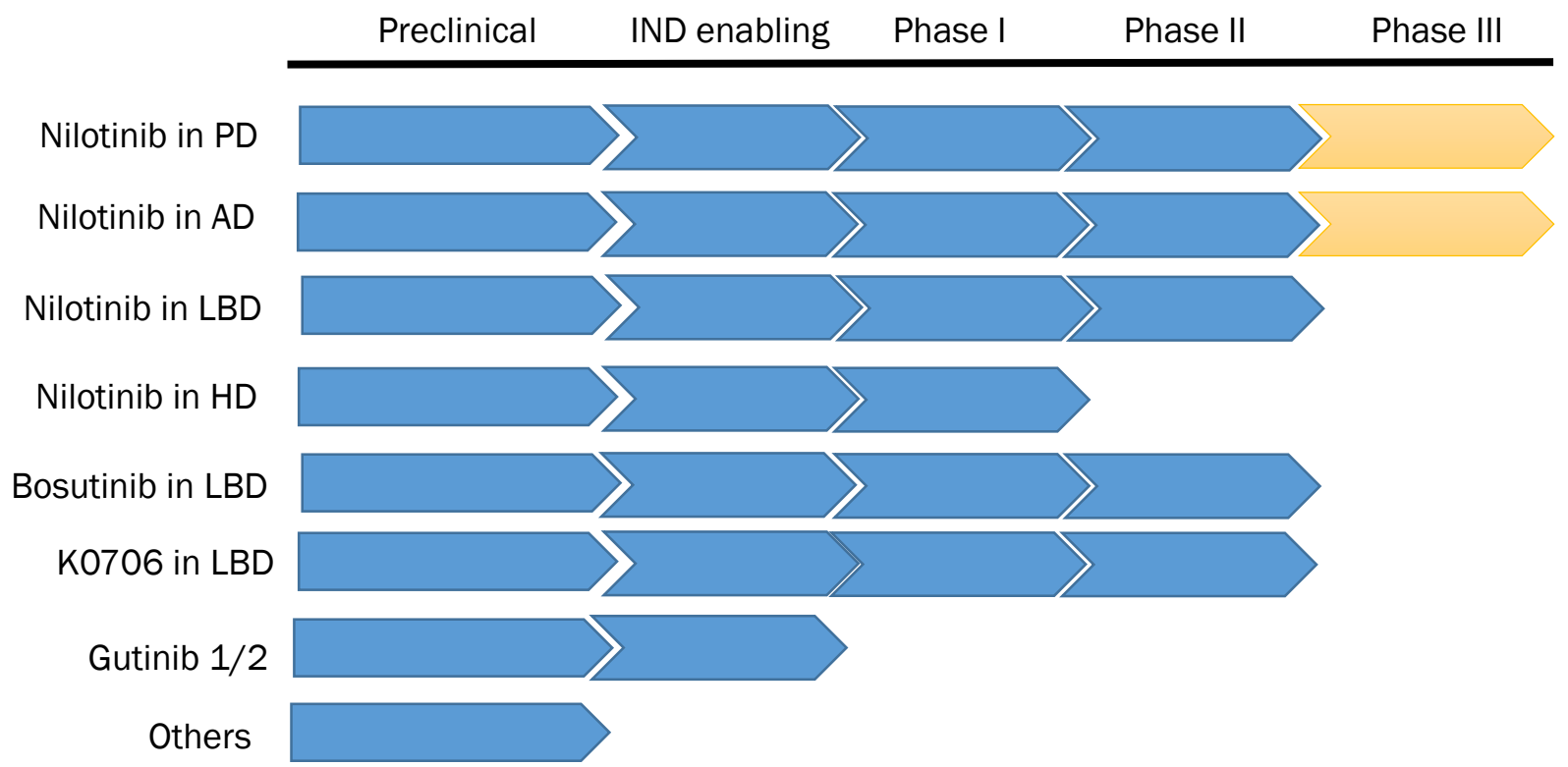








SUMMARY



Discoindin Domain Receptors (DDRs) are upregulated in AD and PD and are potential therapeutic targets

Nilotinib achieves pharmacologically sufficient CSF concentrations to inhibit DDRs

Nilotinib increases brain dopamine levels in patients receiving Levodopa (PD) and Levodopa-naïve patients (AD)

Nilotinib reduces CSF levels of oligomeric alpha-Synuclein and phospho-tau

Nilotinib reduces amyloid burden via PET Imaging in AD

Nilotinib appears to have an effect on motor, non-motor and cognitive functions > 12 months

Nilotinib should be investigated in adequately powered phase III studies to better understand its safety and efficacy in neurodegeneration